DESULPHURIZATION OF CERTAIN SULPHUR-CONTAINING INTERMEDIATES AND DYES

A Thesis
submitted by

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- CONTENTS -

Page

GENERAL INTRODUCTION :

PART I :

PART II :

Alkylation of amines with alcohols in the presence of Raney nickel :

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GENERAL INTRODUCTION

Raney Nickel Reductions

In 1925 and 1927 Raney introduced a new method of preparation of active catalysts.[1] The method consists of alloying a catalytically active metal with a non-active one. The inactive metal is dissolved from the alloy leaving behind a highly active catalyst. Although Raney claimed that useful catalysts can be made from nickel-aluminium alloys containing 10-85% nickel or 15-90% aluminium, the alloy which is generally used contains about 50% nickel. The nickel catalyst, generally known as Raney nickel, is prepared by treating the nickel-aluminium alloy with aqueous sodium hydroxide, when aluminium is dissolved leaving behind the active nickel catalyst as a grey-black powder which is pyrophoric. Raney nickel-aluminium alloy is marketed by Gilman Paint and Varnish Co., Chattanooga, Tennessee, U.S.A.

Various workers like Adkins,[2] Paul and Hilly,[3] DuPont and Piganiol[4], Ruggli[5] and Mozingo[6] have published methods for the preparation of the active nickel catalyst. The activity of the catalyst is influenced by the method of its preparation. Thus the concentration of sodium hydroxide and its temperature during addition of the Raney alloy, the temperature and duration of digestion, and the method of washing the catalyst free of alkali influence the activity of the catalyst. Adkins and his coworkers have classified the catalysts as W-1, W-2, W-3, W-4, W-5, W-6 and W-7 after a detailed study of the above factors, the classification being based on the hydrogenation of β-naphthol.[7-9] Hurd and Rudner[10] have based their classification of the catalysts on their ability to desulphurize thiophene in boiling xylene.

Bougault *et al.* have demonstrated that Raney nickel catalyst retains hydrogen.[11] Freshly prepared catalyst contains so much hydrogen that it ~~ma~~ may be represented by the formula Ni_2H, but on keeping hydrogen is slowly lost[12] and the catalyst gets progressively deactivated.[6] It behaves electrochemically like a reversible hydrogen electrode and has the same reducing potential as platinized platinum or platinum black.[13]

The presence of some unwashed alkali and sodium aluminate mostly increases the activity of the catalyst. Aubray[13] has claimed that if aluminium is removed completely the activity of the catalyst decreases. Presence of sodium hydroxide has been reported to activate the catalyst[14-16] but under certain conditions it may also retard the hydrogenation.[17] Delepine and Horeau[14], DuPont[18] have reported that addition of metals of the platinum group, particularly platinum, increases the activity of the catalyst. Lieber and Smith have also noted the promoter action of platinic chloride.[19] Halogens have poisoning effect on Raney nickel.[20] Sulphur also acts as a powerful poison for the catalyst. The activity of the catalyst decreases in the presence of the aldehydes and ketones because of their strong adsorption by the catalyst.[21]

Raney nickel has been widely used as a hydrogenation catalyst in the presence of external hydrogen at pressures up to 200 ~~tmx~~ atmospheres and under a very wide range of temperature. Mozingo and his co-workers have been able to reduce compounds by Raney nickel in absence of gaseous hydrogen, but this method requires large quantities of the catalyst.[22] In another method developed by Whitman, Schwenk and their coworkers, Raney (nickel-aluminium) alloy is added to a suspension or solution of the compound to be reduced in aqueous caustic soda.[23] The reduction in this method is due to the liberation of hydrogen which is then activated by the presence of the nickel catalyst. If instead of the nickel-aluminium alloy, only aluminium is added to the alkaline solution, no reduction occurs.[24]

Several reviews are available on the action of Raney nickel on organic compounds.[25] The following account gives a brief survey of the subject.

Reduction of acetylene and ethylene bonds :

Reduction of acetylene bonds in the presence of Raney nickel takes place easily. Terminal acetylene bonds are reduced with great speed, and it is not possible to get pure ethylenes after one mole of hydrogen has been absorbed. However, if an acetylene bond is located elsewhere in an alkyl chain it can be selectively hydrogenated to the intermediate ethylenic stage. Often there is an inflexion in the velocity curve of hydrogen absorption at the half-way reduction stage. If the reaction is interrupted at this stage good yields of ethylenes may be obtained.[18]

Ethylene bonds are reduced readily by Raney nickel and hydrogen at normal pressures and temperatures. Terminal double bonds are reduced at constant speed in compounds such as n-heptene and styrene.[26] Reduction of secondary double bonds, either in an open chain, as in 2-octene or in a cyclic compound as in cyclohexene, is slower than the reduction of a primary double bond. If two double bonds are present they activate each other, and selective reduction is not possible unless one of them is tertiary which will not be attacked. Reduction of conjugated double bonds is much slower than of isolated double bonds.[27] In unsaturated alcohols, the position of an hydroxyl group has no apparent influence on the reduction of the double bonds.[28,29] Carbonyl groups, if they are not too far away, can activate the double bonds. During reduction the carbonyl group is also attacked, thus cinnamic aldehyde gives dihydrocinnamaldehyde, dihydrocinnamic alcohol and unattacked cinnamic aldehyde when one mole of hydrogen is absorbed.[30] Substituted cinnamic acids have been reduced by Raney nickel in the presence of hydrogen as well as by Raney alloy in aqueous alkali. Reduction is easier with o-substituted than with α-substituted cinnamic acids.[31] In the presence of a hydrogen donor like diethylcarbinol and cyclohexanol, Raney nickel can act as an oxidation-reduction catalyst. Thus stilbene has been converted to dibenzyl.[32]

Carbonyl groups :

Delepine and Horeau after a detailed study of the reduction of carbonyl compounds by Raney nickel state that the rate of reduction differ greatly with individual compounds.[33] The reduction is also affected by the temperature, hydrogen pressure and the amount of catalyst, and rapid reaction takes place at high temperatures and pressures.[34] Addition of small amounts of alkali and noble metals to the catalyst greatly increases the rate of hydrogen absorption.[33,14] Ketones are reduced to carbinols,[35,36] keto-alcohols[37] and diketones to glycols[38] and keto-acids to hydroxyacids. Carbonyl groups also can be reduced by oxidation-reduction reaction in the presence of a hydrogen donor like cyclohexanol. Thus D-glucose has been reduced to sorbitol,[39] benzoin to dibenzyl and cholestanone to dihydrocholesterol.[32] Mozingo has reduced the carbonyl groups in acetone, cyclopentanone, ethyl acetoacetate and benzalacetone to the corresponding hydroxyl groups by using excess of Raney nickel in the absence of gaseous hydrogen. But benzaldehyde under these conditions gave toluene.[22] By using Raney alloy and aqueous alkali, Whitman and his coworkers have reduced estrone to a mixture of α- and ~~α~~ β-estradiols.[23] They have found that by this method carbonyl groups directly attached to aromatic nucleus are reduced to the hydrocarbon, whereas those attached through alkyl groups as in $Ph(CH_2)_xCOR$, where x is 1 or greater, give the corresponding carbinols.[24]

Carboxylic acids and their derivatives :

Although Raney nickel is not commonly employed for the reduction of carboxyl groups, by using high temperatures and hydrogen at high pressures esters of carboxylic acids have been reduced to the corresponding hydroxy derivatives. Reduction of esters of leucin to leucinol and the ester of phenylaminoacetic acid to 2-phenyl-2-aminoethanol and 2-cyclohexyl-2-aminoethanol has been reported by Ovakimian *et al.*[40] Adkins has also reported the hydrogenation of esters of α-amino acids to corresponding amino alcohols.[41,42] Phenyl propionate gives a mixture of cyclohexyl propionate, propionic acid and cyclohexane. This is specific for aryl esters since neither cyclohexyl-*n*-butyrate nor ethyl cinnamate undergo this cleavage.[43] Benzyl cinnamate gives dihydrocinnamic acid and toluene.[44] The cyclic derivatives of dicarboxylic acids are easily reduced. *N*-Substituted succinimides yield *N*-substituted pyrrolidones[45] and phthalic anhydride is reduced to phthalide in good yields.[46]

Ethers :

Dialkyl and aryl alkyl ethers are in general stable towards hydrogenolysis. Benzyl aryl and benzyl alkyl ethers are easily cleaved at 100-150° and hydrocarbons and alcohols or phenols are obtained. Diaryl ethers require somewhat higher temperatures, i.e. 150-200° for hydrogenolysis.[47]

Whitman and his coworkers have reported that by using Raney alloy and aqueous alkali, alkoxy groups are displaced from disubstituted benzene derivatives when they are ortho or para to a meta-directing group, thus o-methoxybenzoic acid and p-anisic acid give benzoic acid. In trisubstituted benzene derivatives, $RC_6H_3R'R''$, where R is a meta-directing group, other than carboxyl, R' is either a hydroxyl or alkoxyl group and R" is an alkoxyl group, the meta-directing group is displaced by hydrogen. This displacement is independent of the position relationship of the three groups, thus both 2:3- and 3:4-dimethoxybenzaldehyde give veratrole.[48]

Ozonides :

Ozonides react vigorously with Raney nickel to give aldehydes or ketones and nickel oxide.[49]

Alcohols :

Alcohols are dehydrogenated by Raney nickel to aldehydes or ketones at or below their boiling points. The yields of the oxidation products are low and Paul believes that dehydrogenation stops because the carbonyl compounds which are formed are more strongly adsorbed by Raney nickel than alcohols. Dehydrogenation of alcohols by Raney nickel may be accompanied by reduction which converts part of the alcohols to hydrocarbons or in case of unsaturated alcohols reduces the double bond. Thus, furfuryl alcohol gives furfural, furan and methyl furan; allyl alcohol gives propionaldehyde and methylethylacrolein, and cinnamic alcohol gives hydrocinnamaldehyde, hydrocinnamic alcohol, propylbenzene and propenylbenzene.[50] Dubois has reported the conversion of 2-heptanol to 2-heptanone in 88% yield.[51] Aromatic alcohols behave likewise and anisaldehyde was obtained from anisyl alcohol. However $2{:}3\text{-}(MeO)_2C_6H_3CH_2OH$ was reduced to $2{:}3\text{-}(MeO)_2C_6H_3Me$.[52] Thonon has reported that the rate of dehydrogenation of secondary alcohols on Raney nickel decreases with increase in molecular weight.[53] Raney nickel in the presence of an hydrogen acceptor may be used to catalyse the oxidation of secondary alcohols to corresponding ketones. Thus in the presence of cyclohexanone, cholesterol has been converted to cholestenone and benzoin to benzil.[32] Benz~~o~~yl alcohol on treatment with Raney alloy and aqueous alkali gives toluene.[24]

Conversion to amino groups :

Nitro and nitroso groups are easily reduced by Raney nickel at moderate temperatures and hydrogen pressures. Adkins has reported the reduction of nitrobenzene by Raney nickel to azo- and azoxybenzene at room temperature in absence of gaseous hydrogen.[2] Albert and Ritchie have reduced nitro compounds like 2:6-dinitrotoluene, 3:5-dinitrobenzoic acid, ~~p~~ *o*- and *m*-nitrophenols to the corresponding amino compounds by Raney nickel at room temperature and hydrogen at atmospheric pressure. They suggest that reduction takes the following course: $RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2$.[54] Nitroarylarsonic acids have been reduced to aminoarylarsonic acids.[55] Nitroguanidines are reduced to aminoguanidines, the first step in the reduction being the formation of nitrosoguanidines.[56] Selective reduction of the nitro group has also been reported. Thus nitrocinnamic acids gave aminocinnamic acids[57] and 4-nitro-4'-acylaminodiphenyl sulphone gave the corresponding amino compound without desulphurization.[58] Both α-nitro and 1:5-dinitronaphthalenes give *ar*-

tetrahydronaphthylamine by Raney alloy and aqueous alkali.[59] Aliphatic nitro compounds have~~e~~ also been reduced to amino compounds by Raney nickel.[60]

p-Nitrosophenol and *p*-nitrosodimethylaniline are reduced almost quantitatively over Raney nickel at room temperature.[61]

Oximes are easily reduced by Raney nickel and both primary and secondary amines are formed.[61-63]

Reduction of nitriles to amines has been reported by Paty who obtained quantitative yields of ethylamine and phenylethylamine by the reduction of acetonitrile and benzonitrile.[64] However, generally secondary amines are also formed in 10-25% yield, but higher yields of primary amines are obtained when reduction is carried out in the presence of ammonia.[65-67]

Raney nickel is also a useful catalyst for direct conversion of compounds containing a carbonyl group into amines by the action of ammonia or a primary or a secondary amine. Adkins has converted carbonyl compounds to amines at 150°, thus *n*-butyraldehyde and ammonia over Raney nickel gave *n*-butylamine, di-*n*-butylamine and 2-*n*-propyl-3:5-

diethylpyridine.[61,67] Aromatic aldehydes give better yields and 90% yield of primary amines is obtained.[68] Poorer yields are however obtained with ketones. Phenylethylamine has been obtained from acetophenone in 45-50% yields.[69] Emerson has reported alkylation of aromatic amines and nitro,nitroso and azo compounds in the presence of Raney nickel and sodium acetate at room temperature and hydrogen at 3 atmospheres.[70] Adkins has reported that primary and secondary alcohols react with amines in the presence of Raney nickel at 180-250° and hydrogen at 125 atmospheres to give secondary amines.[67] Metayer has reported the formation of 1-ethyloctahydroindole during the hydrogenation of indole in ethanol in the presence of Raney nickel and hydrogen at 72 kg. pressure at 160°.[71] Mozingo has reported that nitrobenzene, hydrazobenzene ~~and azoxyben~~ and azoxybenzene are reduced and alkylated to N-ethylaniline by excess of Raney nickel in boiling ethanol.[72] During desulphurization of benzidinesulphone under similar conditions, Shah et al.[73] have obtained N:N'-diethylbenzidine. Alkylation of primary aryl and alkylamines by means of alcohols in the presence of Raney nickel is described later (Part II).

Aromatic and heterocyclic compounds :

Reduction of benzene to cyclohexane in the presence of Raney ~~xx~~ nickel requires high temperature and pressure, i.e., 150° and hydrogen at 100 atmospheres. Toluene and other simple monoalkylbenzenes behave similarly.[74] Naphthalene is readily reduced to tetralin and decalin.[75,76] During the hydrogenation of naphthols both the substituted and unsubstituted rings are reduced.[73,76-78] By using Raney alloy and alkali, naphthalene is reduced in good yield to tetralin. α-Naphthol, α-nitronaphthalene, β-naphthoic acid, α-naphthaleneacetic acid yield corresponding *ar*-tetrahydro derivatives. With β-naphthol and α-naphthoic acid reduction occurs in both the substituted and unsubstituted rings. 1:5- and 1:6-Dihydroxynaphthalenes gave 5-hydroxy- and 6-hydroxy-α-tetralones respectively.[59]

Anthraquinone is hydrogenated by Raney nickel to octahydroanthrahydroquinone and octahydroanthraquinone; anthrone to octahydroanthranol and dihydroanthracene to octahydroanthracene.[79] Phenanthrene is hydrogenated by Raney nickel to a mixture of hydrogenated products.[80]

The hydrogenation of the furanoid nucleus occurs under somewhat milder conditions than those used for benzenoid ring. Alkylfurans readily give tetrahydro derivative.[81] The furan nucleus is reduced without side reactions during the hydrogenation of salts, esters or amides of furan carboxylic acids.[82]

Raney nickel reduction of pyrone gives hydroxytetrahydropyran~~s~~.[83] Benzopyrones, the chromones, are reduced to a mixture of chromanones and hydroxychromans.[84]

Pyrrole and its alkyl derivatives in which nitrogen is unsubstituted, can be reduced only with difficulty to pyrrolidines. If the nitrogen in the pyrroles ring carries a substituent the reduction is easier.[85]

Adkins and his coworkers have reported the hydrogenation of pyridines, carbazoles, phenylpyrroles, indoles and acridines.[86] Carbazole is reduced to 1:2:3:4-tetrahydrocarbazole by excess of

Raney nickel in boiling alcohol. 3-Aminocarbazole under similar conditions also gives 1:2:3:4-tetrahydrocarbazole as a result of deamination.[73]

Halogen compounds :

Reduction of compounds containing halogens by Raney nickel may be carried out with two objects in view: replacement of halogen atom by hydrogen and reduction of some unsaturated group. Dehalogenation by Raney nickel will occur depending upon the temperature and on the nature of halogen bond. Dehalogenation is easier in aliphatic series than in aromatic, and the activity of halogen increases from chlorine to iodine. Winans has reported that generally below 150° ~~dehydrogenati~~ dehalogenation does not occur in aromatic halogen compounds. The substituents, attached to the halogenated aromatic nucleus, which can be reduced by Raney nickel without dehalogenation are olefinic, acetylenic, nitro, nitroso, cyano, oximino, azo and carbonyl groups. In aliphatic series double bonds attached to the carbon atom holding the halogen, as in ω-chlorostyrene, tetrachloroethylene and *sym*-dichloroethylene, resist saturation.[87]

Dehalogenation can be achieved by using Raney nickel with hydrogen at 3 atmospheres in the presence of alkali to neutralize the hydrogen halide formed.[88] Formation of acridan from 9-chloroacridine has been reported when the reduction was carried out in the presence of alkali and gaseous hydrogen.[89] In absence of alkali and gaseous hydrogen 9-chloroacridine in boiling methanol gives 9:9'-biacridine. Similarly dehalogenation of benzyl chloride leads either to toluene or bibenzyl.[90] Chlorolepidine has been converted to lepidine in the presence of alkali and gaseous hydrogen.[91] Aromatic halogen compounds when treated with Raney alloy and aqueous alkali give dehalogenated products in good yields.[48] Under similar conditions Gump and Vitucci have dechlorinated 5:5'-dichloro-2:2'-dihydroxydiphenyl sulphide to dihydroxydiphenyl sulphide.[92] Use of Raney alloy and aqueous alkali has been suggested for quantitative determination of halogens in organic compounds.[93]

Desulphurization :

Desulphurization of organic compounds by Raney nickel has been comprehensively reviewed by McOmie.[25]

Bougault, Cattelain and Chabrier were first to use Raney nickel for desulphurization of both organic as well as inorganic compounds.[94] They used Raney nickel without gaseous hydrogen to convert thioglycollanilide, $HSCH_2CONHPh$ to acetanilide and thioglycollic acid and dithioglycollic acid, $(-SCH_2CO_2H)_2$ to acetic acid. x During desulphurization of thiourea they found that C-N linkage is cleaved, thus thiourea gives ~~methanol~~ methane, methylamine and ammonia and benzylthiourea gives ammonia, methylamine and toluene. Removal of thiophene and methylthiophene from benzene and toluene by the action of Raney nickel has been reported. The removal of sulphur by Raney nickel is not catalytic and they suggest that desulphurization takes place in two stages: (1) a combination with nickel and (2) a destruction of the combination to form NiS with liberation of hydrogen in most cases. These observations have been considerably extended by Mozingo and his collaborators[22] who have shown that Raney nickel removes sulphur from a variety of organic compounds without gaseous hydrogen at moderate temperatures and in the presence of solvents such as alcohol, according to the scheme :

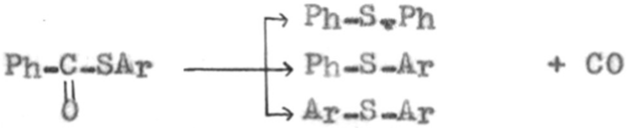
$$RSR' \xrightarrow{Ni(H)} RH + R'H$$

Bonner has shown that hydrogen retained by the catalyst brings about the hydrogenolysis by carrying out the reactions in benzene which cannot act as hydrogen donor.[95] The removal of sulphur by Raney nickel has played a vital part in elucidating the structure and stereochemistry of β-biotin methyl ester[96] and benzylpenicillin.[97]

Wolfrom and Karabinos[98] have used the desulphurization by Raney nickel for the reduction of carbonyl compounds to the corresponding methylene derivatives. The carbonyl compound is first converted to a mercaptal which is then subjected to treatment with Raney nickel:

This method has been used by Hauptmann,[99] Woodward[100] and others[101] in the steroid series, and for the elucidation of the constitution of streptomycin.[102]

Hauptmann[103] has reported that mercaptals, mercaptols and disulphides are ~~trans~~ transformed into simple thioethers by the action of Raney nickel that has been freed from hydrogen by heating <u>in vacuo</u> at 200°. When hydrogen is not completely removed binuclear hydrocarbons such as diphenyl and dibenzyl are formed. When benzaldehyde mercaptals or acetophenone mercaptols are used stilbene or its substituted products are obtained in addition to thioethers. Treatment of thiobenzoic esters with "hydrogen-free Raney nickel" gives mixed thioethers:



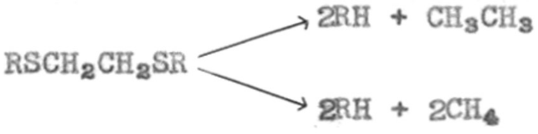
$$\text{Ph-}\underset{\displaystyle\overset{\|}{\text{O}}}{\text{C}}\text{-SAr} \longrightarrow \begin{cases} \text{Ph-S-Ph} \\ \text{Ph-S-Ar} \\ \text{Ar-S-Ar} \end{cases} + \text{CO}$$

Desulphurization of thiolesters with Raney nickel yields alcohols[104] or aldehydes.[105]

$$\text{RCOSR} \longrightarrow \text{RCHO or } \text{RCH}_2\text{OH}$$

Freshly prepared Raney nickel leads to the formation of alcohols, but good yield of aldehydes is obtained if Raney nickel is deactivated by refluxing it with acetone.[106] Preparation of aldehydes by this method has been used in simple aliphatic and aromatic compounds[105] as well as in steroids.[106] Aliphatic, aromatic and heterocyclic acids have also been converted by this method to the corresponding alcohols in good yields.

