143. *Nuclear Methylation of Phenols by Means of Methanolic Sodium Methoxide.*

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The *C*-methylation of substituted pyrroles by means of sodium methoxide is a useful synthetic reaction which has not hitherto been applied in other series. It is now shown that reactive phenols such as β-naphthol and resorcinol can be methylated under similar conditions. The yield is improved if the phenol is first converted into a methylene-bis-derivative or into a *N*-piperidylmethyl derivative.

The theory of the process is discussed.

If the nuclear methylation of pyrrole derivatives (cf. Fischer-Orth, " Die Chemie des Pyrrols," Leipzig, **1934**, I, **33**, 287) is regarded as a straightforward interaction with sodium methoxide, it appears anomalous from the electrochemical point of view because the pyrrole nucleus is decidedly anionoid in polar character and sodium methoxide is an anionoid reagent. Fission into Me^+, O^{--}, and Na^+, which might explain the result, appears highly improbable.

If the pyrrole is assumed to function as an anionoid reagent in the reaction, a natural deduction is that *C*-methylation should succeed with other strongly anionoid substances such as the aromatic tertiary amines and phenols. The latter class was selected for study in the first place because the phenoxide ion is highly reactive and the products in some instances would be useful intermediates for syntheses in progress in the laboratory. It was found that phenol, catechol, quinol and α-naphthol were recoverable unchanged after treatment with methanolic sodium methoxide at 220°.

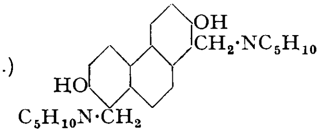
β-Naphthol was partly converted under similar conditions into 1-methyl-2-naphthol and both resorcinol and phloroglucinol afforded dihydroxymesitylene; this reduction of phloroglucinol is significant. Pyrogallol gave a complex mixture of volatile products.

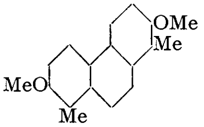
2 : 2′-Dihydroxydi-α-naphthylmethane furnished 1-methyl-2-naphthol in 75% yield, reckoning both nuclei as possible sources of the product. This shows that the nascent β-naphthol produced by the reduction of the methylene derivative is much more effectively methylated than ordinary β-naphthol.

A mixture of methylenedinaphthol (10%) and β-naphthol showed no improvement over the result with the naphthol alone. Hence it is unlikely that the methylenedinaphthol reacts with sodium methoxide so as to give 2 mols. of 1-methyl-2-naphthol and formaldehyde, and in any case such formaldehyde could not long survive under the conditions of the experiment. Thus formaldehyde in small concentration cannot be postulated as a catalyst in a cycle of operations. If it is an intermediate, it must be continuously produced, a portion becoming effective and a portion oxidised and polymerised.

The view that methylenedinaphthol is reduced to methylnaphthol and naphthol is confirmed by the behaviour of benzylidenedi-β-naphthol, which was converted into 1-benzyl-2-naphthol, methylnaphthol and naphthol. 1-Piperidino-2-naphthol is similarly reduced to 1-methyl-2-naphthol and analogously 4-methyl-1-naphthol may be obtained by this modification of the method. Again 2 : 7-*dihydroxy*-1 : 8-*bispiperidinomethylphenanthrene* (I) was reduced by methanolic sodium methoxide to a product, isolated as the *dimethyl ether*, probably (II).

(I.)





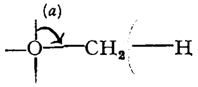
(II.)

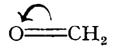
Caldwell and Thompson (*J. Amer. Chem. Soc.*, 1939, **61**, 765) showed that a piperidinomethylxylenol could be hydrogenated to a trimethylphenol at 165° in the presence of copper chromite. There are several further examples in the literature of the reduction of substituted benzylamine salts to toluene or its derivatives (cf. Emde, *Arch. Pharm.*, 1909, **247**, 369; *Ber.*, 1911, **44**, 3224).

In all the processes sodium formate was produced whether methylation occurred or not.

Our view of the mechanism of the reaction is that activated formaldehyde is generated by decomposition of methoxyl ion (A) in presence of a reducible substance. If the negative, reducing hydrogen is detached before the process (*a*) becomes a complete transfer of the unshared electrons to covalency, formaldehyde is available in a form strongly cationoid at the carbon atom (B). This will react at once with phenoxide ions to give an arylcarbinol or diarylmethane, which, as independent experiment shows, can be reduced to arylmethane. After the oxygen in the closed system is exhausted, the reducible substances that may be present are the phenol and its transformation products, arylcarbinol and diarylmethane, formaldehyde and its condensation products, sodium formate and methyl alcohol. In addition, hydrogen may be liberated. An analysis of the gaseous products has not yet been carried out, but is desirable, for it may throw light on the details of the mechanism.

(A.)





(B.)

We have also considered the possibility that sodium formate may be a formylating agent or that an equilibrium may exist between sodium formate–methyl alcohol and formaldehyde–sodium methoxide. These suggestions are modifications of the general hypothesis and further evidence is necessary before they can be dismissed. The common ground is that sodium methoxide is not itself the methylating agent but that oxidation is a preliminary. The oxidation product then condenses with the phenol and reduction is the final stage.

EXPERIMENTAL.

The phenolic substance (10 g.) was heated in an autoclave at 220°, during the times stated below, with a solution of sodium methoxide (12 g. of sodium) in methanol (150 c.c.).

