LXXXVI.—*Elimination of the Amino-group of Tertiary Amino-alcohols. Part IV. The Displacement of the Amino- by the Hydroxy-group.*

By ALEX. MCKENZIE and ROBERT ROGER.

As was stated in Part I (J., 1923, **123**, 79) of this series of papers, the study of the deamination of tertiary amino-alcohols was initiated from its bearing on the rôle of nitrous acid in the Walden inversion. It was anticipated that the action of nitrous acid on an optically active amino-alcohol, such as *d*-β-hydroxy-αββ-triphenylethylamine, would proceed on the orthodox lines, and by giving either *d*- or *l*-triphenylethylene glycol would provide additional data for the Walden inversion :

$$d\text{-}C_6H_5{\cdot}CH(NH_2){\cdot}CPh_2{\cdot}OH \longrightarrow d\text{- or } l\text{-}C_6H_5{\cdot}CH(OH){\cdot}CPh_2{\cdot}OH.$$

It is, however, impossible to realise this change experimentally, as the product is invariably the optically inactive ketone, phenyldeoxybenzoin (J., 1925, **127**, 283). That this reaction, which involves the migration of a hydrocarbon residue, is a very general one is obvious from the following examples :

$$OH{\cdot}CPhR{\cdot}CHR'{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}CHPhR'$$

(R = R′ = Ph : J., 1923, **123**, 79; 1925, **127**, 283.
R = Me; R′ = Ph : J., 1923, **123**, 79; 1924, **125**, 844.

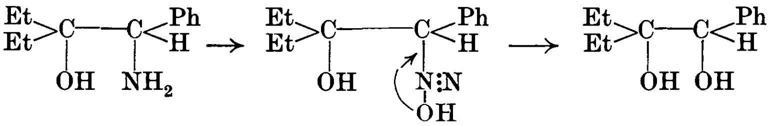
$R = C_{10}H_7$; $R' = Ph$: J., 1924, **125**, 2105; Orékhov and Tiffeneau, *Compt. rend.*, 1924, **178**, 1619.
*$R = Ph$; $R' = Me$: J., 1925, **127**, 283.
*$R = Ph$; $R' = CH_2Ph$: J., 1925, **127**, 283.
$R = Ph$; $R' = H$: Bettzieche, *Z. physiol. Chem.*, 1924, **140**, 273; Orékhov and Roger, *Compt. rend.*, 1925, **180**, 70.)

$$OH{\cdot}CRR'{\cdot}CHR''{\cdot}NH_2 \longrightarrow R{\cdot}CO{\cdot}CHR'R''$$

($R = Ph$; $R' = C_6H_4{\cdot}OMe$; $R'' = H$: Orékhov and Roger, *loc. cit.*
$R = Ph$; $R' = C_{10}H_7$; $R'' = H$: Luce, *Compt. rend.*, 1925, **180**, 145.
$R = R' = CH_2Ph$; $R'' = Ph$: J., 1926, 779; Bettzieche and Ehrlich, *Z. physiol. Chem.*, 1925, **150**, 197.)

Despite the regularity with which a hydrocarbon residue migrates in those reactions, we thought that it might be possible to select a suitable amino-alcohol in which the normal displacement of the amino- by the hydroxy-group could be effected by the aid of nitrous acid. This has now been accomplished in two instances, in one of which the glycol was the main product, whilst in the other the glycol also was isolated, although the main product was the ketone.

When β-amino-αα-diethyl-β-phenylethyl alcohol, prepared by the method of Thomas and Bettzieche (*Z. physiol. Chem.*, 1924, **140**, 244), was acted on by nitrous acid, the crystals which were isolated consisted of α-phenyl-ββ-diethylethylene glycol, which had previously been prepared by Tiffeneau and Lévy from magnesium ethyl bromide and ethyl *dl*-mandelate (*Bull. Soc. chim.*, 1923, **33**, 735). The mechanism of the action may be outlined as follows :



As in semipinacolinic deamination, the formation of an intermediate unstable diazo-compound is assumed, but water is not produced, the hydroxy-group migrating from nitrogen to carbon. No transposition of the ethyl group was detected.