Snyder and Cannon[107] have reported that in certain ethers of ethylenedithiols carbon-carbon cleavage might also occur along with desulphurization.

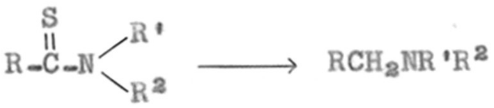


$$RSCH_2CH_2SR \rightarrow 2RH + CH_3CH_3$$
$$RSCH_2CH_2SR \rightarrow 2RH + 2CH_4$$

Desulphurization of sulphoxides and sulphones by Raney nickel has been reported by Mozingo.[108]

$$RSOR' \longrightarrow RH + R'H$$
$$RSO_2R' \longrightarrow RH + R'H$$

Kornfeld has reported the reductive desulphurization of thioamides in the presence of Raney nickel gives good yields of the corresponding amines. With some thioamides, which are unsubstituted on nitrogen, formation of secondary, rather than primary amines, was observed.[109]

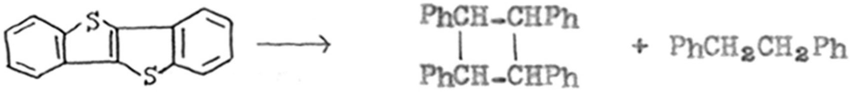


$$R-\overset{S}{\overset{\|}{C}}-N{<}^{R'}_{R^2} \longrightarrow RCH_2NR'R^2$$

Desulphurization of substituted thioureas to the corresponding formamidines by Raney nickel has been reported by Ashworth.[110]

Thiophene derivatives by treatment with Raney nickel gives the corresponding alkyl derivatives. Thus thionaphthene and 3-hydroxythionaphthene gives ethylbenzene. Dibenzothiophene gives diphenyl and thiophene-2-carboxylic acid gives valeric acid.[111] Thionaphthenequinone is converted to mandelic acid by the action of Raney alloy and aqueous alkali. Mandelic acid itself on similar treatment remains unchanged except for the formation of traces of phenylacetic acid.[112]

Baker has reported that desulphurization of 4':5':4:5-dibenzothiopheno(2':3'-3:2)thiophene with freshly prepared Raney nickel in ethanol gave 1:2:3:4-tetraphenylcyclobutane but with Raney nickel which had been kept for three months it gave, in addition to the above product, dibenzyl also. When the reduction was carried out in methanol in both cases dibenzyl was the only product.

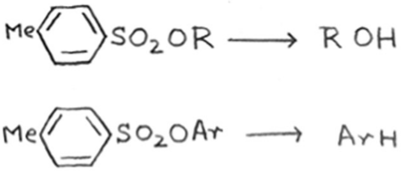


$$\xrightarrow{} \begin{array}{c} PhCH-CHPh \\ | \quad\ \ | \\ PhCH-CHPh \end{array} + PhCH_2CH_2Ph$$

Thiodiphenylamine by the treatment with Raney nickel in alcohol gives diphenylamine.[73]

Cook and Heilbron have found that sulphur atom in the thiazole ring system is unaffected by mild treatment with Raney nickel. Thus a number of 2-mercaptothiazoles have been converted to thiazoles.[114]

By the action of Raney alloy in aqueous alkali, reductive displacment of ~~o~~ sulphonic acid groups from benzenesulphonic acid, *o*- and *m*-sulphobenzoic acids and 2-naphthol-6-sulphonic and 3:6-sulphonic acids has been reported by Whitman and his coworkers.[48] Under similar conditions J-acid gives 6-amino-1-naphthol.[73] However, toluene-*p*-sulphonic acid and its methyl ester are unaffected when treated with ~~kx~~ Raney nickel.[115] Kenner and Murray have reported that on treatment with hydrogen and Raney nickel alkyl esters of toluene-*p*-sulphonic acid yield the corresponding alcohols, but aryl esters give the aromatic hydrocarbons. Alkyl and aryl esters of benzylsulphonic acid are rapidly reduced to the hydroxy-compounds, and benzylsulphonanilides to anilines although toluene-p-sulphonamides are resistant to hydrogenation.[116]



$$PhCH_2SO_2OR \longrightarrow ROH$$

$$PhCH_2SO_2OAr \longrightarrow ArOH$$

$$PhCH_2SO_2NHPh \longrightarrow PhNH_2$$

Desulphurization of esters of toluene-p-sulphonic acid has been used for the removal of hydroxyl groups in the flavone series and for the preparation of γ-resorcylic acid.[117]

Organometallic compounds, arsanilic acid and phenylmercuric acetate on treatment with Raney alloy in aqueous alkali give aniline and diphenyl respectively.[48] Raney nickel has been used for the removal of selenium from organo-selenium compounds. Thus, dibenzoselenophene, dibenzoselenophene oxide and dibenzoselenophene dichloride give diphenyl on treatment with Raney nickel.[118]

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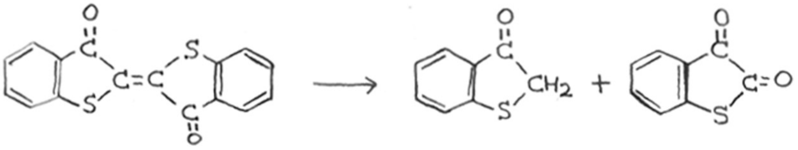
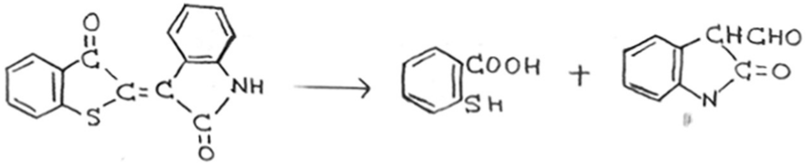
Part I

DESULPHURIZATION OF THIOINDIGOID DYES AND SULPHUR-CONTAINING INTERMEDIATES

The study of the action of Raney nickel on dye intermediates and dyes of the thioindigoid series was undertaken with two objects in view: (1) to use this method for determining the constitution of sulphur-containing dyes and other sulphur-heterocyclics; and (2) to synthesise difficultly accessible organic compounds such as diphenacyl and 1:4-diphenylbutane derivatives which were expected to be formed by the removal of sulphur from the thioindigoid dyes, followed by reduction of the resulting sulphur-free products. Diphenacyl and its derivatives are not easily accessible and are usually prepared by hydrogenation of the corresponding dibenzoylethylenes.[1] Di- and tetrahydroxy derivatives of diphenacyl have been prepared as by-products in the condensation of succinic acid or anhydride with phenol or resorcinol, the major products being the corresponding succineins.[2]

Several methods are known for the degradation of thioindigoid dyes. Friedlander and Sander[3] have reported that thioindigo is cleaved to thioindoxyl and 2:3-thionaphthenequinone by treatment with alcoholic caustic potash. 2-Thionaphthene-3'-indole-indigo on similar treatment gave thiosalicylic acid



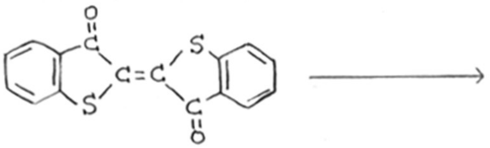


and oxindole-3-aldehyde.[4]

Although indigo can be easily oxidised to isatin by the action of nitric or chromic acid,[5] oxidation of thioindigo by these agents does not give thioisatin in good yield. Thioindigo-S-oxide is obtained when thioindigo is treated with concentrated nitric acid[6] or chromic acid.[7] By the action of a mixture of concentrated and fuming nitric acid on thioindigo, Riesz[8] obtained *o*-sulphobenzoic acid. By prolonged treatment of thioindigo in hot acetic acid by nitrous gases Posner and Wallis[9] obtained a small yield of 2:3-thionaphthenequinone, major portion of the dye being recovered unchanged. Furst and Pollak[10] have reported cleavage of thioindigo by means of ozone into two molecules of thionaphthenequinone in good yields. Whereas the above methods of degradation of thioindigoid dyes involve fission of the carbon chain linking the two aryl residues, desulphurization by means of Raney nickel has the distinctive feature that the carbon skeleton of the molecule remains largely intact.

Removal of sulphur from organic compounds by means of Raney nickel at atmospheric pressure is carried out by treatment of the compound (1 part) with a large excess of active Raney nickel[11] (10-30 parts) in a suitable solvent at temperatures up to the boiling point of the solvent.[12] Another method of desulphurization consists in the treatment of the compound (1 part) with Raney (nickel-aluminium) alloy (usually 3 parts) in hot aqueous alkaline solution according to Papa, Schwenk and their collaborators,[13a] who have suggested that the reduction is due to the activation of hydrogen, liberated by the dissolution of aluminium in aqueous alkali, by the finely divided nickel catalyst. If the nickel catalyst is omitted and the alkaline solution treated with aluminium, no reduction occurs. The mechanism of desulphurization by active Raney nickel, therefore, appears to be the same in both the procedures, but the amount of the catalyst employed when Raney alloy is ~~smaller~~ used is smaller because of the greater availability of the hydrogen produced by the dissolution of aluminium in aqueous alkali. In the present study, both of these methods were employed for desulphurization.

Desulphurization of thioindigo, the parent member of the *bis*-thionaphthene-indigo series of dyes, was first studied. The reduction was carried out by treatment of the dye with varying amounts of Raney alloy in aqueous alkaline solution at about 100°. Reduction of the dye with equal parts of Raney alloy in aqueous alkaline solution gave diphenacyl (I) in about 1.5% yield, together with traces of benzoic acid; and about 50% of the dye was recovered unchanged. The isolation of benzoic acid even under mild conditions of reduction is of interest. When the dye (1 part) was reduced with Raney alloy (4.5 parts), most of the dye was desulphurized, but only a small amount of sulphur-free products could be isolated in the pure state. Thus the yield of pure diphenacyl was only 12% together with a smaller quantity of benzoic acid. The yield of the sulphur-free products was slightly increased by precipitation of thioindigo from sulphuric acid prior to reduction. Reduction of the dye (1 part) with Raney alloy (6 parts) gave 1:4-diphenylbutane (II) as the major product (yield 14%), a small quantity of diphenacyl (about 1%) and benzoic acid (5%). While the formation of diphenacyl and 1:4-diphenylbutane was anticipated, the formation of benzoic acid from thioindigo cannot be readily accounted for. The isolation of benzoic acid, together with toluene and p-cresol methyl ether, from the Raney nickel reduction products of p-methoxybenzyl alcohol has been recorded by Papa *et al.*[13b] and it has been suggested that benzoic acid is produced by the scheme: dehydrogenation to anisaldehyde ⟶ reduction to benzaldehyde ⟶ Cannizzaro reaction to benzoic acid and benzyl alcohol (the latter being reduced further to toluene). Whereas the desulphurization of the



$PhCOCH_2CH_2COPh$ (I)

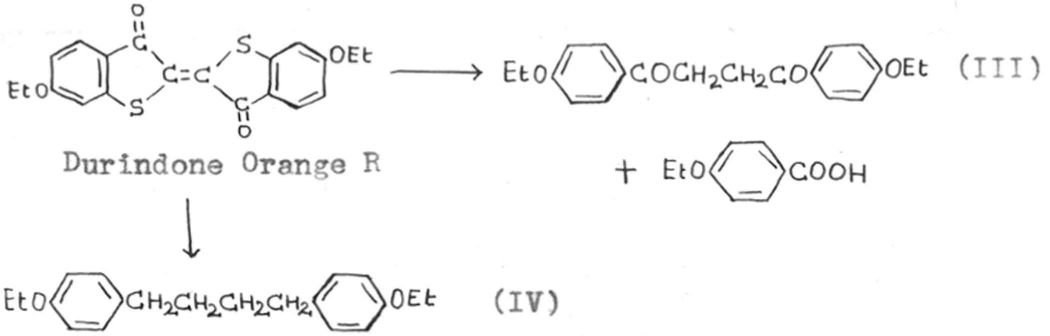
$+ PhCH_2CH_2CH_2CH_2Ph$ (II)

$+ PhCOOH$

dye by Raney alloy in aqueous alkali gave several reduction products, its treatment with Raney nickel in boiling alcohol gave 1:4-diphenylbutane (II) as the only reduction product in 76% yield.

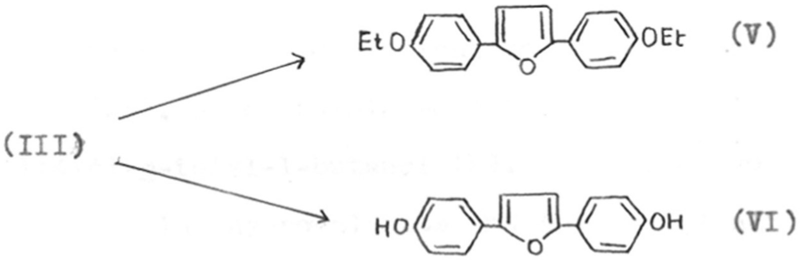
The constitution of (II) was proved by its oxidation to benzoic acid, by 5% nitric acid in a sealed tube at 150-80°.

Desulphurization of 6:6'-diethoxythioindigo (Durindone Orange R) was next studied. The dye (1 part), purified by extraction with boiling water and 5% hydrochloric acid, was treated with Raney alloy (4.5 parts) in hot aqueous alkaline solution in the usual manner. Since 50% of the dye was unchanged by this treatment, the purified dye (8 g.) was brought into a finely divided state by dissolving in concentrated sulphuric acid and reprecipitating by drowning in water. When the wet cake was reduced with Raney alloy, reddish orange needles (5.3 g., yield 79%),



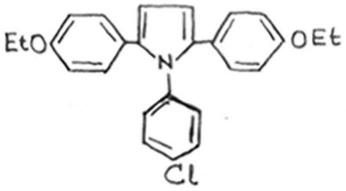
m.p. 120-25°, and p-ethoxybenzoic acid (0.13 g.) were isolated. The former substance crystallized from alcohol and acetone in pink needles, m.p. 131.5-132°, identical with 4:4'-diethoxydiphenacyl (III), m.p. 132°, prepared by Holleman[14] through a series of reactions starting from phenetole. When the dye was treated by Raney nickel in boiling alcohol, 1:4-bis-p-ethoxyphenylbutane (IV) was obtained, as the only reduction product, in 59% yield. Oxidation of (IV) gave p-ethoxybenzoic acid.

Cyclization of (III) by treatment with hydrochloric and acetic acids gave 2:5-bis-p-ethoxyphenylfuran (V) in 92% yield. Attempting to deethylate (III) by heating with pyridine hydrochloride, the product



was 2:5-bis-p-hydroxyphenylfuran (VI) by simultaneous ring closure and deethylation.

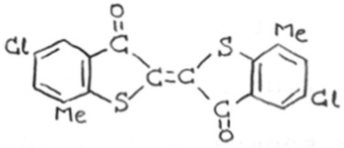
Reaction of (III) with excess of p-chloraniline in the presence of a little acetic acid (cf. Buu Hoi[15]) gave the corresponding pyrrole (VII). These



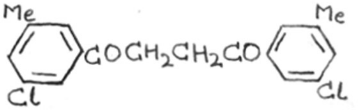
(VII)

reactions of (III) show its 1:4-diketone structure.

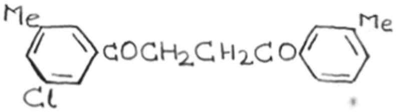
Treatment of 5:5'-dichloro-7:7'-dimethylthioindigo (Durindone Red 3BS) by Raney alloy in aqueous alkali left the dye largely unaffected, and it was found necessary to vat the dye before treatment with Raney alloy. When the dye, obtained in finely divided form by precipitation from sulphuric acid, was vatted with glucose and aqueous caustic soda and then treated with Raney alloy, the isolable sulphur-free degradation products were 3:3'-dichloro-5:5'-dimethyldiphenacyl (VIII), 3-chloro-5:5'-dimethyldiphenacyl (IX) and 1:4-di-m-tolyl-1-butanol (X). When the dye was vatted by sodium hydrosulphite and aqueous alkali and then desulphurized by Raney alloy, a larger yield of the desulphurized product was obtained from which (VIII) and (IX) were again isolated, but the major constituent was a chlorine-free liquid which was not identified. Desulphurization of the dye by Raney nickel in boiling alcohol gave 1:4-di-m-tolylbutane (XI), the constitution of which was confirmed by oxidation to isophthalic acid. Cyclization of the diphenacyl derivative (VIII) gave 2:5-di-(3'-chloro-5'-methyl)phenylfuran (XII).



Durindone Red 3BS



(VIII)



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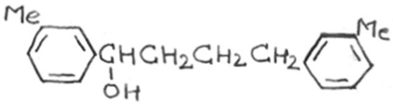
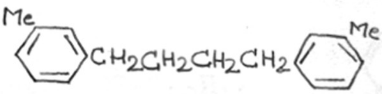


(X)



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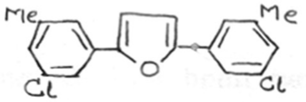
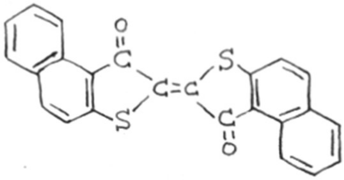
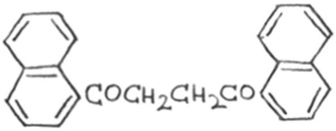


(XII)

Reduction of Durindone Brown GS (XIII), the naphthalene analogue of thioindigo, with Raney alloy in aqueous alkali gave 1:2-di-α-naphthoylethane (XIV) and a yellow nonfluorescent liquid (b.p. 140-2°/ 12 mm.) which analysed for 1:4-di-α-tetralylbutane (XV). Cyclization of (XIV) gave 2:5-di-α-naphthylfuran (XVI). When the dye was desulphurized with Raney nickel in alcohol a colourless liquid (b.p.215-20°/1 mm.) exhibiting a blue fluorescence was obtained, and it analysed for 1:4-di-α-tetralylbutane (XV). The two di-α-tetralylbutanes are apparently the 1:2:3:4- and 5:6:7:8-tetrahydronaphthalene derivatives.