Resorcinol (10 hours).—The solution was acidified, steam-distilled, clarified with charcoal, and concentrated to 100 c.c. under diminished pressure. On cooling and keeping, light yellow crystals (3·5 g.) were deposited. Purified by sublimation, or crystallisation from benzene, the substance formed flattened, pointed, colourless needles, m. p. 151° (Found : C, 70·7; H, 8·0. Calc. for $C_9H_{12}O_2$: C, 71·1; H, 7·9%). The m. p. and analysis indicate that the substance is 2 : 4 : 6-trimethylresorcinol (dihydroxymesitylene, mesorcinol) (Knecht, *Ber.*, 1882, **15**, 1377). The b. p., reactions with ferric chloride, lead acetate, silver nitrate and Fehling's solution, and the fluorescein test also corresponded with the description by Knecht.

By ether extraction of the residue, formic acid and a small quantity of an acid forming slender needles from water, m. p. 196° (decomp.), were isolated. This acid gives a bluish-violet ferric reaction and is probably a *C*-methyl- or *C*-dimethyl-β-resorcylic acid, but the amount obtained was insufficient for full investigation.

Phloroglucinol (9 hours).—Worked up as above, only a little tar separated. The solution was repeatedly extracted with ethyl acetate; the residue after removal of the solvent crystallised and was drained on a porous tile (2·5 g.). The material was freed from acidic substances by solution in ether and washing with aqueous sodium bicarbonate. The recovered mesorcinol crystallised from water in needles, m. p. 151° alone or mixed with the specimen from resorcinol.

β-Naphthol (11 hours).—The solvent was steam-distilled, and the solution acidified. When cold the precipitate was collected and heated for 2 hours on the steam-bath with water (50 c.c.), formaldehyde (6 c.c. of 40%), and potassium hydroxide (12 g.), whereby unchanged β-naphthol was converted into the sparingly soluble methylenedinaphthol. The recovered naphthols were repeatedly extracted with boiling water, from which 1-methyl-2-naphthol crystallised in long needles (1·8 g.), m. p. 109—111° (Found : C, 83·4; H, 6·6. Calc. for $C_{11}H_{10}O$: C, 83·6; H, 6·3%). The m. p. was not depressed by an authentic specimen. When the reaction mixture was heated for 22 hours, the yield rose to 3·2 g. β-Naphthol (9 g.) and methylenedinaphthol (1 g.) (10 hours) gave 2·0 g. of methylnaphthol.

Methylenedinaphthol (11 hours).—In this case the condensation of the product with formaldehyde was omitted (needles, m. p. 108—111°; yield, 7 g. and 1 g. more from mother-liquors). Judged by the chloroform–alcoholic sodium hydroxide test, this material contained only a trace of β-naphthol. Assuming quantitative reductive fission to methylnaphthol and naphthol, the latter has furnished about twice as much methylnaphthol as in the experiment starting with preformed β-naphthol.

This method of preparation of methylnaphthol is probably the best now available. On a larger scale, methylenedinaphthol (50 g.), sodium (23 g.), and methyl alcohol (300 c.c.) were heated in a revolving autoclave at 210—220° for 7 hours. The crude product was almost free from β-naphthol and on methylation (35 c.c. of methyl sulphate and 150 c.c. of 10% sodium hydroxide solution) afforded 40 g. of 2-methoxy-1-methylnaphthalene, b. p. 150—155°/10 mm. After one crystallisation from alcohol, the colourless needles had m. p. 41—42°.

Benzylidenedi-β-naphthol (10 hours).—The 1-benzyl-2-naphthol was separated from a mixture of naphthol and methylnaphthol by fractionation in a high vacuum. It crystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 111—112°, depressed to 85—95° by admixture with 1-methyl-2-naphthol (cf. Claisen, *Z. angew. Chem.*, 1923, **56**, 478). The mixture (m. p. 80—95°) of β-naphthol and 1-methyl-2-naphthol constituted the major product; it was treated with formaldehyde in the usual way and methylenedinaphthol and methylnaphthol were separated and identified.

1-*Piperidinomethyl*-2-*naphthol* (6 hours).—The mixture was diluted and acidified, and the product crystallised from water. The yield of 1-methyl-2-naphthol was 4·6 g. (70%) and β-naphthol was absent in this case. Similarly, 4-piperidino-1-naphthol (5 hours) afforded 4-methyl-1-naphthol (4 g.); needles, m. p. 84—85°, after two crystallisations from light petroleum. The properties of the substance were in agreement with the description by Lesser (*Annalen*, 1914, **402**, 8), who prepared it from 4-amino-1-methylnaphthalene.

2 : 7-*Dihydroxy*-1 : 8-*bispiperidinomethylphenanthrene* (I).—A solution of 2 : 7-dihydroxyphenanthrene (5 g.) in alcohol (50 c.c.), piperidine (4·1 g.), and aqueous formaldehyde (4 g. of 36·7%) was kept for 12 hours. The solid (8·5 g.) crystallised from ethyl acetate in colourless leaflets, m. p. 219—220° (Found : C, 77·2; H, 7·8; N, 6·6. $C_{26}H_{32}O_2N_2$ requires C, 77·2; H, 7·9; N, 6·9%).

2 : 7-*Dimethoxy*-1 : 8-*dimethylphenanthrene* (II).—The above crude piperidinomethyl compound (5 g.) was reduced as usual (sodium, 10 g.; methanol, 150 c.c.; 6 hours' heating at 200°). The crude phenolic product (2·7 g.) was isolated by means of ether after acidification and at once methylated by treatment with methyl sulphate and sodium hydroxide solution. The resulting dimethyl ether was purified by sublimation at 250°/10 mm. (1·5 g.) and by several crystallisations from benzene, and then from xylene, and obtained in foliated, colourless needles, m. p. 256—257° (Found : C, 81·2; H, 6·8. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%).

Hydrogenation of the dihydroxybispiperidinomethylphenanthrene gave a mixture of products from which no individual substance could be separated. Analysis indicated that octahydro-derivatives of dihydroxydimethylphenanthrene predominated.

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