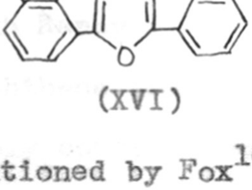
(XIII)



(XIV)

$C_{10}H_{11}CH_2CH_2CH_2CH_2C_{10}H_{11}$

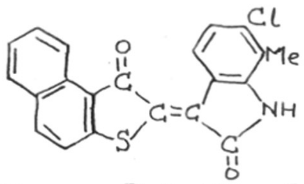
(XV)



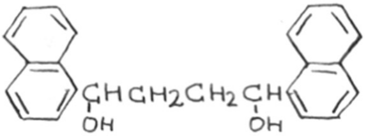
(XVI)

Ciba Brown 2R has been mentioned by Fox[16] as equivalent to Indanthrene Printing Brown 3R which is 2-(4:5-benzothionaphthene)-3'-(6'-chloro-7'-methylindole)-

indigo; but elementary analysis of purified Ciba Brown 2R and the shade on cotton indicate that it is probably identical with Durindone Brown GS (XIII). This was confirmed by desulphurization with Raney alloy in aqueous alkali when it gave 1:2-di-α-naphthoylethane (XIV) and 1:4-di-α-tetralylbutane (XV). It also gave a small amount of a substance which was probably the diol (XVII).



Indanthrene Printing Brown 3R

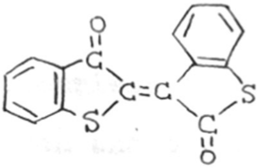


(XVII)

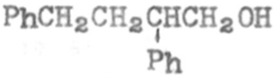
Desulphurization of Ciba Brown 2R by Raney nickel in alcohol gave 1:4-di-α-tetralylbutane (XV).

The desulphurization of unsymmetrical dyes was next studied. On treatment with Raney alloy in aqueous alkali 2:3'-bis-thionaphthene-indigo (XVIII) gave a compound which is probably constituted as 2:4-diphenyl-1-butanol (XIX). The alternative structure 1:3-diphenyl-1-butanol is improbable because Papa *et al.*[17]

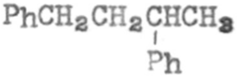
have shown that, under the conditions employed, a carbonyl group attached to a benzene nucleus is reduced to CH_2, whereas a carbonyl group not directly attached to the aryl residue undergoes reduction to an alcoholic group. Desulphurization of (XVIII) with Raney nickel in alcohol gave 1:3-diphenylbutane (XX).



(XVIII)

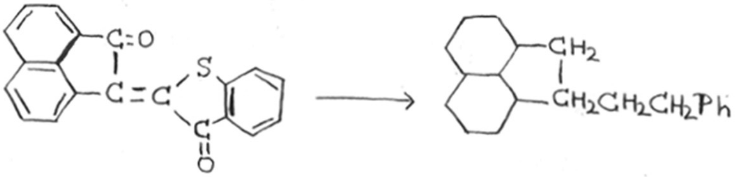


$\mathrm{PhCH_2CH_2}\underset{\substack{|\\ \mathrm{Ph}}}{\mathrm{C}}\mathrm{HCH_2OH}$ (XIX)



$\mathrm{PhCH_2CH_2}\underset{\substack{|\\ \mathrm{Ph}}}{\mathrm{C}}\mathrm{HCH_3}$ (XX)

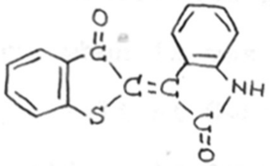
Desulphurization of Ciba Scarlet G by treatment with Raney alloy in aqueous alkali gave a complex mixture from which was isolated a pale yellow liquid, which analysed for $C_{20}H_{20}O$. Desulphurization of the dye by Raney nickel in alcohol gave a hydrocarbon, $C_{20}H_{28}$, which may be represented as α-perhydroacenaphthenyl-β-phenylethane (XXII). Attempts to dehydrogenate the above hydrocarbon by treatment with selenium were unsuccessful.



(XXI)

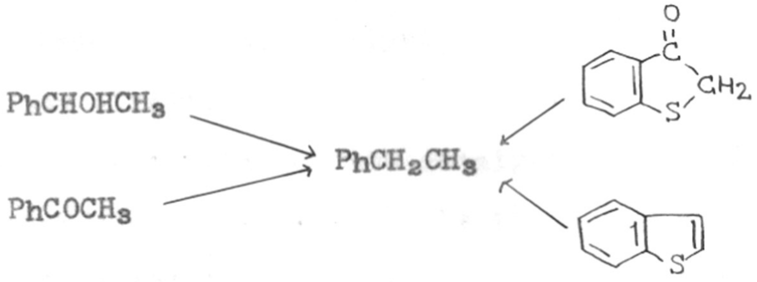
Ciba Scarlet G

Thioindigo Scarlet R, 2-thionaphthene-3'-indole-indigo on treatment with Raney nickel in alcohol, gave a small amount of the unconverted dye. The major product was a sulphur-free solid, which crystallized in colourless needles, m.p. 91-2°, and contained nitrogen and oxygen. This product, when chromatographed on a column of activated alumina in ultraviolet light, separated in four bands. The strongly adsorbed band gave the major fraction, which crystallized from dilute alcohol in colourless needles, m.p. 154°. It contained nitrogen and oxygen, and could not be identified.



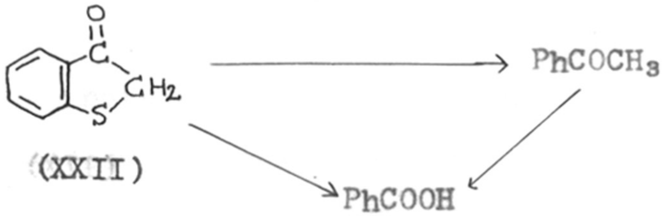
Thioindigo Scarlet R

Reduction of thioindoxyl (XXII) was next studied, since it is the intermediate from which thioindigo is prepared by oxidation. Blicke and Sheets[18] have desulphurized thioindoxyl by Raney nickel in methanol solution. They expected methylphenylcarbinol or acetophenone as reduction product but obtained only ethylbenzene. The latter is also obtained by Raney nickel reduction of thionaphthene, acetophenone and methylphenylcarbinol. Papa <u>et</u> <u>al</u>.[17] also obtained ethylbenzene by the reduction of acetophenone with Raney alloy in aqueous alkali.



(XXII)

Thioindoxyl on treatment with Raney alloy in aqueous alkali on a water-bath gave benzoic acid in 8% yield. However, when it was treated with Raney nickel in aqueous alkali at 0-5°, acetophenone was obtained in 72% yield. Acetophenone also gave benzoic acid when treated with Raney alloy in aqueous alkali.

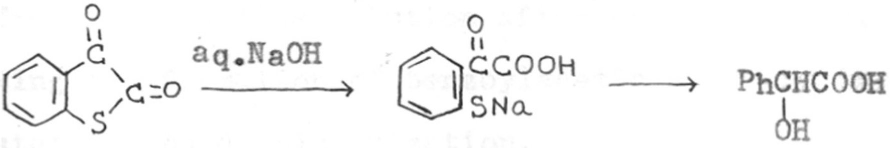


(XXII)

In the absence of the catalyst, it remains unaffected in aqueous alkali.

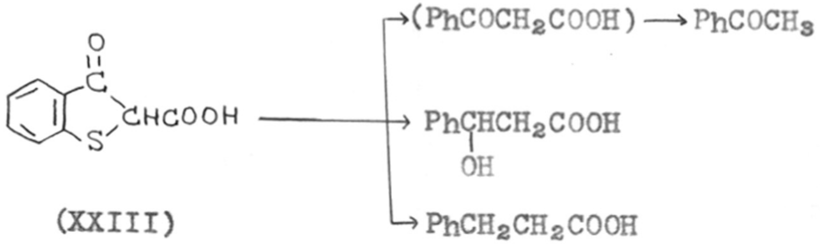
The deactivation of the catalyst by poisoning with sulphur may account for the formation of acetophenone from thioindoxyl and for the isolation of diphenacyl from thioindigo, which on further reduction give ethylbenzene and 1:4-diphenylbutane respectively. Isolation of benzoic acid from thioindigo, thioindoxyl and acetophenone when treated with Raney alloy in aqueous alkali on a water-bath indicates the cleavage of C-C linkage under these conditions.

Papa et al.[19] have observed that thioisatin by treatment with Raney alloy in aqueous alkali gave mandelic acid, which except for the formation of traces



of phenylacetic acid, remains unaffected when treated under similar conditions. By treating thionaphthene-2-carboxylic acid with Raney nickel in aqueous sodium carbonate solution, Blicke and Sheets[20] obtained β-phenylpropionic acid in 93% yield.

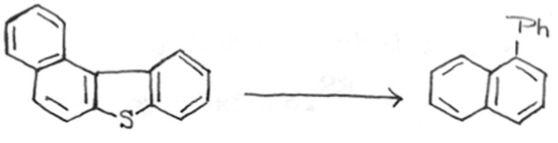
When 3-hydroxythionaphthene-2-carboxylic acid (thioindoxylic acid, XXIII) was treated with Raney nickel in boiling alcohol, β-phenyl-β-hydroxypropionic acid and β-phenylpropionic acid were obtained. β-Phenyl-β-hydroxypropionic acid (in 75% yield) and β-phenylpropionic acid (in 20% yield) were also obtained when thioindoxylic acid was treated with Raney nickel in aqueous alkali on a boiling water-bath. Only β-phenyl-β-hydroxypropionic acid (yield 86%) was isolated, when the reaction was carried out in an ice-bath for 1 hour. Thioindoxylic acid was completely desulphurized in 5 minutes by the action of Raney nickel in ice-cold aqueous alkali with the formation of β-phenyl-β-hydroxypropionic acid (46% yield) as the major product. Acetophenone was also obtained from the alkaline solution after acidification, indicating the formation of benzoylacetic acid, as the first step in the desulphurization, which during subsequent working up decomposes to give acetophenone.



(XXIII)

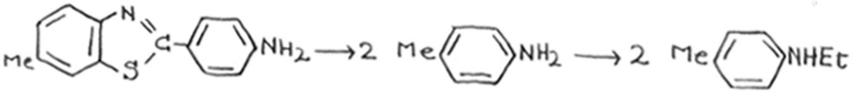
The constitution of 1:2-benzo-9-thiafluorene (XXIV) and 3:4-benzo-9-thiafluorene (XXV), which have been recently reported,[21] was proved by desulphurization with Raney nickel in alcohol. The former gave 2-phenylnaphthalene and the latter 1-phenylnaphthalene.

(XXIV)



(XXV)

Desulphurization of dehydrothio-p-toluidine (XXVI) was next studied. Green[22] has reported that on zinc-dust distillation it gives p-toluidine. When dehydrothio-p-toluidine was treated with Raney nickel in boiling alcohol it was completely desulphurized in 2 hours. The reaction product gave a p-tosyl derivative which was found to be identical with N-ethyl-N-p-tosyl-p-toluidine. N-ethyl-p-toluidine in 89% yield, was also the only reduction product when the reaction was carried out at room temperature. It appears likely that in the above



(XXVI)

degradation after the sulphur in dehydrothio-p-toluidine is removed, the remaining skeleton is cleaved at C-N bond leading to two molecules of p-toluidine. The latter is then alkylated by the action of alcohol and Raney nickel. Such N-alkylation during Raney nickel reduction has been reported by Mozingo.[23]

Similar cleavage of C-N bond was also observed when benzylaniline on treatment with Raney nickel in alcohol at room temperature gave N-ethylaniline.

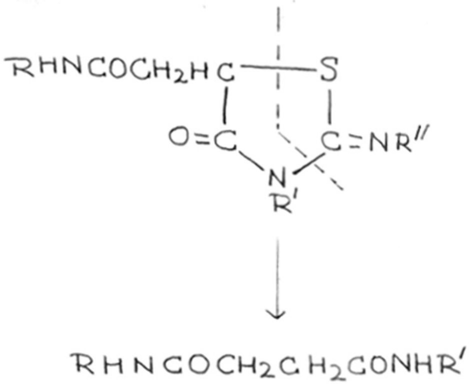
$$PhNHCH_2Ph \xrightarrow{\qquad} PHNHEt$$

It has been reported earlier that benzylaniline during its hydrogenation over platinum or palladium catalysts gives aniline and toluene or their hydrogenation products.[24]

Cleavage of C-N linkage during Raney nickel treatment has been observed earlier. Bougault *et al*.[25] have reported ammonia, methylamine and toluene as the reaction products of Raney nickel desulphurization of benzylthiourea. N-Ethylpiperidine was obtained by Kornfeld[26] by the reduction of phenylthioacetopiperidide (XXVII) with Raney nickel in alcohol. During desulphurization with Raney nickel,

(XXVII)

Marrian[27] has observed the cleavage of C-N linkage in a ring structure :-



Benzene was obtained when diphenyl diselenide was treated with Raney nickel in alcohol, showing that

$$C_6H_5\text{-Se}\overset{-\mathrm{Se}}{\wedge}\text{-}C_6H_5 \longrightarrow C_6H_5$$

selenium can be removed from organo-selenium compounds by Raney nickel. After this work was completed, Wiseman and Gould[28] have reported similar results.

EXPERIMENTAL

Reduction of Thioindigo :

Method A. - Durindone Red B 400 pdr. was purified by extraction with boiling water and then with boiling 5% hydrochloric acid, filtered, washed and dried. The purified dye (10 g.) and 10% caustic soda solution (100 cc.) were mixed in a three-neck flask, fitted with reflux condenser and mercury seal stirrer. The mixture was heated on a water bath to 90° and Raney alloy (10 g.) was gradually added. After the addition of the alloy, the mixture was further heated on a boiling water bath for 3 hours under stirring and then filtered. The unreacted dye (4.8 g.) was precipitated by aeration of the filtrate and filtered. The alkaline filtrate was then acidified by pouring into excess of concentrated hydrochloric acid. The acidified solution was ether extracted, and the ether extract after washing, was shaken with 5% sodium bicarbonate solution. The sodium bicarbonate-insoluble substance left after removal of ether was found to contain sulphur and was a sticky solid, which could not be crystallized. The sodium bicarbonate extract was acidified and the small quantity of precipitate which separated was collected and crystallized from water, when it gave colourless needles, m.p. 121°, undepressed when mixed with benzoic acid. The nickel residue was left overnight in dilute hydrochloric acid and then filtered. The filtrate was ether extracted, when a very small amount of sulphur containing oil was isolated. The nickel residue was finally extracted with benzene in a Soxhlet. The benzene extract on cooling gave 0.16 g. of the dye, which was separated, and the filtrate gave on concentration pale pinkish needles (0.15 g.), m.p. 138-40°, identical with diphenacyl.

<u>Method B</u>. - The purified dye (10 g.) was reduced with Raney alloy (45 g.) in 10% caustic soda solution (450 cc.) for 6 hours on a water bath and the reaction mixture was worked up as above. The dye was completely reduced under these conditions. A small quantity of benzoic acid was isolated from alkaline solution after removal of nickel residue. The nickel residue gave a mixture (3.7 g.) of a crystalline solid and a red oil. The oily portion was readily removed by means of ether. The ether soluble oil (1.2 g.) which contained sulphur was distilled under vacuum when it gave three liquids having different boiling points. The ether

insoluble crystalline residue gave needles (1.2 g.) from alcohol, m.p. 143-5°, raised to 144-5° by recrystallization from the same solvent (Found: C, 80.3; H, 5.8; Calc. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9%). The m.p. of the product was undepressed when mixed with diphenacyl,[29] prepared by the reduction of <u>trans</u>-dibenzoylethylene. The latter was obtained by the reaction of benzene with fumaryl chloride in presence of aluminium chloride.[30] It gave a <u>bis</u>-2:4-dinitrophenylhydrazone which crystallized from acetic acid as a microcrystalline powder, m.p. 264° (decomp.) in agreement with the known diphenacyl <u>bis</u>-2:4-dinitrophenylhydrazone,[31] m.p. 265° (decomp.)(Found: N, 18.6. Calc. for $C_{28}H_{22}N_8O_8$: N, 18.7%). Like diphenacyl, the reduction product gives a green solution in concentrated sulphuric acid which turns red and fluorescent on heating.

<u>Method C</u> : When the dye (10 g.) was finely divided by precipitation from sulphuric acid and then reduced as above, the desulphurized product was obtained in greater yield (4.5 g.). On macerating the product with ether and removal of the ether-soluble oil, diphenacyl was left as a crystalline residue (1.5 g.).

Method D : The purified dye (10 g.) was reduced with Raney alloy (60 g.) and 10% caustic soda solution (600 cc.) for 7 hours on a water bath. Benzoic acid (0.49 g.) was isolated from the alkaline extract of the reduction mixture. The nickel residue gave a red oil (3.5 g.) which on distillation under reduced pressure yielded two fractions boiling at 160-200°/11 mm. and 260-300°/11 mm. The higher boiling fraction was found to be diphenacyl. The lower boiling fraction (1.32 g.) gave colourless plates from alcohol, m.p. 49-52°, raised to 51.5-52° by recrystallization from the same solvent. The product was finally distilled when a colourless liquid, b.p. 162-5°/13 mm., was obtained, which quickly solidified on cooling to a white solid, m.p. 51.5-52°, found to be identical with 1:4-diphenylbutane (Freund and Immerwahr,[32] m.p. 52°) (Found: C, 91.5; H, 8.5. Calc. for $C_{16}H_{18}$: C, 91.4; H, 8.6%).

Method E : Thioindigo (5 g.) was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring for 7 hours and filtered. The filtrate, on removal of alcohol, gave a liquid which was dissolved in ether and extracted with 5% sodium bicarbonate solution. Removal of ether gave a liquid (2.7 g.) which on distillation (b.p.140-50°/2 mm.) ~~gave~~ gave a pink solid, m.p. 50-51°, undepressed when mixed with 1:4-diphenylbutane (II). The bicarbonate extract did not give any product.

Oxidation of (II) :

A mixture of (II)(0.2 g.) and 5% nitric acid (22.5 cc.) was heated in a sealed tube at 150-80° for 12 hours. The mixture was extracted with ether. The ether extract was shaken with 5% sodium bicarbonate solution. The bicarbonate extract was acidified and ether extracted. Removal of ether gave a cream coloured product (0.2 g.), which was crystallized from water. A pale yellow solid (0.025 g., m.p. 170-75°), which contained nitrogen, first separated and was filtered off. The mother liquor was concentrated when needles (0.1 g.), m.p. 117-18°, were obtained. Recrystallization from water gave colourless needles, m.p. 122°, undepressed when mixed with benzoic acid.

Reduction of Durindone Orange R :

Durindone Orange R 400 pdr. was purified by successive extraction with boiling water and with boiling 5% hydrochloric acid, and was then employed for reduction.

Method A. - The purified dye (8 g.) was finely divided by precipitation from concentrated sulphuric acid, and the wet cake was treated with Raney alloy (40 g.) in 10% caustic soda solution (400 cc.) for 1 1/2 hours on a water bath, when nearly all the dye was found to have decomposed. The mixture was worked up as usual. The dried nickel residue was extracted in a Soxhlet with benzene, and the benzene extract on cooling gave a small quantity (0.07 g.) of the less soluble original dye and a more soluble orange solid (5.3 g.; yield, 79%), m.p. 120-5°, from the benzene mother liquor. The orange solid on crystallization from alcohol gave needles (3.2 g.), m.p. 124-7°, which after four recrystallizations from alcohol and two recrystallizations from acetone yielded pale pink needles melting constantly at 131.5-132°. The elementary analysis and the m.p. show that the substance is 4:4'-diethoxydiphenacyl (Holleman,[14] m.p. 132°) (Found: C, 73.9; H, 6.8. Calc. for $C_{20}H_{22}O_4$: C, 73.6; H, 6.8%). The substance gives an intense green solution in concentrated sulphuric acid which quickly changes to deep purple. The purple solution exhibits a deep blue fluorescence. On heating, the colour of the acid solution changes to purple, while heating to the boil gives a pale red solution.

Concentration of the benzene mother liquor, after separation of 4:4'-diethoxydiphenacyl, gave a small yield of an oil which distills between 240-50°/10 mm. and remains to be identified. The alkaline filtrate, after removal of the nickel residue, did not yield any unreacted dye on aeration. It was then acidified and ether extracted, and the ether extract shaken with 5% sodium bicarbonate solution. The bicarbonate extract on acidification gave a white solid (0.13 g.) which crystallized from dilute alcohol in colourless needles, m.p. 194-5°, ℓ undepressed when mixed with authentic p-ethoxybenzoic acid.

Method B : Reduction of the purified dye (10 g.) with Raney alloy (60 g.) in 10% caustic soda solution

(600 cc) gave p-ethoxybenzoic acid (0.08 g.), 4:4'-diethoxydiphenacyl (3.27 g.) and a red oil which was found to be a mixture of several substances.

Method C : Durindone Orange R (12 g.) was extracted with boiling water and the residue (5 g.) was reduced with Raney nickel (50 g.) in boiling alcohol (500 cc.) for 7 hours under stirring. The mixture was left overnight and filtered. The filtrate on removal of alcohol gave a sticky product (A)(0.93 g.). The nickel residue was treated with hydrochloric acid, filtered, washed and extracted in a Soxhlet with acetone and benzene. The residue obtained on removal of the solvents was extracted with ether. Removal of ether gave a low melting product (2.4 g.) which was mixed with (A) and was distilled at 145-50°/2 mm. It crystallized from alcohol in colourless plates, m.p. 74-76°, raised to 76-77° by recrystallization from the same solvent. It analysed for 1:4-bis-p-ethoxyphenylbutane (IV) (Found: C, 81.0; H, 8.6. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%).

Oxidation of (IV):

A mixture of (IV)(0.45 g.) and 5% nitric acid

(32 cc.) was heated in a sealed tube at 150-80° for 12 hours. The crude acid, isolated by extraction with aqueous sodium bicarbonate, crystallized from aqueous alcohol in colourless needles, m.p. 195°, undepressed when mixed with p-ethoxybenzoic acid.

2:5-Bis-p-ethoxydiphenylfuran (V) :

4:4'-Diethoxydiphenacyl (1 g.) was refluxed with a mixture of glacial acetic acid (20 cc.) and conc. hydrochloric acid (16 cc.) for 10 minutes when a white solid separated. The mixture was diluted with crushed ice (20 g.) and the precipitate collected. The product (0.92 g.), m.p. 166-70°, crystallized from alcohol in colourless, shining plates, m.p. 176-7°, raised to 177-177.5° by recrystallization from the same solvent (Found: C, 77.6; H, 6.4. $C_{20}H_{20}O_3$ requires C, 77.9; H, 6.5%). The substance gives a greenish blue colour with concentrated sulphuric acid, which changes to a deeper blue on keeping and exhibits a purple colour in transmitted light. On heating, the acid solution changes to red violet. Solutions of the furan in organic solvents show faint violet fluorescence in day light and more intense violet in ultraviolet light.

2:5-Bis-p-hydroxyphenylfuran (VI) :

Pyridine hydrochloride (2 g.) and 4:4'-diethoxydiphenacyl (0.5 g.) were heated at 200-220° for 3 1/2 hours. The mixture was diluted with water and the precipitate which separated was extracted with 5% sodium hydroxide solution. The alkaline extract was acidified and the mixture extracted with ether. The ether extract gave a brown powder (0.38 g.), m.p. 190-200°, which crystallized from dilute alcohol in colourless prismatic needles, m.p. 207-10°, raised to 214-5° by recrystallization from benzene-alcohol (Found: C, 76.0; H, 4.9. $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8%). The dihydroxydiphenylfuran gives a red solution in concentrated sulphuric acid, having a bluish violet fluorescence. On heating, the colour of the acid solution changes to deep violet. Solutions of the furan in organic solvents exhibit a pale violet fluorescence in day light and a more brilliant fluorescence in ultraviolet light.

1-p-Chlorophenyl-2:5-bis-p-ethoxyphenylpyrrole (VII):

4:4'-Diethoxydiphenacyl (0.5 g.) and p-chloraniline (0.5 g.) were heated with a few drops of acetic acid at 140-60° for one hour. The product, m.p. 80-100°, was extracted with hot water. The water-insoluble portion was dissolved in ether; concentration and cooling gave colourless plates (0.55 g.), m.p. 130-2° raised to 140-41° by three recrystallizations from <u>n</u>-hexane (Found: C, 75.4; H, 6.2; N, 3.2. $C_{26}H_{24}ClNO_2$ requires C, 74.7; H, 5.8; N, 3.4%). The substance gives a red colour in concentrated sulphuric acid, which on slow heating changes to green, brown, violet, and finally brown on boiling. In organic solvents the pyrrole has faint violet fluorescence in day light, much more intense in ultra-violet light.

<u>Reduction of Durindone Red 3BS</u> :

<u>Method A</u> :- Durindone Red 3BS was purified by successive extractions with boiling water and 5% boiling hydrochloric acid. The purified dye (10 g.) was precipitated from a solution in oleum, filtered and washed. The wet cake was vatted with glucose (50 g.) and 10% caustic soda solution (500 cc.) at 70-80°. The solution was treated with Raney alloy (95 g.) in 10% caustic soda solution (500 cc.) for 7 hours on a water-bath, left overnight, and filtered.

The nickel residue was treated with hydrochloric acid, filtered, washed and extracted with benzene in a Soxhlet. The product (3.6 g.), recovered from the extract, was ether-extracted when an insoluble residue (0.36 g.) was obtained which crystallized from aqueous acetone in colourless plates, m.p. 180-81°. It analysed for 3:3'-dichloro-5:5'-dimethyldiphenacyl (VIII) (Found: C, 64.6; H, 5.2. $C_{18}H_{16}Cl_2O_2$ requires C, 64.5; H, 4.8%). The ether extract, after removal of the above product, gave an oil (3.2 g.) ~~separated~~ which was treated with n-hexane. A brown product (0.51 g.) separated which crystallized from aqueous acetone in colourless plates, m.p. 113-14°. It analysed for 3-chloro-5:5'-dimethyldiphenacyl (IX) (Found: C, 71.3; H, 6.4. $C_{18}H_{17}ClO_2$ requires C, 71.9; H, 5.6%). The product (2.64 g.), obtained from the hexane solution, was distilled when a pale yellow liquid, b.p. 196-200°/10 mm. was obtained. It analysed for 1:4-bis-m-tolyl-1-butanol (X)(Found: C,84.4; H, 8.3. $C_{18}H_{22}O$ requires C, 85.0; H, 8.7%). Attempts to isolate pure degradation products from the alkaline solution obtained after removal of nickel were unsuccessful.

Method B :- The commercial dye (6 g., containing 4.5 g. of the pure dye) was vatted with sodium hydrosulphite (6 g.) and 1.5% caustic soda solution (1000 cc.) at 85°. Caustic soda (20 g.) was added, followed by Raney alloy (50 g.). The mixture was stirred for 2 hours on a water bath and filtered. The filtrate, as in Method A, did not yield any pure products. The nickel residue was extracted with benzene as in Method A. The sticky product (2.0 g.) obtained on removal of benzene was extracted with ether. The ether-insoluble product (0.3 g.) crystallized from alcohol in colourless plates, m.p. 176-78°, undepressed when mixed with (VIII). The product from the ether solution was treated with n-hexane. The hexane-insoluble solid (0.33 g.) was dissolved in benzene and chromatographed on alumina. The major ~~ø~~ fraction gave colourless plates, m.p. 112-13° from aqueous acetone, undepressed when mixed with (IX). The hexane-soluble liquid (1.3 g.) on distillation gave a chlorine-free liquid, b.p. 165-70°/5 mm. (Found: C, 83.5; H, 8.1%).

Method C :- The purified dye (5 g.) was reduced with Raney nickel (50 g.) in boiling alcohol (500 cc.)

for 7 hours under stirring and filtered hot. The product obtained from the alcoholic solution was dissolved in ether and extracted with aqueous sodium bicarbonate. The bicarbonate extract did not give any product. The ether solution gave an oil (2 g.) which was dissolved in benzene, and chromatographed on alumina. The major zone yielded a product (1.8 g.), which on distillation gave 1:4-di-m-tolylbutane (XI), colourless liquid, b.p. 145-50°/1.5 mm. (Found: C, 90.6; H, 9.4. $C_{18}H_{22}$ requires C, 90.8; H, 9.2%).

Oxidation of (XI):

A mixture of (XI)(0.10 g.) and 5% nitric acid (22.5 cc.) was heated in a sealed tube at 150-80° for 12 hours. The pale yellow product (0.026 g.) crystallized from water in colourless needles, m.p. 332-33° undepressed when mixed with isophthalic acid.

2:5-Di-(3'-chloro-5'-methyl)phenylfuran (XI^{I}):

A mixture of (VIII) (0.1 g.), glacial acetic acid (5 cc.) and conc. hydrochloric acid (5 cc.) was refluxed for 3 hours and poured over crushed ice. The product which separated was filtered and washed. Crystallization from alcohol gave colourless needles, m.p. 162-63°, of the furan (XII) (Found: C, 67.7; H, 4.7. $C_{18}H_{14}Cl_2O$ requires C, 68.1; H, 4.4%).

Reduction of Durindone Brown GS :

Method A :- Durindone Brown GS was extracted with boiling water and boiling 5% hydrochloric acid, filtered, washed and dried. The purified dye (20 g.) was precipitated from conc. sulphuric acid and the wet cake was treated with Raney alloy (90 g.) in 10% caustic soda solution (900 cc.) on a water bath for 1 1/2 hours. The mixture was filtered. The alkaline filtrate did not yield any organic material. The nickel residue was extracted with benzene, and evaporation of the solvent gave a dark coloured product (14.12 g.), which was extracted with ether. The ether-insoluble solid (5.61 g.) crystallized from alcohol in colourless plates, m.p. 141-42°, undepressed when mixed with 1:2-di-α-naphthoylethane (XIV), prepared according to Lutz[33] ~~et al.~~[33] by the reduction of trans-dinaphthoylethylene which was obtained by the reaction of naphthalene with fumaryl chloride in presence of aluminium chloride. The ether extract after separation of the above product gave an oil (8.51 g.), which was distilled. The fraction boiling at 140-42°/12 mm. was a yellow liquid which analysed for 1:4-di-α-tetralylbutane (XV)(Found: C, 90.3; H, 9.3. $C_{24}H_{30}$ requires C, 90.6; H, 9.4%).

Method B :- The purified dye (5 g.) was treated with Raney nickel in boiling alcohol (500 cc.) under stirring for 7 hours and filtered hot. Removal of alcohol gave an oil (2.0 g.), which was dissolved in benzene and chromatographed on alumina. The major zone gave a product (1.9 g.) which distilled as a colourless liquid, b.p. 215-20°/1 mm., having a blue fluorescence in ultraviolet light and analysing for 1:4-di-α-tetralylbutane (XV) (Found: C, 90.0; H, 9.0. $C_{24}H_{30}$ requires C, 90.6; H, 9.4%).

2:5-Di-α-naphthylfuran (XVI):

A mixture of (XIV)(0.2 g.), glacial acetic acid (5 cc.) and conc. hydrochloric acid (8 cc.) was refluxed for 6 1/2 hours, and added to crushed ice. Crystallization of the product from alcohol gave colourless plates, m.p. 85-6°, which analysed for the furan (XVI) (Found: C, 89.4; H, 5.0. $C_{24}H_{16}O$ requires C, 90.0; H, 5.0%).

Reduction of Ciba Brown 2R :

Ciba Brown 2R was purified by successive extractions with boiling water and with 5% boiling hydrochloric acid, filtered, washed and dried. Three crystallizations from o-dichlorobenzene gave brown needles, which did not contain chlorine or nitrogen (Found: S, 16.1; Calc. for $C_{24}H_{12}O_2S_2$: S, 16.2%).

Method A :- The purified dye (5 g.) was precipitated from conc. sulphuric acid and the wet cake was treated with Raney alloy (27.5 g.) in 10% caustic soda solution (275 cc.) for 5 hours on a water bath. The mixture was filtered and the nickel residue extracted with benzene as usual. On cooling the benzene extract (300 cc.), a substance (0.1 g.), separated which crystallized from benzene in colourless plates, m.p. 213-14° (Found: C, 83.5; H, 6.7. $C_{24}H_{22}O_2$ requires C, 84.2; H, 6.2%). The stated theoretical figures for C and H are for 1:4-di-α-naphthyl-1:4-butanediol (XVII). The benzene mother liquor was concentrated to 20 cc. and cooled, when a colourless substance (0.61 g.) separated, which crystallized from alcohol in colourless plates, m.p. 139-40°, undepressed when mixed with (XIV). The benzene mother liquor on removal of the solvent gave an oil (2.3 g.), which after repeated distillation gave a colourless liquid, b.p. 225°/7-8 mm., showing a blue fluorescence in ultraviolet light (Found: C, 90.2; H, 9.0. $C_{20}H_{30}$ requires C, 90.6; H, 9.4%). The required C,H values corresponds to those for 1:4-di-α-tetralylbutane (XV).

Method B :- The purified dye (5 g.) was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring for 7 hours and filtered hot. The filtrate on removal of alcohol gave an oil (1.84 g.), which was dissolved in benzene and chromatographed on a column of alumina. The major zone gave a product (1.7 g.), which distilled as a colourless liquid, b.p. 220-25°/1 mm., exhibtting a blue fluorescance in ultraviolet light, and analysing for 1:4-di-α-tetralylbutane (XV) (Found: C, 90.1; H, 9.2. $C_{24}H_{30}$ requires C, 90.6; H, 9.4%).

Reduction of 2:3'-bis-thionaphthene-indigo (XVIII):

Method A :- 2:3'-*Bis*-thionaphthene-indigo (5 g.) was treated with Raney alloy (22.5 g.) in 10% caustic soda solution (225 cc.) for 2 hours on a water bath and the mixture filtered. The nickel residue was extracted with benzene as usual, and the oil (1.0 g.) obtained was ~~extracted~~ dissolved in benzene and chromatographed on a column of alumina. The major zone led to a yellow liquid (0.4 g.), b.p. 165-70°/7 mm., having a bluish violet fluorescence and analysing for 2:4-diphenyl-1-butanol (XIX) (Found: C, 85.2; H, 8.4. $C_{16}H_{18}O$ requires C, 85.0; H, 8.0%).

<u>Method B</u> :- 2:3-<u>Bis</u>-thionaphthene-indigo (5 g.) was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring for 7 hours and filtered hot. The filtrate, on removal of alcohol, gave a red, bicarbonate-insoluble liquid (2.7 g.), which was dissolved in benzene and chromatographed on alumina. The major zone gave a colourless liquid (1.7 g.), b.p. 105-10°/1 mm., which analysed for 1:3-diphenylbutane (XX), prepared earlier by Stobbe and Posnjak[34] (Found: C, 91.3; H, 8.7. Calc. for $C_{16}H_{18}$: C, 91.4; H, 8.6%).

<u>Reduction of Ciba Scarlet G</u> :

Ciba Scarlet G was purified by successive extraction with boiling water and boiling 5% hydrochloric acid. The purified dye crystallized from benzene in scarlet needles, m.p. 269-70° (Found: S, 9.9. Calc. for $C_{20}H_{10}O_2S$: S, 10.2%).

Method A :- The purified dye (10 g.) was precipitated from conc. sulphuric acid and the wet cake was treated with Raney alloy (45 g.) in 10% aqueous caustic soda solution (450 cc.) for 90 mins. on a water bath and filtered. The nickel residue was treated as usual and extracted with alcohol. The product (8.86 g.) obtained from the alcoholic extract was dissolved in carbon tetrachloride and chromatographed on alumina, when it separated into 6 zones. The major zone yielded a thick brown liquid which was rechromatographed, when it again separated into 5 zones. The major zone gave a pale yellow liquid, b.p. 170-75°/5 mm., which analysed for $C_{20}H_{20}O$ (Found: C, 87.5; H, 7.2. $C_{20}H_{20}O$ requires C, 87.0; H, 7.2%). It gave 2:4-dinitrophenylhydrazone which could not however be crystallized.

Method B:- The purified dye (5 g.) was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring for 7 hours and filtered hot. The product (2.9 g.) obtained on removal of alcohol was dissolved in benzene and chromatographed on alumina. The major zone gave a yellow oil (2.7 g.), b.p. 168-72°/1 mm., analysing for(XXI)(Found: C, 89.3; H, 9.4. $C_{20}H_{28}$ requires C, 89.6; H, 10.4%).

Preparation of 2-thionaphthene-3'-indole-indigo (Thioindigo Scarlet R) :

Thioindoxyl melt (obtained through the courtesy of Messrs.I.C.I. Ltd., 60 g.) was dissolved in water (600 cc.) and acidified under stirring by cold conc. hydrochloric acid. The mixture was filtered and dried under vacuum. The cake was put in acetic acid (400 cc.); isatin (14.7 g.) and conc. hydrochloric acid (5 drops) were added and the mixture refluxed under stirring for 1/2 hour when the dye separated. It was cooled and filtered. The cake was extracted with 5% caustic soda solution (100 cc.), washed free of alkali and dried (23.9 g.; 85.5% yield). It crystallized from nitrobenzene in scarlet needles, m.p. 370° (Found: S, 11.0. Calc. for $C_{16}H_{19}NO_2S$: S, 11.5%).

Reduction of Thioindigo Scarlet R:

Thioindigo Scarlet R (5 g.) was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring for 7 hours and filtered hot. The nickel residue was treated with dilute hydrochloric acid, filtered, washed, dried and extracted with benzene in a Soxhlet. The original dye (0.2 g.) was obtained from the solvent extract. The alcoholic filtrate obtained after the removal of the nickel residue, gave a sulphur-free sticky solid (3.98 g.), which crystallized from alcohol in colourless needles, m.p. 91-2° (Found: C, 77.4; H, ~~7~~ 6.6; N, 6.3%). It distilled at 200-5°/1 mm. as a colourless liquid which solidified on cooling (Found: C, 77.2; H, 6.8%). It was dissolved in benzene and chromatographed on alumina. In ultra-violet light it separated in 3 bands having green fluorescence. First two bands gave very small amounts of solid which could not be worked up. The deeply absorbed top band gave the major portion which crystallized from dilute alcohol in colourless needles, m.p. 153-54°; and distilled at 200°/1 mm. as a colourless liquid; which solidified on cooling. It was recrystallized from dilute alcohol, m.p. 154° (Found: C, 76.5; H, 6.4; N, ~~7~~ 6.2%).

Reduction of thioindoxyl :

Method A : "Thioindoxyl melt" (I.C.I., 33.4 g.) was dissolved in water, acidified and steam distilled. Caustic soda (90 g.) was added to the distillate (900 cc.) and Raney alloy (45 g.) was added at about 90°. After heating for 3 hours, the reaction mixture was worked up. The nickel residue after acidification and ether extraction gave an oil (0.02 g.), which did not yield a 2:4-dinitrophenylhydrazone. The alkaline filtrate was ether extracted, when a red oil was obtained which was not identified. The alkaline solution was then acidified and the product which precipitated (0.8 g.) crystallized from water in colourless needles, m.p. 121°, undepressed when mixed with benzoic acid.

<u>Method</u> B :- "Thioindoxyl melt" (I.C.I., 40 g.) was dissolved in cold water (200 cc.), the solution treated with norit and filtered. The filtrate was cooled and acidified by cold dilute sulphuric acid. The precipitate of 3-hydroxythionaphthene-2-carboxylic acid (XXIII) was suspended in water and made alkaline to Brilliant Yellow paper by addition of 5% caustic soda solution. The solution was stirred on a water bath at 60-70° to effect decarboxylation of thioindoxylic acid (XXIII). After the decarboxylation was complete (30 mins.), the mixture was made alkaline (phenolphthalein), treated with norit and filtered. The alkaline solution was cooled and acidified. The very pale pink precipitate of thioindoxyl was washed with cold water and dried in ~~a~~ vacuum. The substance (7.7 g.) was

treated with Raney nickel (50 g.) in 10% caustic soda solution (250 cc.) at 0-5° for 90 minutes, when a sample of the reaction mixture did not give the red dye on ~~x~~ oxidation. It was filtered. The alkaline filtrate was extracted with ether. The ether extract on removal of the solvent gave an oil (4.43 g.). Fractionation yielded a colourless liquid, b.p. 202-3°. It formed a 2:4-dinitrophenylhydrazone, m.p. 236-37° (dec.) undepressed when mixed with acetophenone dinitrophenylhydrazone.

Action of Raney alloy in aqueous alkali on acetophenone:

Acetophenone (10 g.) was reduced with Raney alloy (30 g.) in 10% caustic soda solution (300 cc.) for 3 hours on a water bath. The nickel residue gave a very small yield of an oil which was not examined. The alkaline filtrate on ether extraction gave an oil (0.2 g.) which distilled between 130-45° (b.p. of ethylbenzene 135°). The alkaline solution on acidification gave a product (0.12 g.) which crystallized from water and was identified as benzoic acid.

Action of aqueous alkali on acetophenone :

Acetophenone (10 g.) was stirred with 10% caustic soda solution (300 cc.) on a water bath for 5 hours. The mixture on cooling and extraction with ether gave a liquid (9.9 g.), b.p. 202-3°, which formed a 2:4-dinitrophenylhydrazone, m.p. 236-7° (dec.), undepressed when mixed with acetophenone dinitrophenylhydrazone. The alkaline solution on acidification and ether extraction did not yield any product. Acetophenone is therefore unaffected by the treatment with alkali under the above conditions.

Reduction of thioindoxylic acid (XXIII):

Method A :- Thioindoxylic acid (5 g.), prepared as before from thioindoxyl melt (20 g.), was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring for 9 hours and filtered hot. The alcoholic filtrate, on removal of solvent, gave a liquid (1.6 g.), which was extracted with 10% sodium bicarbonate solution. The bicarbonate-insoluble liquid (0.34 g.) distilled at 100-40°, and it did not give a dinitrophenylhydrazone. The bicarbonate solution, on acidification and ether extraction, gave a liquid (1.2 g.). This was extracted with petroleum ether (b.p. 65-75°), when a solid (0.19 g.), m.p. 84-6°

separated, which crystallized from benzene in colourless prisms, m.p. 92°, undepressed when mixed with β-phenyl-β-hydroxypropionic acid. The petroleum ether solution on concentration and cooling gave colourless prisms, m.p. 46-7°, undepressed when mixed with β-phenylpropionic acid.

Method B:- Thioindoxylic acid (5 g.) was treated with Raney nickel (50 g.) in 10% caustic soda solution (250 cc.) under stirring, first at room temperature for 3 hours and then on a water-bath for 6 hours; a sample of the reaction mixture after filtration, acidification and oxidation with hydrogen peroxide did not give the red precipitate of the dye showing that all the thioindoxylic acid had desulphurized. The reaction mixture was filtered. The filtrate on ether extraction did not yield any alkali-insoluble product. The alkaline solution was cooled and made slightly acidic with cold dilute hydrochloric acid and ether extracted. On removal of ether, a sulphur free liquid (4.10 g.) was obtained. It was extracted with petroleum ether, when a solid (3.2 g.) separated which crystallized from benzene in colourless prisms, m.p. 92°, undepressed when mixed with β-phenyl-β-hydroxypropionic acid (75% yield). The petroleum ether solution on concentration and cooling gave colourless prisms (0.8 g.), m.p. 46-7°;(undepressed when mixed with β-phenylpropionic acid (20% yield).

Method C :- Thioindoxylic acid (5 g.) was treated with Raney nickel (50 g.) in 10% caustic soda solution (200 cc.) in an ice-bath for 1 hour under stirring when all the thioindoxylic acid was found to be reduced. The mixture was filtered. The filtrate on ether extraction did not yield any alkali-insoluble product. The alkaline solution was cooled and acidified with cold dilute hydrochloric acid and ether extracted. The extract on removal of ether in a current of dry air gave a white solid (3.7 g., 86% yield), m.p. 88-90°, ~~m.p. 92°~~ It crystallized from benzene in colourless prisms, m.p. 92°, undepressed when mixed with β-phenyl-β-hydroxypropionic acid.

Method D : - Thioindoxylic acid (5 g.) was treated for 5 mins. with Raney nickel (50 g.) and 3% caustic soda solution (150 cc.) in ~~for~~ an ice-bath under stirring, when all the thioindoxylic acid was desulphurized. The mixture was then filtered. The filtrate on ether extraction did not yield any alkali-insoluble product. The alkaline solution was cooled and made slightly acidic with cold dilute hydrochloric acid, and ether extracted. The extract on removal of ether in a current of dry air gave an orange coloured liquid. On trituration with petroleum ether a solid (2.0 g.) separated, which crystallized from benzene in colourless prisms, m.p. 92°, undepressed when mixed with β-phenyl-β-hydroxypropionic acid. The petroleum ether solution, on removal of solvent yielded a sticky substance (1.1 g.), which contained acetophenone identified as the 2:4-dinitrophenylhydrazone.

Reduction of 1:2-benzo-9-thiafluorene (XXIV):

A mixture of (XXIV)(0.8 g.), Raney nickel (8 g.) and alcohol (100 cc.) was refluxed under stirring for 2 1/2 hours when the green fluorescence, in ultraviolet light, of the original solution is replaced by a deep blue fluorescence. The mixture was filtered hot. Removal of alcohol from the filtrate gave a sticky substance (0.68 g.). It was distilled at 130-50°/0.7 mm., when a colourless liquid distillate was obtained which soon solidified. Crystallization from alcohol gave colourless plates, m.p. 100-1°, undepressed when mixed with 2-phenylnaphthalene prepared according to Hey *et al.*[35]

Reduction of 3:4-benzo-9-thiafluorene (XXV):

A mixture of (XXV)(0.8 g.), Raney nickel (8 g.) and alcohol (100 cc.) was refluxed under stirring for 3 1/2 hours when the pale green fluorescence, in ultraviolet light, of the original solution, is replaced by a deep blue fluorescence. The mixture was filtered hot. The alcoholic filtrate on removal of solvent gave a red liquid (0.57 g.). The fluorescent solution in benzene was chromatographed on alumina in ultraviolet light. The major zone gave an orange liquid (0.47 g.) which distilled at 135-40°/1 mm. to a colourless liquid with a blue fluorescence (Found: C, 93.7; H, 6.4. Calc. for $C_{16}H_{12}$: C, 94.1; H, 5.9%). The absorption spectrum was identical with that of 1-phenylnaphthalene.[36]

Reduction of dehydrothio-p-toluidine :(XXVI)

Method A:- Dehydrothiotoluidine (5 g.) was treated with Raney nickel (50 g.) in boiling alcohol (500 cc.) under stirring. When a sample of the reaction mixture did not show the greenish-blue fluorescence in ultraviolet light of the original solution (2 hours), the mixture was filtered. The filtrate, on removal of alcohol, gave a yellow liquid (2.14 g.), which contained nitrogen, but no sulphur. It reacted with *p*-toluenesulphonyl chloride to give only an alkali-insoluble product, m.p. 68-9°, which crystallized from *n*-hexane in colourless plates, m.p. 70-1°, undepressed when mixed with *N*-ethyl-*N*-(*p*-tosyl)-*p*-toluidine. No alkali soluble or acid soluble product was obtained. The crude reduction product on distillation gave a colourless liquid, b.p. 217-18°.

Method B :- Dehydrothiotoluidine (5 g.) was stirred with Raney nickel (50 g.) in alcohol (500 cc.) for 4 1/2 hours in an ice bath and left overnight. The mixture was then stirred for 3 hours at room temperature. The mixture at this stage did not show the greenish-blue fluorescence of the parent compound in ultraviolet light. The mixture was now filtered and the filtrate on removal of alcohol gave a yellow liquid (5 g., 88.9% yield), which contained nitrogen but no sulphur. It reacted with *p*-toluenesulphonyl chloride to give an alkali-insoluble product, m.p. 67-8°, which crystallized from *n*-hexane in colourless plates, m.p. 70-71°, ~~which~~ undepressed when mixed with *N*-ethyl-*N*-(*p*-tosyl)-*p*-toluidine. No alkali soluble or acid soluble product was obtained, indicating the absence of primary and tertiary amines in the reaction product. The crude reduction product on distillation gave a colourless liquid, b.p. 217-18°.

Action of Raney nickel on benzylaniline :

Benzylaniline (5 g.) was stirred with Raney nickel (50 g.) in alcohol (200 cc.) at room temperature for 7 1/2 hours and filtered. The filtrate on removal of solvent gave a liquid (2.5 g.) which was completely soluble in dilute hydrochloric acid and gave a faint test for diazotization and coupling. The product (0.5 g.) was reacted with *p*-toluenesulphonyl chloride (2 g.) in 12% aqueous caustic soda (40 cc.) on water bath for 3 hours. The reaction mixture was cooled and ether extracted. The alkali solution on acidification and ether extraction gave a solid (0.05 g.) which crystallized from alcohol in colourless needles, m.p. 102-3°, undepressed when mixed with *N*-*p*-tosylaniline, indicating the presence of aniline in the reduction product. The ether solution on extraction with dilute hydrochloric acid, did not give any acid soluble product, indicating the absence of any tertiary amine. The ether solution on removal of solvent gave a solid (1.0 g.) which crystallized from alcohol in colourless needles, m.p. 87-8°, undepressed when mixed with *N*-ethyl-*N*-*p*-tosylaniline indicating the presence of *N*-ethylaniline in the reduction product.

Reduction of diphenyl diselenide :

Diphenyl diselenide (2 g.) was treated with Raney nickel (20 g.) in boiling absolute alcohol (200 cc.) under stirring for 4 hours when a sample in Beckmann spectrophotometer gave ϵ max =0.025 at λ = 332 mμ as against the ϵ max =0.584 of the original solution at the same wavelength. The reaction mixture was filtered. The filtrate was distilled till 10 cc. of the residue was left. The residue on cooling gave very small amount of colourless needles which could not be identified. The ultraviolet spectrum of the distillate was identical with that of benzene in alcohol (λ max in mμ were: 239, 243, 249, 255, and 261).

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Part II

ALKYLATION OF AMINES WITH ALCOHOLS IN THE PRESENCE OF RANEY NICKEL

INTRODUCTION

The facile conversion of dehydrothio-p-toluidine to N-ethyl-p-toluidine by the action of Raney nickel in ethyl alcohol (see page 51) led to the study of the use of Raney nickel in the synthesis of secondary N-alkylarylamines from primary arylamines and primary and secondary alcohols. The action of Raney nickel on primary aliphatic amines either alone or in the presence of alcohols was also studied.

Secondary amines are generally prepared by the following methods:

(1) Primary amines react with alkyl halides to give secondary and tertiary amines.[1] The composition of the final product depends largely on the proportion of the reactants employed and on the experimental conditions. In general, it is difficult to obtain either secondary or tertiary amines exclusively and the reaction product usually consists of a mixture of both. Acid-binding agents are usually employed to combine with the liberated hydrogen halide. The introduction of an aryl group by the use of an aryl halide is more difficult owing to the inactivity of the halogen atom in the aryl residue. Copper-bronze or cuprous iodide[2] is generally used to facilitate

the latter reaction.

Besides alkyl halides, alkyl nitrates,[3] potassium alkyl sulphates,[4] dialkyl sulphates[5] and alkyl arylsulphonates[6] may be used for the alkylation of primary amines.

2. Secondary amines are obtained by the alkylation of arylsulphonamides, such as benzenesulphonamide and p-toluenesulphonamide with alkyl halides[7] or dialkylsulphates[8] followed by the hydrolysis of the resulting substituted sulphonamides. Starting from primary amines, pure secondary amines can be prepared by reacting the primary amine with arylsulphonyl chloride to obtain mono-alkylarylsulphonamide which is then alkylated and the alkylated product hydrolysed to give the secondary amine :

$$ArSO_2NH_2 \xrightarrow{2RX} ArSO_2NR_2 \longrightarrow R_2NH$$

$$\begin{tikzcd} ArSO_2Cl + RNH_2 \arrow[r] & ArSO_2NRH \arrow[r, "R'X"] & ArSO_2NRR' \arrow[d] \\ & & RR'NH \end{tikzcd}$$

By this method pure secondary amines can be prepared but the overall yield~~s~~ of the amines is often unsatisfactory.

Substituted amides of the type RCONHR' also react in the same way with alkyl halides and formyl derivatives of primary amines have been used for the preparation of secondary amines.[9]

$$\mathrm{RCONHR'} \longrightarrow \mathrm{RCONR'Na} \longrightarrow \mathrm{RCONR'R''}$$
$$\longrightarrow \mathrm{RCO_2H} + \mathrm{R'R''NH}$$

Cyanamide may also be used in a similar manner for the preparation of simple secondary amines.[10]

$$\mathrm{NH_2CN} \longrightarrow \mathrm{R_2NCN} \longrightarrow \mathrm{R_2NH}$$

3. Nitrosation of di-alkylanilines and hydrolysis of the resulting nitroso derivatives leads to pure secondary amines.[11]

4. Secondary amines are obtained by catalytic hydrogenation of tertiary amines containing one benzyl group.[12]

$$\mathrm{C_6H_5CH_2NRR'} \longrightarrow \mathrm{RR'NH} + \mathrm{C_6H_5CH_3}$$

5. Primary amines are converted to secondary amines by reacting the arylidene derivatives of the primary amines with alkyl halides when unstable quaternary salts are formed which are readily hydrolysed by water to give secondary amines.[13]

$$RNH_2 + C_6H_5CHO \rightarrow RN = CHC_6H_5$$

$$\xrightarrow{R'X} \left[RNR' = CHC_6H_5 \right] X \longrightarrow RR'NH + C_6H_5CHO$$

6. Secondary amines are prepared by the condensation of primary amines and carbonyl compounds and subsequent reduction of the Schiff's bases. The latter are reduced by sodium and alcohol,[14] zinc dust and aqueous alkali,[15] by reduction with hydrogen under pressure in the presence of catalysts like platinum,[16] nickel[17] and copper chromite[18] or by electrolytic reduction.[19] A modification of this method consists of a one step synthesis of secondary amines by the reaction of an aldehyde or a ketone with a primary amine in a solvent in the presence of a hydrogenation catalyst and hydrogen under pressure ranging from 20-150 atmospheres.[20] This method of synthesis is sometimes referred to as "reductive alkylation."[21] In place of aromatic amines, aromatic nitro,[22] nitroso and azo[23] compounds can also be used for obtaining secondary amines.

7. Secondary amines can be prepared by the reduction of substituted amides with sodium and alcohol,[24] lithium aluminium hydride[25] or copper

chromite and hydrogen.[26]

8. Catalytic hydrogenation of primary arylamines, cyanides, oximes, nitro and nitroso compounds often gives secondary amines.

9. <u>Alkylation of amines by alcohols</u> : (a) Reaction of alcohols with salts of primary amines under pressure at about 200° gives arylalkylamines. This method is used in industry for the preparation of alkylanilines. Copper powder, copper halides and sodium halides have been claimed to be efficient catalysts for this reaction.[27]

Alkylation of amines by alcohols is usually carried out in industrial practice at high temperatures with catalysts like nickel,[28] copper, cobalt, iron,[29] alumina alone[30] or with Fe_2O_3[31], Cr_2O_3, Co_2O_3, NiO;[32] silica gel[33] and BF_3.[34]

(b) Secondary amines are obtained by passing a gaseous mixture of an alcohol and an amine over dehydrating catalysts, such as tungsten trioxide or thorium dioxide at 250-60°.[35] This method is more convenient than Merz's[36] method in which mono-, di- and trialkylamines are obtained by heating alcohols at 250-60° with zinc ammonium chloride, $ZnCl_2.2NH_3$.

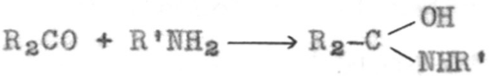
(c) The alkylation of amines by alcohols under pressure at 150-80° in the presence of hydrogenation catalysts like nickel, cobalt, copper and iron has been reported by Guyot and Fournier[37] and they have prepared a number of secondary alkylarylamines by this method. During the hydrogenation of aniline in ethanol, using nickel catalyst at 200° and hydrogen at 250-290 atmospheres, ~~a~~Adkins and his co-workers obtained ethylcyclohexylamine.[38] The alkylation of amines like piperidine, cyclohexylamine and α- and β-methylpiperidines with ethanol, cyclohexanol and 1-butanol under similar conditions has also been reported.[39] Raney nickel has also been used for similar alkylations employing hydrogen at 125 atmospheres at 200-250°.[40] Adkins has reported that 1:4- and 1:5-glycols react with primary amines in the presence of copper chromium oxide catalysts at 250-60° and hydrogen at 200-400 atmospheres to give pyrrolidines and piperidines.[41] Kindler[42] has used palladium catalyst for similar reactions. Formation of piperazine derivatives from β-hydroxyalkylamines in the presence of copper chromite catalyst at 250-70° has been reported by Bain and Pollard.[43] Ovakimian and his co-workers[44] have also reported the formation of piperazine derivatives during the reduction of esters of amino acids by Raney nickel. Mozingo[45] has reported that nitrobenzene, hydrazobenzene and azoxybenzene are reduced and alkylated to give N-ethylaniline by excess of Raney nickel in boiling ethanol, about 100° below the usual range of temperature for alkylation of amines by alcohols as discussed above. During desulphurization of benzidine-sulphone, Shah et al.[46] obtained N:N'-diethylbenzidine.

Mechanism of the alkylation of amines by means of alcohols in the presence of catalysts like Raney nickel:

Adkins[40] has suggested that since tertiary alcohols do not alkylate amines, the primary function of the catalysts is to dehydrogenate the alcohol to an aldehyde or ketone. The latter then reacts with the amine to give a product which is readily hydrogenated giving a secondary amine as follows :-

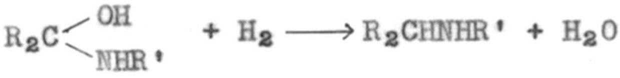
1) $R_2CHOH \longrightarrow R_2CO + H_2$

2)



$$R_2CO + R'NH_2 \longrightarrow R_2{-}C\left\langle\begin{matrix}OH\\NHR'\end{matrix}\right.$$

3)



$$R_2C\left\langle\begin{matrix}OH\\NHR'\end{matrix}\right. + H_2 \longrightarrow R_2CHNHR' + H_2O$$

Guyot and Fournier[37] have suggested that the reaction takes place through the formation of the

Schiff's base as follows :-

a) Dehydrogenation: $RCH_2OH \longrightarrow RCHO + H_2$

b) Condensation : $RCHO + R'NH_2 \longrightarrow RCH = NR'$

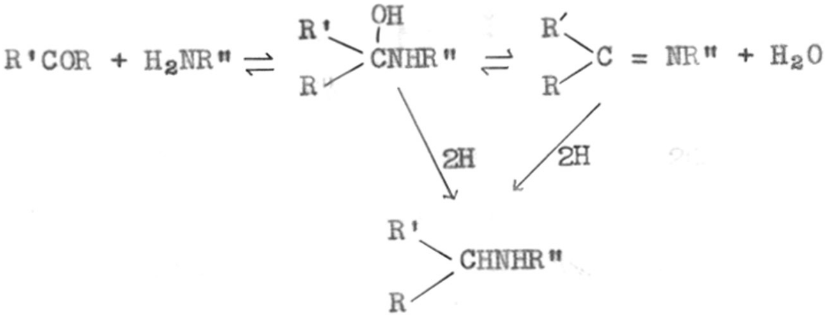
c) Hydrogenation : $RCH = NR' \longrightarrow RCH_2NHR'$

The overall reaction in both cases is the same, i.e. the primary amine reacts with alcohol to form secondary amine with the elimination of water.

$$RCH_2OH + R'NH_2 \longrightarrow RCH_2NHR' + H_2O$$

In both the reaction mechanisms described above, dehydrogenation of alcohols by the catalyst is suggested as the first step. Dehydrogenation of alcohols to aldehydes or ketones in the presence of Raney nickel at or below their boiling points has been reported by Paul[47] who has dehydrogenated a number of alcohols like ethyl, allyl, furfuryl, isopropyl and 2-butanol. Isopropyl alcohol on refluxing for 16 hours with Raney nickel gave 29% yield of acetone. He suggests that dehydrogenating activity of the catalyst ~~cases~~ ceases because aldehydes and ketones which are formed are more strongly absorbed by Raney nickel than alcohol. Dubois[48] similarly reported that 2-heptanol when heated for 8 hours at 100-20° with Raney nickel gave 56% yield of 2-heptanone while by continuous distillation 88% yield of the ketone was obtained. Dodecanol has been reported to give lauraldehyde by the action of Raney nickel.[49] Tsatsas[50] obtained anisaldehyde on refluxing anisyl alcohol with Raney nickel. Thonon and Jungers[51] have observed that the rate of dehydrogenation of alcohols by means of Raney nickel decreases with increase in their molecular weight.

The second step in the alkylation of amines by alcohols involves reaction between the carbonyl compound and the amine. Emerson[21] is of the view that in most instances Schiff's base is probably formed which is immediately reduced.



Condensation of aliphatic aldehydes with aliphatic[52] or aromatic[53] amines takes place readily with warming.[53] The reaction between ketones and amines takes place less readily than with aldehydes and zinc chloride[54] and iodine[55] have to be used as condensing agents. However, Sapiro has reported that formation of cyclohexanone-anil in absence of a condensing agent is also quite rapid at atmospheric pressure and at 20°.[56]

Hydrogenation of the Schiff's bases, suggested by Guyot and Fournier as the last step in the alkylation of amines by alcohols, has been carried out by the use of catalysts like platinum,[16] nickel[17] and copper chromite.[18] Raney nickel also has been used for such hydrogenations.[57]

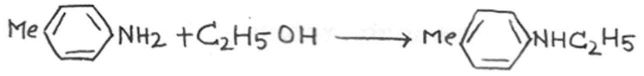
During the reaction of primary alkylamines with alcohols in presence of hydrogenation catalysts, the amine may react with itself to give secondary amines by the loss of ammonia. Rosenmund,[58] Kindler[42] and Adkins[39] have observed that primary alkylamines when treated with hydrogen in the presence of hydrogenation catalyst like palladium and nickel lead to secondary amines, no tertiary amines being detected. Adkins has however observed that aniline under these conditions did not form diphenylamine.[39]

It will be seen from the above review that with the exception of Mozingo[45] and Shah *et al.*,[46] other workers have carried out the alkylation of amines with alcohols at high temperatures and hydrogen pressures. The alkylation of amines with alcohols in the presence of Raney nickel at atmospheric pressure and at moderate temperatures (below 100°) has now been studied further in order to see if this method could be used for preparative purposes.

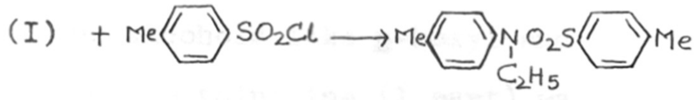
PRESENT WORK

Alkylation of aromatic amines with primary alcohols:

p-Toluidine (1 part) when treated with Raney nickel (5 parts) in excess of boiling ethyl alcohol was converted to N-ethyl-p-toluidine in 2 hours. The reaction mixture was filtered and the product was isolated from the filtrate by distilling off the solvent. No primary or tertiary amine was found to be present in the reaction product when it was analysed by tosylation according to the Hinsburg's[59] method. N-Ethyl-p-toluidine (I) was the only reaction product isolated in the above reaction (yield, 71%). When 1 part of Raney nickel was used for 1 part of p-toluidine in excess of boiling ethyl alcohol, the latter was completely alkylated in 2 hours and N-ethyl-p-toluidine was formed in 88% yield. Reaction of p-toluidine (1 part) with ethyl alcohol in the presence of Raney nickel (1 part) for 18 hours at room temperature also gave N-ethyl-p-toluidine (yield, 87%). Lower yield of N-ethyl-p-toluidine when more Raney nickel was used might be due to some loss of the amine due to absorption on the larger quantity of the nickel residue. Complete conversion of *p*-toluidine in the above and subsequent experiments was followed by the diazotization reaction.

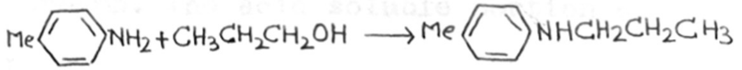


(I)

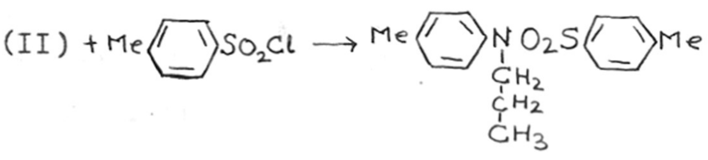


p-Toluidine was not alkylated by boiling methyl alcohol in the presence of Raney nickel even after 16 hours and the unreacted primary amine was the only product isolated from the reaction mixture.

When *p*-toluidine (1 part) was treated with Raney nickel (1 part) in excess of boiling *n*-propyl alcohol for 2 hours, *N*-*n*-propyl-*p*-toluidine (II) was obtained as the only reaction product (yield, 90%). It reacted with *p*-toluenesulphonyl chloride to give *N*-*n*-propyl-*N*-*p*-tosyl-*p*-toluidine (III) as a colourless liquid. *N*-*n*-Propyl-*p*-toluidine has been



(II)



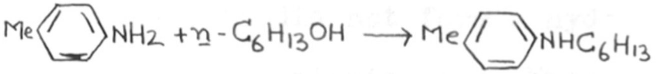
(III)

prepared earlier by the action of *n*-propyl iodide on *p*-toluidine under pressure at 160°.[60]

p-Toluidine was next alkylated with higher boiling alcohols like *n*-hexyl and lauryl alcohols.

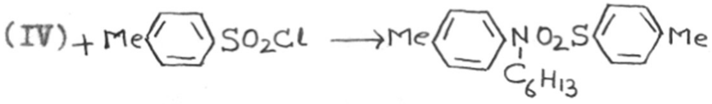
When *p*-toluidine (1 part) was treated with Raney nickel (1 part) in excess of *n*-hexyl alcohol on a water bath, no unreacted primary amine was found in the reaction mixture after seven hours. The reaction mixture was filtered. The filtrate on extraction with dilute hydrochloric acid gave only a very small amount of acid-soluble product. It was therefore made acidic and steam-distilled to remove *n*-hexyl alcohol. The residue was not completely soluble in hydrochloric acid. The acid-insoluble portion even after repeated distillations under vacuum (0.5 mm.) decomposed during distillation (temperature, 100-120°). Finally a yellow liquid, b.p. 105-7°/0.5 mm. was obtained which contained nitrogen. The acid soluble portion was isolated by treatment with alkali and ether extraction. It gave a colourless liquid on distillation, b.p. 105°/0.7 mm. which analysed for *N*-*n*-hexyl-*p*-toluidine (IV); yield, 58%). It reacted with *p*-toluenesulphonyl chloride to give an alkali-insoluble liquid, b.p. 205-10°/1 mm. (air bath temp.), which analysed for *N*-*n*-hexyl-*N*-*p*-tosyl-*p*-toluidine (V).

When 5 parts of Raney nickel were used for 1 part of p-toluidine in excess of n-hexyl alcohol



(IV)

+ an acid-insoluble liquid



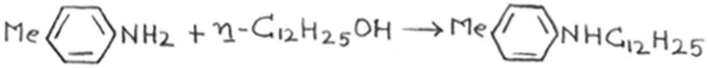
(V)

on a water bath, no unreacted p-toluidine was present in the reaction mixture after 4 hours and N-n-hexyl-p-toluidine was isolated in 48% yield as above. An acid-insoluble product was isolated in this experiment also.

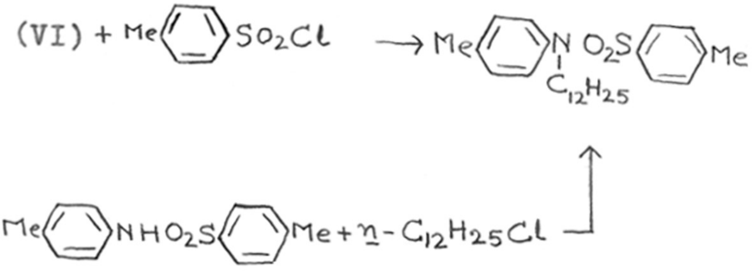
In order to study the effect of increase in temperature on the above reaction, p-toluidine (1 part) was treated with Raney nickel (1 part) in boiling n-hexyl alcohol for 18 hours. Acid-soluble reaction product contained some unreacted p-toluidine mixed with N-n-hexyl-p-toluidine. However, the major portion of the reaction product was the acid-insoluble product.

The acid-insoluble product obtained in these experiments was then studied. Although it contained nitrogen its analysis did not indicate to any expected product such as a Schiff's base. When hydrochloric acid gas was passed through its solution in ether, it did not form a hydrochloride. It did not react with picric acid. When it was shaken with Raney nickel with hydrogen at 44 lbs. per sq. inch it gave a small yield of an acid-soluble product, indicating that it might be the Schiff's base. The fact that it does not analyse for the Schiff's base might be due to decomposition during distillation. However, it could not be hydrolysed by boiling with 10% aqueous caustic soda and 30% sulphuric acid. The product is being studied further.

Alkylation of p-toluidine (1 part) by lauryl alcohol in the presence of Raney nickel (1 part) on a water bath took 22 hours. After the removal of nickel residue by filtration, the mixture was acidified and lauryl alcohol was removed by steam-distillation. The residue was found to be insoluble in hydrochloric acid. On distillation the major fraction was obtained at 180-90°/0.8 mm. as a colourless liquid, which solidified on cooling. It crystallized from n-hexane in colourless plates, m.p. 55-55.5°, which analysed for *N*-*n*-dodecyl-*p*-toluidine (VI; yield, 50%). It gave a *p*-tosyl derivative (VII), which crystallized from alcohol in colourless plates, m.p. 41-2°. The m.p. of the latter was undepressed when mixed with an authentic sample of *N*-*n*-dodecyl-*N*-*p*-tosyl-*p*-toluidine prepared by the reaction of lauryl chloride with *N*-*p*-tosyl-*p*-toluidine.



(VI)



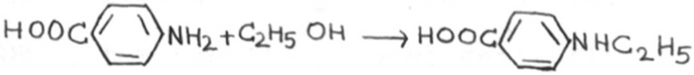
(VII)

The longer time required for the dehydrogenation of higher alcohols by means of Raney nickel referred to earlier[51] probably accounts for the longer time required for alkylation of *p*-toluidine by *n*-dodecyl alcohol. The lower yield of secondary amines when higher boiling alcohols were used is probably due to the losses during the isolation of the secondary amines which become increasingly difficult with higher boiling alcohols. Steam-distillation of these alcohols is also slow.

With the view to study the alkylation of less basic amines, alkylation of aniline and p-aminobenzoic acid was investigated. N-Ethylaniline (VIII) was obtained (yield, 80%) when aniline (1 part) was treated with Raney nickel (1 part) in boiling ethyl alcohol for 4 1/2 hours.

$$PhNH_2 + C_2H_5OH \longrightarrow PhNHC_2H_5 \qquad (VIII)$$

Reaction of p-aminobenzoic acid (1 part) with ethyl alcohol in the presence of Raney nickel (5 parts) for 3 1/2 hours gave N-ethyl-p-aminobenzoic acid (IX ; yield,70%).

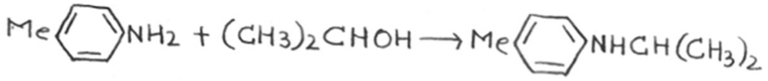


(IX)

In order to study the influence of ste~~a~~ric factors on the alkylation of primary arylamines, alkylation of m-2-xylidine was studied. m-2-Xylidine (1 part) was not alkylated by boiling ethyl alcohol in the presence of Raney nickel (5 parts) even after 54 hours, the unreacted primary amine being the only product isolated from the reaction mixture. The sterically hindered amino group in m-2-xylidine is therefore not amenable to alkylation under the above conditions.

Alkylation of p-toluidine with secondary alcohols :

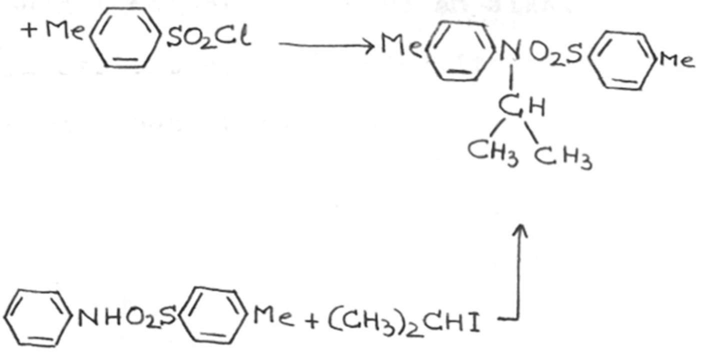
When p-toluidine (1 part) was treated with Raney nickel (1 part) in excess of boiling isopropyl alcohol, no unreacted primary amine could be detected in the reaction mixture after 24 hours. The reaction product, which was soluble in dilute hydrochloric acid, on distillation gave two fractions boiling at 42°/2 mm. and 70-2°/2 mm. The higher boiling fraction was identified as N-isopropyl-p-toluidine (X; yield, 48%), through its p-tosyl derivative (XI). The lower boiling fraction also gave an alkali-insoluble p-tosyl derivative, indicating its secondary amine character but it could not be identified. When ten parts of Raney nickel were used for one part of p-toluidine in excess of boiling isopropyl alcohol, no unreacted ~~p~~ p-toluidine could be detected after 7 hours. As in the previous experiment the reaction product gave N-isopropyl-p-toluidine and an unidentified acid-soluble product.



(X)

+ an unidentified amine

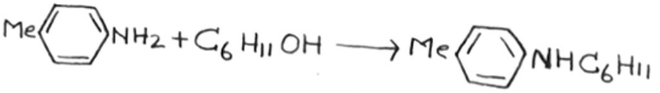
(X)



(XI)

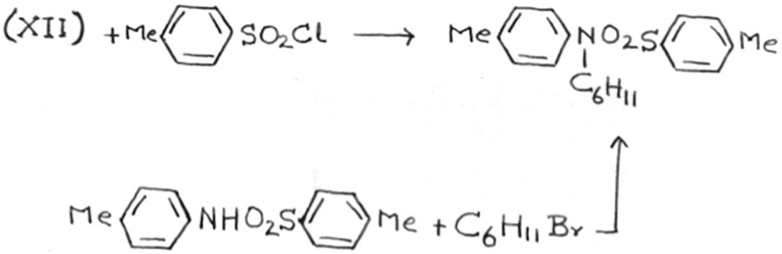
N-Isopropyl-p-toludine has been prepared earlier by the action of isopropyl iodide on p-toluidine at 130° under pressure[60] and its p-tosyl derivative (XI) has been described by Young.[61]

When p-toluidine (1 part) was treated with Raney nickel (10 parts) in excess of cyclohexanol on water-bath no primary amine was detected in the reaction mixture after 4 hours. The reaction product which was soluble in dilute hydrochloric acid, on distillation gave two fractions boiling at 80-90°/2 mm. and 110-20/2 mm. The higher boiling fraction was identified as N-cyclohexyl-p-toluidine (XII; yield, 46%), through its p-tosyl derivative (XIII). The lower boiling fraction reacted with p-toluenesulphonyl chloride to give an alkali-insoluble liquid tosyl derivative indicating its secondary amine character but it could not be identified.



(XII)

+ an unidentified amine



(XIII)

N-Cyclohexyl-*p*-toluidine has been prepared earlier by the action of bromocyclohexane on *p*-toluidine at 140-50°,[62] and its *p*-tosyl derivative (XIII) has been described by Hickinbottom.[63]

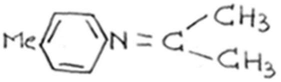
It will be observed that the yield~~s~~ of secondary amines from secondary alcohols is lower than that from primary alcohols. *N*-Isopropyl-*p*-toluidine was obtained in 48% yield as against 90% yield of *N*-*n*-propyl-*p*-toluidine. In the alkylation of *p*-toluidine with isopropyl alcohol and cyclohexanol acid-soluble by-products were also formed. As these by-products have been isolated only in alkylation of *p*-toluidine by secondary alcohols, it appears that ketones which are probably formed by dehydrogenation of the secondary alcohols react in some way other than the normal reaction of the formation of Schiff's base (ArN=CRR').

Mechanism of alkylation of *p*-toluidine with isopropyl alcohol in the presence of Raney nickel :

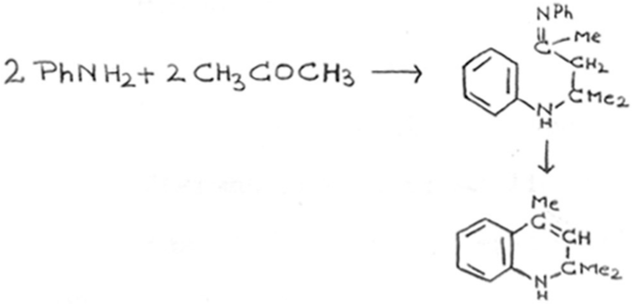
On the basis of earlier literature, reaction of *p*-toluidine with isopropyl alcohol in the presence of Raney nickel ~~ix~~ probably proceeds through the following stages:

(1) conversion of isopropyl alcohol to acetone;

(2) reaction of acetone with *p*-toluidine to give the Schiff's base:



and (3) reduction of the above Schiff's base to *N*-isopropyl-*p*-toluidine. Knoevenagel[55] reported that aniline and *p*-toluidine react with acetone in the presence of iodine to give the corresponding Schiff's bases, but later work has shown that the reaction product of acetone and aniline is not the expected Schiff's base but is constituted as 2:2:4-trimethyl-1:2-dihydroquinoline (XIV).[64]



(XIV)

In order to study the mechanism of alkylation of *p*-toluidine by means of isopropyl alcohol, the following experiments were carried out :-

(1) Reaction of *p*-toluidine with boiling acetone.

(2) Reaction of *p*-toluidine with boiling acetone in the presence of a small quantity of sodium hydroxide (Raney nickel might contain residual alkali which may act as a condensing agent).

(3) Reaction of *p*-toluidine with boiling acetone in the presence of Raney nickel (to see if Raney nickel acts as a catalyst in the reaction of acetone with *p*-toluidine).

In all the three experiments *p*-toluidine and acetone were recovered unchanged. It is well known that acetone deactivates Raney nickel[65] and excess of boiling acetone might have deactivated the catalyst. The above failure of acetone to react with *p*-toluidine either in the presence or absence of Raney nickel, indicates that the alkylation of *p*-toluidine by isopropyl alcohol probably follows a course different from that outlined earlier.

Formation of *N*-cyclohexyl-*p*-toluidine by the reaction of cyclohexanol and *p*-toluidine in the presence of nickel hydrogenation catalyst at a temperature above 150° has been reported.[66] Cyclohexanone reacts with aniline at 20° in absence of a condensing agent to give the cyclohexanone anil.[56]

Alkylation of aliphatic amines :

When butyl amine (1 part) was treated with Raney nickel (1 part) in boiling ethyl alcohol, after 3 1/2 hours no primary amine could be detected in the reaction mixture. The reaction product on working up gave *N*-ethyl-*n*-butylamine, di-*n*-butylamine and a very small amount of a fraction which appears to be diethylbutylamine from its boiling point. When the reaction was carried out at room temperature for 20 hours, *N*-ethyl-*n*-butylamine and di-*n*-butylamine were again formed.

$$\begin{aligned} C_4H_9NH_2 + C_2H_5OH \xrightarrow{\text{Raney nickel}} \; & C_4H_9NHC_2H_5 \\ & + (C_4H_9)_2NH \\ & + C_4H_9N(C_2H_5)_2 \quad (?) \end{aligned}$$

Formation of di-*n*-butylamine in both these experiments indicated that under these conditions, *n*-butylamine itself forms the secondary amine by deamination. *n*-Butylamine is stable at its b.p. and can be distilled without change at atmospheric pressure. When *n*-butylamine (1 part) was treated with Raney nickel (1 part) in aqueous solution on a water bath, di-*n*-butylamine and tri-*n*-butylamine were obtained.

$$C_4H_9NH_2 \xrightarrow{\text{Raney nickel}} (C_4H_9)_2NH + (C_4H_9)_3N$$

In the reaction of n-butylamine with ethanol in the presence of Raney nickel, therefore, both alkylation of the amine by alcohol and loss of ammonia between two or three molecules of the amine are simultaneously taking place.

The complete conversion of n-butylamine and cyclohexylamine used in the above and subsequent experiments was followed by Rimini's and Simon's tests.[67] The primary and secondary amines were characterized by the preparation of thiourea derivatives, and tertiary amines by picrates.

When cyclohexylamine (1 part) was treated with Raney nickel (1 part) in boiling ethyl alcohol for 13 hours, N-ethylcyclohexylamine was the major reaction product and a very small amount of dicyclohexylamine was formed.

$$C_6H_{11}NH_2 + C_2H_5OH \xrightarrow{\text{Raney nickel}} C_6H_{11}NHC_2H_5 + (C_6H_{11})_2NH$$

When only cyclohexylamine (1 part) was refluxed with moist Raney nickel (1 part) for 10 hours, the major reaction product was cyclohexanol and dicyclohexylamine was also isolated in low yield.

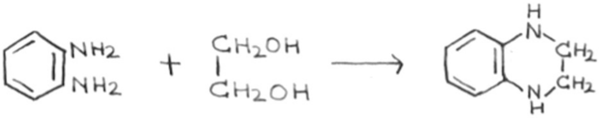
$$C_6H_{11}NH_2 + H_2O \xrightarrow{\text{Raney nickel}} C_6H_{11}OH + (C_6H_{11})_2NH$$

Whereas in the alkylation of aromatic primary amines by alcohols,secondary amines were obtained with the exclusion of tertiary amines, in the case of aliphatic primary amines besides alkylation of amines by alcohols to give secondary amines, two molecules of the primary amine themselves combined to give the corresponding dialkylamine, with the loss of ammonia. Tertiary alkylamines were also formed in small amounts both by the action of Raney nickel on the aliphatic primary amine itself and also by the interaction between the aliphatic amine and two molecules of the alcohol used.

Synthesis of nitrogen-heterocyclics from o-diamines and glycols :

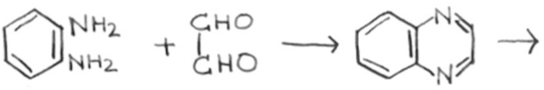
The alkylation of aromatic and aliphatic amines by means of alcohols in the presence of Raney nickel may be employed to synthesise quinoxaline, by the action of Raney nickel on ~~p~~ o-phenylenediamine and ethylene glycol. If glyoxal is formed by the dehydrogenation of ethylene glycol by Raney nickel, it would condense with o-phenylenediamine to give quinoxaline. However, the reaction may proceed in an alternative direction~~s~~ also. Thus the glycol may be converted to the intermediate oxidation product, glycollic aldehyde, which may then lead to other reaction products.

When o-phenylenediamine (1 part) was treated with Raney nickel (5 parts) in ethylene glycol on water bath, o-phenylenediamine could not be detected in the reaction mixture after 14 hours.The reaction product on working up gave a fraction which was identified as 1:2:3:4-tetrahydroquinoxaline (XV). The other fraction was a liquid which contained nitrogen and oxygen and remains to be identified.



(XV)

+ an unidentified liquid



(XV)

Cavagnol and Wiselogle[68] have obtained 1:2:3:4-tetrahydroquinoxaline by the hydrogenation of quinoxaline with Adam's catalyst, (PtO_2), under 50-80 lbs. pressure of hydrogen. When quinoxaline was shaken with Raney nickel at room temperature under 40 lbs. pressure of hydrogen 1:2:3:4-tetrahydroquinoxaline was obtained in 32% yield. It proved to be identical with the product prepared from o-phenylenediamine and ethylene glycol as described above.

Although the yield of 1:2:3:4-tetrahydroquinoxaline is low, the above method nevertheless is a novel application of Raney nickel in organic synthesis. It also represents a new synthesis of 1:2:3:4-tetrahydroquinoxaline which may lead to other hitherto unknown quinoxaline derivatives. Further work in this connection is in progress.

EXPERIMENTAL

General remarks

Preparation of Raney nickel for alkylation of amines:

Raney nickel was prepared by treating Raney alloy (Gilman Paint and Varnish Co., Chattanooga, Tennessee, U.S.A.) with aqueous sodium hydroxide according to the method described by Mozingo.[69] It was washed free of alkali with distilled water by decantation. In the following experiments when water-miscible alcohols were used, water accompanying the settled nickel powder was removed by washing the nickel ~~powder~~ by decantation with the alcohol which was to be used in the experiment. In the case of water-immiscible alcohols, like *n*-hexyl alcohol, lauryl alcohol and cyclohexanol, the precipitated nickel was filtered under slight suction and the cake was washed with the required alcohol. During the washing care was taken that there was always some liquid above the settled Raney nickel, in order to keep the pyrophoric nickel from catching fire.

General procedure for alkylations of amines and isolation of reaction products :

The alkylation of p-toluidine and other primary arylamines by the appropriate alcohols was carried out, in general, by treating the mixture with varying amounts of Raney nickel under stirring on a boiling water bath till a filtered sample of the reaction mixture showed absence of p-toluidine by the diazotisation reaction (diazotisation and coupling with aqueous alkaline β-naphthol). The mixture was filtered hot and the nickel residue was washed with the relevant alcohol. The unreacted alcohol from the filtrate was removed by distillation and the crude alkylated amine obtained as residue was dried (by treating its etherial solution with anhydrous sodium sulphate) and purified by vacuum distillation. In the case of higher boiling alcohols, the filtrate after removal of Raney nickel was acidified by dilute hydrochloric acid and the unreacted alcohol was removed by steam distillation. The crude alkylated amine was liberated by alkali and isolated by ether extraction.

N-Ethyl-p-toluidine (I)

Method A :- p-Toluidine (10 g.) was refluxed with Raney nickel (50 g.) in boiling ethyl alcohol (200 cc.) under stirring. Test on a sample after one hour showed the presence of unreacted p-toluidine, but after two hours no unreacted p-toluidine could be detected. The reaction mixture on working up gave a yellow liquid (9.0 g.~~)~~; 71.3% yield), which distilled as a colourless liquid b.p. 217-18° (b.p. of N-ethyl-p-toluidine is 217°)[70].

The above product was analysed for its primary, secondary and tertiary amines content by the Hinsberg's method, as described below. The reaction product (1 g.) was suspended in 12% aqueous sodium hydroxide (20 cc.) and p-toluenesulphonyl chloride (2.5 g.) was added. The mixture was heated on a water bath for 2 hours, cooled and ether extracted. The alkaline solution on acidification and ether extraction did not yield any product, showing the absence of a p-tosyl derivative of a primary amine. This confirmed the earlier observation based on diazotisation reaction that all p-toluidine had reacted. The ether solution was extracted with dilute hydrochloric acid. The acid extract was made alkaline to phenolphthalein by sodium hydroxide and ether extracted. Removal of ether did not yield any product showing the absence of tertiary amines in the reaction mixture. The ether solution after alkali and acid extractions as described above and after removal of ether by distillation gave a product (1.95 g.), m.p. 68-9°. On recrystallization from *n*-hexane it gave colourless needles, m.p. 69-70°, undepressed when mixed with *N*-ethyl-*N*-*p*-tosyl-*p*-toluidine, m.p. 69-70°.[71] The latter was prepared by alkylation of *N*-*p*-tosyl-*p*-toluidine by the following method :-

N-*p*-Tosyl-*p*-toluidine was prepared by treatment of *p*-toluidine with *p*-toluenesulphonyl chloride in 12% aqueous sodium hydroxide on a boiling water bath.

N-*p*-Tosyl-*p*-toluidine (5 g.) was dissolved in 10% aqueous potassium hydroxide (80 cc.) and ethyl iodide (8 cc.) was added. The mixture was gradually warmed on a water bath and finally heated for three hours on a boiling water bath. After cooling the mixture was extracted with ether. The ether extract on removal of the solvent gave a product (4.5 g.), m.p. 67-8°, which crystallized from n-hexane in colourless needles, m.p. 69-70°.

In subsequent experiments also, the crude product, obtained by alkylation of the primary arylamine with alcohols in the presence of Raney nickel, was analysed for the presence of primary, secondary and tertiary amines by the Hinsberg's method as described above.

When the alkylated arylamine and its p-tosyl derivative were liquid, both have been analysed. In the case of known alkylated arylamines which gave solid p-tosyl derivative, which has been reported earlier, these products were not analysed, but the constitution of the amine was confirmed by direct comparison with the authentic p-tosyl derivative.

Method B :- p-Toluidine (10 g.) was treated with Raney nickel (10 g.) in ethyl alcohol (200 cc.) as above. After 2 hours no unreacted p-toluidine could be detected. The reaction mixture gave N-ethyl-p-toluidine as a yellow liquid (11.13 g.; yield, 88.2%). On distillation, a colourless liquid, b.p. 217-18°, was obtained. Tosylation of the product gave exclusively an alkali-insoluble derivative, m.p. 68-9°. Crystallization of the tosyl derivative from n-hexane gave colourless needles, m.p. 69-70°, undepressed when mixed with authentic N-ethyl-N-p-tosyl-p-toluidine, m.p.69-70°.

Method C :- p-Toluidine (10 g.) was treated with Raney nickel (10 g.) in ethyl alcohol (200 cc.) under stirring at room temperature for 6 hours and left overnight. After stirring for 30 minutes more, no unreacted p-toluidine could be detected. Isolation of the product in the usual way gave a yellow liquid (11.0 g.; yield, 87.2%) which was identified as N-ethyl-p-toluidine from its b.p. and by tosylation in the manner described earlier.

Action of Raney nickel on p-toluidine in methyl alcohol :

Method A :- A mixture of p-toluidine (10 g.) and Raney nickel (10 g.) was refluxed in boiling methyl alcohol (200 cc.) under stirring. The reaction was continued for 16 hours, but a pronounced primary amine test persisted. The reaction mixture gave a product (9.8 g.), which on tosylation gave exclusively an alkali-soluble p-tosyl derivative, m.p. 116-17°. Recrystallization from n-hexane gave colourless needles, m.p. 117-18°, undepressed when mixed with N-p-tosyl-p-toluidine, m.p. 117-18°.[72]

Method B :- p-Toluidine (10 g.) was treated with Raney nickel (50 g.) in boiling methyl alcohol (200 cc.) under stirring for 16 hours. The mixture, as above, gave only the unreacted p-toluidine (9.5 g.).

The above experiments indicate that methyl ~~alco~~ alcohol cannot be employed for alkylation of p-toluidine in the presence of Raney nickel under the above conditions.

N-n-Propyl-p-toluidine (II)

Treatment of p-toluidine (10 g.) with Raney nickel (10 g.) in n-propyl alcohol (200 cc.) under stirring on a water bath for 2 hours, gave a red coloured liquid (12.5 g.; yield, 89.8%), which was free from unreacted p-toluidine and was soluble in dilute hydrochloric acid. The product on distillation at 60-2°/0.4 mm. gave a colourless liquid, b.p. 230°. B.p. of N-n-propyl-p-toluidine reported in literature is 230-3°.[60] (Found: C, 80.0; H, 10.0;

N, 9.7. Calc. for $C_{10}H_{15}N$, C, 80.5; H, 10.1; N, 9.4%). On treatment with *p*-toluenesulphonyl chloride the reaction product gave exclusively an alkali-insoluble tosyl derivative which distilled as a colourless liquid, b.p. 158-60°/0.2 mm. (Found: C, 66.8; H, 7.2; N, 4.7. $C_{17}H_{21}NO_2S$ requires C, 67.3; H, 6.9; N, 4.6%). *N*-*n*-Propyl-*N*-*p*-tosyl-*p*-toluidine prepared by the reaction of *n*-propyl bromide with *N*-*p*-tosyl-*p*-toluidine was also a colourless liquid, b.p. 158-60°/0.2 mm.

N-*n*-Hexyl-*p*-toluidine (IV) :

Method A : *p*-Toluidine (10 g.) was stirred with Raney nickel (10 g.) in *n*-hexyl alcohol (200 cc.) on a water bath. After 7 hours no unreacted *p*-toluidine could be detected in the reaction mixture. The reaction mixture was filtered hot and the nickel residue was washed with more *n*-hexyl alcohol. The filtrate on extraction with dilute hydrochloric acid gave only a very small amount of an acid-soluble portion. It was therefore made acidic and steam-distilled. The acidic residue on extraction with ether gave an acid-insoluble product (5.4 g.), which distilled under vacuum leaving behind a dark residue.

In successive distillations also the product left a dark-coloured residue. After two redistillations a yellow liquid, b.p. 105-7°/6.5 mm. was obtained which could not be identified (Found: C, 80.3; H, 11.1; N, 8.6%). The acidic solution, after the removal of the acid-insoluble product, was made alkaline and extracted with ether. Removal of ether gave a liquid (10.44 g.; yield, 58.6%), which on distillation gave a colourless liquid, b.p. 105°/6.7 mm. (Found: C, 81.2; H, 11.6; N, 7.9. $C_{13}H_{21}N$ requires C, 81.7; H, 11.0; N, 7.3%). It reacted with *p*-toluenesulphonyl chloride to give exclusively an alkali-insoluble tosyl derivative, which distilled as a pale yellow liquid, b.p. 205-10° (bath temp.)/ 1 mm. (Found: C, 69.2; H, 8.2; N, 4.1. $C_{20}H_{27}NO_2S$ requires C, 69.5; H, 7.8; N, 4.1%). Other functional derivatives of *N*-*n*-hexyl-*p*-toluidine such as picrate, acetyl, benzoyl, etc. also were liquids. On reaction of *N*-*n*-hexyl-*p*-toluidine with 2:3-dichloro-1:4-naphthoquinone in boiling alcohol, a violet coloured product was obtained which crystallized from ethyl alcohol in needles, but the product melted below room temp. (28°) and also decomposed when distilled in vacuum. It could therefore not be prepared in analytically pure form.

Method B : When p-toluidine (5 g.) was stirred with Raney nickel (50 g.) in n-hexyl alcohol (200 cc.) on a water bath, no unreacted p-toluidine could be detected in the reaction mixture after 4 hours. The reaction mixture, on working up as above, gave N-n-hexyl-p-toluidine (4.3 g.; yield, 48.3%) and an acid-insoluble product (2.2 g.).

Method C : p-Toluidine (10 g.) was treated with Raney nickel (10 g.) in n-hexyl alcohol (100 cc.) in an oil bath at 150-60°, under reflux. Even after 18 hours, primary amine could still be detected in the reaction mixture. The reaction mixture on working up gave an acid-insoluble liquid (11.0 g.) and an acid-soluble liquid (5.5 g.). The latter gave diazotization test. It reacted with p-toluenesulphonyl chloride to give a small amount of alkali-soluble product, which crystallized from n-hexane in colourless needles, m.p. 117-18°, undepressed when mixed with N-p-tosyl-p-toluidine. The major product, however, was an alkali-insoluble tosyl derivative, b.p. 204-8°/1 mm. The acid-insoluble product contained nitrogen and it distilled under vacuum leaving behind a dark residue.

N-*n*-Dodecyl-*p*-toluidine (VI):

p-Toluidine (10 g.) was treated with Raney nickel (10 g.) in lauryl alcohol (200 cc.) on a water bath under stirring. After 22 hours no unreacted *p*-toluidine could be detected. The mixture was filtered and the nickel residue was washed with more lauryl alcohol. The filtrate was made acidic and steam-distilled to remove lauryl alcohol. The acidic residue was extracted with ether. The acidic solution was made alkaline and extracted with ether, but the ~~ether~~ ether extract did not yield any product. The etherial solution of the acid-insoluble portion gave a liquid (15.0 g.). Distillation of the latter gave a colourless liquid (13.0 g.; yield,50.5%), b.p. 180-90°/0.8 mm., which solidified on cooling. The product crystallized from *n*-hexane in colourless plates, m.p. 55-55.5° (Found: C, 82.6; H, 12.0; N, 5.0. $C_{19}H_{33}N$ requires C, 82.9; H, 12.0; N, 5.1%). It reacted with *p*-toluenesulphonyl chloride to give exclusively an alkali-insoluble tosyl derivative which crystallized from alcohol in colourless plates, m.p. 41-2° (Found: C, 72.5; H, 9.2; S, 8.1%). $C_{26}H_{39}NO_2S$ requires C, 72.7; H, 9.1; S, 7.5%). The m.p. of the tosyl derivative was undepressed when mixed with *N*-*n*-dodecyl-*N*-*p*-tosyl-*p*-toluidine, m.p. 41-2°, prepared by the reaction of lauryl chloride on *N*-*p*-tosyl-*p*-toluidine.

N-Ethylaniline (VIII):

Aniline (10 g.) was treated with Raney nickel (10 g.) in boiling ethyl alcohol (200 cc.) under stirring. After 4 1/2 hours no unreacted aniline could be detected. The reaction mixture gave a product (10.41 g.; yield, 80%), which distilled as a colourless liquid, b.p. 203-4° (b.p. of *N*-ethylaniline is 204.7°).[73] It reacted with *p*-toluenesulphonyl chloride to give exclusively an alkali-insoluble tosyl derivative which crystallized from methyl alcohol in elongated prisms, m.p. 86-7°, undepressed when mixed with authentic *N*-ethyl-*N*-*p*-tosylaniline, m.p. 87°,[74] prepared by the action of ethyl iodide on *N*-*p*-tosylaniline.

N-Ethyl-*p*-aminobenzoic acid (IX):

p-Aminobenzoic acid (5 g.) was treated with Raney nickel (50 g.) in boiling ethyl alcohol (500 cc.)

under stirring. After 3 1/2 hours no unreacted *p*-aminobenzoic acid could be detected. The reaction mixture on working up gave a product (4. 2 g.; yield, 69.7%), m.p. 174-5°, which crystallized from benzene in colourless needles, m.p. 177° (m.p. of *N*-ethyl-*p*-aminobenzoic acid is 177-8°)[75]

Action of Raney nickel on *m*-~~m~~2-xylidine in ethyl alcohol :

m-2-Xylidine (b.p. 214°, 10 g.) was treated with Raney nickel (50 g.) in boiling ethyl alcohol (200 cc.) under stirring. Even after refluxing for 54 hours, *m*-2-xylidine was still detected in the reaction mixture. The reaction mixture gave a product (9.1 g.) which distilled as a colourless liquid, b.p. 214-16°. It reacted with *p*-toluenesulphonyl chloride to give exclusively an alkali-soluble tosyl derivative, m.p. 134-5°, which crystallized from methyl alcohol in colourless prisms, m.p. 135-6° (Found: C, 65.1; H, 6.0; N, 5.5 $C_{15}H_{17}NO_2S$ requires C, 65.5; H, 6.2; N, 5.1%). Its m.p. was undepressed when mixed with authentic *N*-*p*-tosyl-*m*-2-xylidine, m.p. 135-6°, prepared by the action of *m*-2-xylidine on *p*-toluenesulphonyl chloride.

m-2-Xylidine therefore cannot be alkylated under the above conditions.

N-p-Tosyl-m-2-xylidine when reacted with ethyl iodide gave N-ethyl-N-p-tosyl-m-2-xylidine, m.p. 96-7°, which crystallized from methyl alcohol in coourless needles, m.p. 97-8° (Found: C, 67.2; H, 6.9; N, 4.4. $C_{17}H_{21}NO_2S$ requires C, 67.3; H, 6.9; N,4.5%).

N-Isopropyl-p-toluidine (X):

Method A :- p-Toluidine (10 g.) was treated with Raney nickel (10 g.) in boiling isopropyl alcohol (200 cc.) under stirring. After 24 hours, no unreacted p-toluidine could be detected. The reaction mixture gave a liquid (~~6~~9.0 g.) which was soluble in dilute hydrochloric acid. It was distilled under vacuum when two fractions boiling at 42°/2 mm. (2.20 g.) ~~4~~ and 70-2°/2 mm. (6.7 g.; yield,48.1%) were obtained. The higher boiling fraction was redistilled at 220-22° (b.p. of N-isopropyl-p-toluidine is 219-21°.[60]). It reacted with p-toluenesulphonyl chloride to give exclusively an alkali-insoluble tosyl derivative, m.p. 105-6°, which crystallized from methyl alcohol in colourless needles, m.p. 106-7°, undepressed when mixed with authentic N-isopropyl-

N-*p*-tosyl-*p*-toluidine, m.p. 107.[61] The latter was prepared by the action of isopropyl iodide on *N*-*p*-tosyl-*p*-toluidine. The lower boiling fraction on further distillation gave a colourless liquid, b.p. 191-2° (Found: C, 73.4; H, 13.3; N, 6.7%). On reacting with *p*-toluenesulphonyl chloride, the latter also gave a alkali-insoluble product which distilled as a colourless liquid, b.p. 155-6°/2 mm. The purified product contained nitrogen and sulphur (Found: C, 60.0; H, 8.6; N, 4.7%). This lower boiling reaction product has not been identified as yet.

Method B :- *p*-Toluidine (5 g.) was treated with Raney nickel (50 g.) in boiling isopropyl alcohol (200 cc.) under stirring. After 7 hours no unreacted *p*-toluidine could be detected. The reaction mixture gave a liquid (5.23 g.) which was soluble in dilute hydrochloric acid. It was distilled when two fractions boiling at 44°/ 2 mm. and 70-2°/ 2 mm. were obtained. The higher boiling fraction was identified as *N*-isopropyl-*p*-toluidine, through its *p*-tosyl derivative. The lower boiling fraction contained nitrogen and it also gave an alkali-insoluble *p*-tosyl derivative, b.p. 155-6°/ 2mm. which appears to be identical with the product prepared similarly in the previous experiment.

Action of acetone on *p*-toluidine :

Method A:- *p*-Toluidine (5 g.) was refluxed with acetone (200 cc.) for 6 hours and acetone was distilled off. The residue was taken up in dilute hydrochloric acid and extracted with ether. The etherial extract, on removal of the solvent, did not give any product. The acidic solution was made alkaline and ether extracted. The etherial solution gave a product (4.87 g.), m.p. 41-2°, undepressed when mixed with *p*-toluidine, m.p. 42°.

Method B:- *p*-Toluidine (5 g.) was refluxed with acetone (200 cc.) in the presence of sodium hydroxide (0.5 g.) for 6 hours. The reaction mixture on working up as in the previous experiment gave exclusively *p*-toluidine (4.9 g.).

Method C :- *p*-Toluidine (5 g.) was treated with Raney nickel (50 g.) in boiling acetone (200 cc.) under stirring. Even after 24 hours, *p*-toluidine was still detected in the reaction mixture. The reaction mixture was filtered and the nickel residue was washed with more acetone. The filtrate, on removal of the solvent, gave a product (4.5 g.), which was dissolved in dilute hydrochloric acid and extracted with ether . The etherial solution, on removal of the solvent, did not give any product. The acidic solution was made alkaline and ether extracted. The etherial solution gave a solid, m.p. 40-1°, undepressed when mixed with p-toluidine.

Acetone, therefore, does not react with p-toluidine either alone or in the presence of alkali or Raney nickel, under these conditions.

N-Cyclohexyl-p-toluidine (XII):

p-Toluidine (5 g.) was stirred with Raney nickel (50 g.) in cyclohexanol (200 cc.) on a water bath. After 4 hours no unreacted p-toluidine could be detected. The mixture was filtered hot and the residue was washed with more cyclohexanol. The filtrate was made acidic and steam-distilled to remove cyclohexanol. The acidic residue, on extraction with ether, did not give any acid-insoluble product. The acidic solution was made alkaline and extracted with ether. The liquid (5.3 g.), obtained by removal of ether, gave on distillation two fractions, b.p.

80-90°/ 2 mm. (1.8 g.) and b.p. 110-20/2 mm.(4.12 g.; yield,46.6%). The higher boiling fraction crystallized from aqueous methyl alcohol in colourless plates, m.p. 41° (m.p. of *N*-cyclohexyl-*p*-toluidine recorded in literature is 41-2°.[62]). It reacted with *p*-toluenesulphonyl chloride to give exclusively an alkali-insoluble tosyl derivative, m.p. 133-34°, which crystallized from methyl alcohol in colourless prisms, m.p. 134°; undepressed when mixed with *N*-cyclohexyl-*N*-*p*-tosyl-*p*-toluidine, m.p. 134.[63] The latter was prepared by the action of bromocyclohexane on *N*-*p*-tosyl-*p*-toluidine. The lower boiling fraction on further distillation gave a colourless liquid, b.p. 80-1°/2 mm. (Found: C, 78.1; H, 12.4; N, 9.8%). It also reacted with *p*-toluenesulphonyl chloride to give exclusively an alkali-insoluble product which contained nitrogen and sulphur.

Action of Raney nickel on ~~n~~ *n*-butylamine in ethyl alcohol :

Method A :- *n*-Butylamine (10 g.) was treated with Raney nickel (10 g.) in boiling ethyl alcohol (80 cc.) under stirring. After one hour a sample was taken out and filtered. The presence of the primary amine was detected in the filtrate by adding to it acetone (1 cc.) and a drop of 1% aqueous sodium nitroprusside when a red-violet colour developed within one minute (Riminie's test).[67] After 3 1/2 hours, no primary amine was detected but the presence of secondary amine was detected in the reaction mixture. To test for the presence of secondary amine a sample was taken out from the reaction mixture, and filtered. Freshly prepared acetaldehyde (1 cc.) was added to the filtrate followed by the addition of one drop of 1% aqueous sodium nitroprusside. A blue colour developed within 5 minutes which showed that a secondary amine was present (Simon's test).[67] The reaction mixture was filtered and the nickel residue was washed with ethyl alcohol. The filtrate was made weakly acidic with hydrochloric acid and the solvent was removed by distillation. The acidic solution was made strongly alkaline and extracted with ether. Removal of ether gave a liquid (10.84 g.) which on fractionation using a fractionating column gave the following three fractions :- Fraction I, b.p. 105-10°(3.89 g.); Fraction II, b.p. 135-40° (0.5 g.) and Fraction III, b.p. 158-60° (4.9 g.). Fraction (I) reacted with α-naphthyl isothiocyanate to give a product which crystallized in colourless needles, m.p. 124°, undepressed when mixed with *N*-α-naphthyl-*N*'-ethyl-*N*'-butylthiourea, m.p. 124-5°, prepared from *N*-ethyl-*n*-butylamine and α-naphthyl isothiocyanate.[52] Fraction (II) neither gave the colour tests for primary or secondary amines nor reacted with α-naphthyl isothiocyanate. From the b.p. 135-40° it is likely that it is diethylbutylamine, b.p. 136-7°. Fraction (III) reacted with α-naphthyl isothiocyanate to give a product which crystallized in colourless needles, m.p. 127-8°, undepressed when mixed with *N*-α-naphthyl-*N*':*N*'-di-*n*-butylthiourea, m.p. 127-8°, prepared from di-*n*-butylamine and α-naphthyl isothiocyanate.

Method B :- *n*-Butylamine (5 g.) was stirred with Raney nickel (5 g.) in alcohol (50 cc.) at room temperature. After stirring for 20 hours, the mixture did not give the test for primary amines but it showed the presence of a secondary amine. The reaction mixture was worked up as before and it gave a liquid (4.5 g.) which on distillation gave two fractions boiling at 105-10° (2.02 g.) and 155-60° (2.1 g.). They were identified as *N*-ethyl-*n*-butylamine and di-*n*-butylamine respectively, through their α-naphthylthiourea derivatives.

The experiment showed that even at room temperature, Raney nickel converted part of *n*-butylamine to di-*n*-butylamine.

Action of Raney nickel on *n*-butylamine :

n-Butylamine (5 cc.) was stirred with Raney nickel (5 g.) in water (10 cc.) at room temperature (26-8°). Even after 36 hours it still gave a test for the presence of a primary amines. It was therefore stirred further on a water bath for 16 hours more. The reaction mixture was free from *n*-butylamine but gave a test for secondary amines. The reaction mixture was filtered and the nickel residue was washed with alcohol. The filtrate was made faintly acidic and the solvent distilled off. The concentrated acidic solution was made strongly alkaline and extracted with ether. Removal of ether gave a liquid (2.1 g.), which on distillation yielded two fractions: b.p. 150-60°(1.1 g.) and 210-20° (0.8 g.). The lower boiling fraction was identified as di-*n*-butylamine through its α-naphthylthiourea derivative.

The higher boiling fraction gave a picrate, m.p. 105°, undepressed when mixed with the picrate, m.p. 105°, of tri-n-butylamine.[76]

Action of Raney nickel on cyclohexylamine in ethyl alcohol :

Cyclohexylamine (25 cc.) was stirred with Raney nickel (20 g.) in boiling ethyl alcohol (200 cc.). After 14 hours, no primary amine could be detected in the reaction mixture but ~~t~~ it gave a test for secondary amines. The reaction mixture was filtered and the nickel residue washed with alcohol. On removal of the solvent a liquid (19.5 g.) was obtained which distilled as a colourless liquid (18.76 g.), b.p. 162-4°, leaving behind some higher boiling liquid as residue. The former gave the colour test for secondary amines and a picrate, m.p. 132-33°, undepressed when mixed with the picrate, m.p. 133°, from N-ethylcyclohexylamine.[77] The residual product was dissolved in ether and dry hydrogen chloride gas was passed into the etherial solution, when a white solid, m.p. 341-4°, separated. The solid was treated with 20% aqueous caustic soda and ether extracted. Removal of ether gave a liquid

(0.2 g.), b.p. 256-8°. It gave a picrate, m.p. 172-3°, undepressed when mixed with the picrate, m.p. 173°, from dicyclohexylamine.[78]

Action of Raney nickel on cyclohexylamine :

Cyclohexylamine (16 g.) was heated with moist Raney nickel (15 g.) in an oil bath at 130-40° under reflux. After 10 hours no primary amine could be detected in the reaction mixture. The reaction mixture gave a liquid (13.09 g.) which distilled as a colourless liquid (10.87 g.), b.p. 160-1°, leaving behind some liquid residue which solidified on cooling. The former did not contain nitrogen and reacted with α-naphthyl isocyanate to give a ureathane, m.p.130°, undepressed when mixed with α-naphthyureathane, m.p. 130°,[79] derived from cyclohexanol. The residual product contained nitrogen. It was ~~idssolved~~ dissolved in ether and dry hydrogen chloride gas was passed into the etherial solution, when a white solid, m.p. 340-45°, separated. The solid on treatment with 20% aqueous potassium hydroxide and ether extraction gave a liquid (0.7 g.), b.p.255-7°. It gave a picrate, m.p. 172-3°, undepressed when mixed with the picrate, m.p.173°,from dicyclohexylamine.

It is interesting to note that dicyclohexylamine when mixed with cyclohexanol gave a solid.

Action of Raney nickel on *o*-phenylenediamine in ethylene glycol :

O-Phenylenediamine (5 g.) was stirred with Raney nickel (50 g.) in ethylene glycol (70 cc.) on a water bath. After one hour a sample of the reaction mixture was diluted with water and filtered. The filtrate on acidification with hydrochloric acid and addition of a small quantity of acetylacetone gave a deep red-violet colour indicating the presence of *o*-phenylenediamine.[80] After stirring for 14 hours on water bath, the reaction mixture became free from *o*-phenylenediamine. The mixture was cooled, diluted with alcohol (300 cc.) and filtered. The filtrate, after ~~on~~ removal of alcohol, under vacuum on a water bath, was made strongly alkaline and extracted with benzene in a liquid-liquid extractor for 14 hours. The benzene extract, on removal of the solvent, gave a red liquid (3.42 g.). It was taken up in water (20 cc.) and extracted with ether. The ether-extract gave a liquid which distilled at 125°/3 mm. (1.25 g.) and solidified on cooling.

The latter product crystallized from n-hexane in colourless plates, m.p. 98°, undepressed when mixed with 1:2:3:4-tetrahydroquinoxaline, m.p. 98°. The aqueous layer, left after the ether extractinn, was acidified and concentrated under vacuum. The concentrated acidic solution was made strongly alkaline and extracted with ether. The ether extract gave a liquid (2.05 g.), which on distillation gave a major fraction boiling at 125-30°/3 mm. On ~~further~~ redistillation it gave a colourless liquid, b.p. 125-7°/3 mm. (Found: C, 65.7; H, 10.2; N, 14.9%), which has not been identified as yet.

1:2:3:4-Tetrahydroquinoxaline (XV):

Quinoxaline (1 g.), prepared by reacting o-phenylenediamine with glyoxal-sodium bisulphite,[81] was shaken with Raney nickel (5 g.) in alcohol (50 cc.) under 40 lbs./sq.inch. hydrogen pressure at room temperature. During the first hour pressure fell by 10 lbs. It was further shaken at 40 ~~lbs~~ lbs. pressure for 36 hours when no further fall in hydrogen pressure was observed. The mixture was then filtered. The filtrate, on removal of alcohol by distillation, gave a sticky solid (0.95 g.). It was taken up in ether and the etherial solution washed with water repeatedly to remove unreacted quinoxaline which is more soluble in water than its tetrahydro derivative. Washing was continued till the aqueous layer showed the presence of tetrahydroquinoxaline. Presence of the latter is indicated if a portion of the aqueous washing gave a blue colour, when mixed with aqueous ferric chloride. The etherial solution gave a product (0.3 g.), which after distillation at 130°/3 mm. was crystallized from *n*-hexane when it gave colourless plates, m.p. 98° (m.p. of 1:2:3:4-tetrahydroquinoxaline recorded in literature[68] is 98.5-99°). The product now prepared gave a red-violet colour when its concentrated solution was mixed with aqueous ferric chloride, whereas its dilute solution gave a blue colour with aqueous ferric chloride. This behaviour also indicates its identity with 1:2:3:4-tetrahydroquinoxaline.[82]

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SUMMARY

The present work was undertaken to study the Raney nickel desulphurization of sulphur-containing intermediates and dyes in order to study their constitution and to synthesize difficultly accessible compounds with the aid of Raney nickel. Alkylation of primary aryl and alkylamines by means of alcohols in the presence of Raney nickel was also studied.

Part I

The desulphurization of intermediates and thioindigoid dyes was carried out by using Raney (aluminium-nickel) alloy and aqueous sodium hydroxide or by using excess of Raney nickel catalyst in alcohol.

Thioindigo on treatment with Raney alloy and aqueous sodium hydroxide gave diphenacyl, 1:4-diphenylbutane and benzoic acid. Durindone Orange R (6:6'-diethoxythioindigo) on similar treatment gave 4:4'-diethoxydiphenacyl and *p*-ethoxybenzoic acid. From Durindone Red 3BS (5:5'-dichloro-7:7'-dimethylthioindigo) 3:3'-dichloro-5:5'-

dimethyldiphenacyl and 3-chloro-5:5'-dimethyldiphenacyl were obtained. Durindone Brown GS and Ciba Brown 2R proved to be identical as both gave 1:2-di-α-naphthoylethane and 1:4-α-tetralylbutane. 2:3'-<u>Bis</u>-thionaphthene-indigo gave 2:4-diphenyl-1-butanol.

When the above dyes were treated with Raney nickel in alcohol, 1:4-diarylbutanes were obtained in good yields. Thus, thioindigo gave 1:4-diphenylbutane and Durindone Orange R gave 1:4-<u>bis</u>-<u>p</u>-ethoxyphenylbutane. 1:4-Di-<u>m</u>-tolylbutane was obtained on reduction of Durindone Red 3BS. Both Durindone Brown GS and Ciba Brown 2R gave 1:4-di-α-tetralylbutane. 2:3'-<u>Bis</u>-thionaphthene-indigo gave 1:3-diphenylbutane. Desulphurization of Ciba Scarlet G and Thioindigo Scarlet R was also studied.

The constitution of diphenacyls was proved by conversion to 2:5-diarylfurans and by synthesis. The constitution of 1:4-diarylbutanes was proved by oxidation to the corresponding benzoic acids.

Both thioindoxyl and acetophenone on treatment with Raney alloy and aqueous sodium hydroxide gave benzoic acid. Thioindoxyl on mild treatment with Raney nickel and aqueous sodium hydroxide gave acetophenone. Treatment of 3-hydroxythionaphthene-2-carboxylic acid (thioindoxylic acid) with Raney nickel in alcohol gave β-phenyl-β-hydroxypropionic acid and β-phenylpropionic acid, whereas mild treatment with Raney nickel in aqueous sodium hydroxide gave only the former acid.

The constitution of 1:2-benzo-9-thiafluorene and 3:4-benzo-9-thiafluorene was proved by their desulphurization with Raney nickel in alcohol. The former gave 2-phenylnaphthalene and the latter 1-phenylnaphthalene.

N-Ethyl-*p*-toluidine was obtained when dehydrothio-*p*-toluidine was treated with Raney nickel in ethyl alcohol. Benzylaniline on similar reduction gave *N*-ethylaniline.

Selenium was removed from diphenyl diselenide by the action of Raney nickel in alcohol, and benzene was obtained as the reduction product.

Part II

Alkylation of primary alkyl and aryl amines to secondary amines by means of primary and secondary alcohols in the presence of Raney nickel at atmospheric pressure and temperatures below 100° was studied.

p-Toluidine was alkylated to N-ethyl-p-toluidine when treated with Raney nickel in boiling ethyl alcohol. The alkylation takes place at room temperature also. p-Toluidine could not be alkylated by boiling methyl alcohol in the presence of Raney nickel. p-Toluidine on treatment with Raney nickel in boiling n-propyl alcohol gave N-n-propyl-p-toluidine.When p-toluidine was treated with Raney nickel in n-hexyl alcohol on a water bath N-n-hexyl-p-toluidine was obtained together with an acid-insoluble product. The acid-insoluble product was the major reaction product when the reaction was carried out in boiling n-hexyl alcohol. N-n-Dodecyl-p-toluidine was ~~obtained~~ obtained when
toluidine wa ~~when~~ treated with Raney nickel in lauryl alcohol on a water bath.

In order to study the alkylation of less basic amines, aniline and p-aminobenzoic acid were alkylated with boiling ethyl alcohol in the presence of Raney nickel. N-Ethylaniline and

N-ethyl-*p*-aminobenzoic acid were obtained in good yields. With the view to study the influence of steric hindrance, alkylation of *m*-2-xylidine was studied. *m*-2-Xylidine could not be alkylated with ethanol under the above conditions.

Alkylation of *p*-toluidine with secondary alcohols was then studied. *p*-Toluidine when treated with Raney nickel in boiling isopropyl alcohol gave *N*-isopropyl-*p*-toluidine and an unidentified secondary amine. When *p*-toluidine was treated with Raney nickel in cyclohexanol on a water bath, *N*-cyclohexyl-*p*-toluidine was obtained together with an unidentified secondary amine.

Butylamine gave *N*-ethylbutylamine and di-*n*-butylamine when treated with Raney nickel in ethyl alcohol. The reaction could be carried out either at room temperature or at boil. When butylamine was refluxed with Raney nickel, di-*n*-butylamine and tri-*n*-butylamine were obtained. Cyclohexylamine on treatment with Raney nickel in boiling ethyl alcohol gave *N*-ethylcyclohexylamine and dicyclohexylamine. When a mixture of cyclohexylamine and moist Raney nickel was refluxed, cyclohexanol and dicyclohexylamine were obtained.

1:2:3:4-Tetrahydroquinoxaline was isolated as one of the reaction products when o-phenylenediamine was treated with ethylene glycol in the presence of Raney nickel. This represents a new synthesis of 1:2:3:4-tetrahydroquinoxaline and a novel application of Raney nickel for the synthesis of nitrogen-heterocyclics.

Publications

1) Raney nickel reductions, Part II.
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2) Raney nickel reductions, Part IV.
ibid., 1953, **38**, 244.

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