The main product of the deamination of β-amino-β-phenyl-αα-dibenzylethyl alcohol, prepared by the action of magnesium benzyl chloride on ethyl *r*-phenylaminoacetate hydrochloride, is

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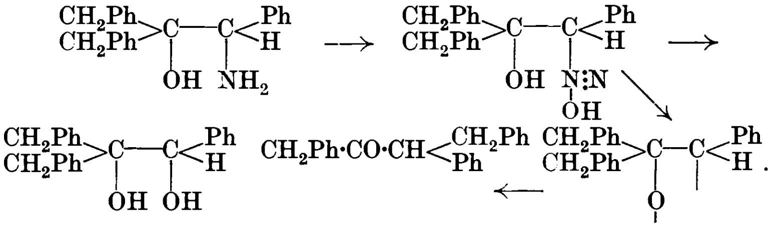
* The preparation of optically active ketones from *d*-alanine, *d*-phenylalanine and *l*-phenylalanine has also been described (J., 1926, 779).

benzyl αβ-diphenylethyl ketone (J., 1926, 779), but the mother-liquors from which this ketone had been crystallised gradually deposited crystals from which α-phenyl-ββ-dibenzylethylene glycol, m. p. 115—116°, has now been isolated. The identity of this glycol was established by comparison with the compound prepared from magnesium benzyl chloride and ethyl *dl*-mandelate (Orékhov, *Bull. Soc. chim.*, 1919, **25**, 111). Here, semipinacolinic deamination was accompanied by the ultimate displacement of the amino- by the hydroxy-group :



$$(CH_2Ph)_2C(OH)\text{—}CH(NH_2)Ph \longrightarrow (CH_2Ph)_2C(OH)\text{—}CH(N{:}N\cdot OH)Ph \longrightarrow (CH_2Ph)_2C(O\text{—})\text{—}CH(\text{—})Ph$$

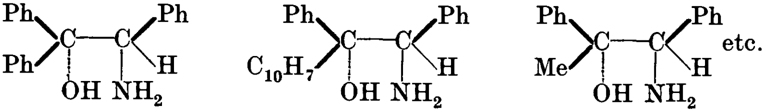
$$(CH_2Ph)_2C(OH)\text{—}CH(OH)Ph \quad CH_2Ph\cdot CO\cdot CH{<}^{CH_2Ph}_{Ph} \longleftarrow$$

From several viewpoints, this normal action of nitrous acid which led to the formation of the two glycols presents points of interest. Thus, it renders the possibility open for the conversion, for example, of *l*-phenylaminoacetic acid into the configuratively-related diethyl-amino-alcohol, and the transformation of the latter into a glycol which could then be contrasted with that obtainable by the action of magnesium ethyl bromide on ethyl *l*-mandelate.

It will also be observed in those cases where nitrous acid behaved normally that the two hydrocarbon residues attached in the amino-alcohol to the carbon atom to which the hydroxy-group is also bound are groups with a small saturation capacity. Ample evidence of the low saturation capacity of both the ethyl and the benzyl group is provided by the important researches of Tiffeneau, Orékhov, and Mlle. Lévy. In the two amino-alcohols under discussion, the hydroxy-group is in each case firmly linked to the carbon atom, and semipinacolinic deamination would accordingly be retarded, if not entirely prevented. On this conception, the amino-alcohols could be depicted as follows :

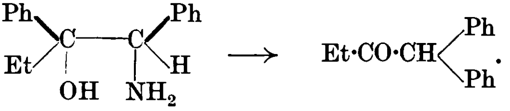
$$Et_2C(OH)\text{—}CH(NH_2)Ph \qquad (CH_2Ph)_2C(OH)\text{—}CH(NH_2)Ph$$

On the other hand, the striking fact emerges that in every instance of semipinacolinic deamination studied by us (with the exception of that of β-amino-β-phenyl-αα-dibenzylethyl alcohol), the strong saturation capacities of the hydrocarbon residues have caused the tertiary hydroxy-group to be comparatively loosely bound, thus :



When such compounds are acted on by nitrous acid, the hydroxy-group should readily combine with hydrogen with the elimination of water, and it actually does this.

It will also be noticed that in the examples quoted both of the hydrocarbon residues associated with the tertiary hydroxy-group have either weak or strong saturation capacities. An example is now described where one of the residues has a strong and the other a weak saturation capacity. A compound possessing this type of grouping was prepared by the action of magnesium ethyl iodide on desylamine hydrochloride, and it was found to undergo semi-pinacolinic change with nitrous acid :



The phenyl group migrated, the sole product isolated being diphenylbutanone. Now, the corresponding glycol, ethylhydrobenzoin, has been dehydrated by Tiffeneau and Orékhov (*Bull. Soc. chim.*, 1921, **29**, 422), who found that, under the influence of concentrated sulphuric acid, this glycol was transformed into a mixture of diphenylbutanone and ethyldeoxybenzoin. Our present experiments show that phenyl has a greater migrational aptitude than ethyl. Further, there was no evidence of the formation of ethylhydrobenzoin, and the hydroxy-group of the amino-alcohol was, therefore, less firmly bound than in the diethyl- or dibenzyl-amino-alcohols.

It should be emphasised that in addition to the effect of the ethyl and benzyl groups in causing the tertiary hydroxy-group to be firmly bound in β-amino-αα-diethyl-β-phenylethyl alcohol and in β-amino-β-phenyl-αα-dibenzylethyl alcohol, the phenyl group, which is attached to the same carbon atom as is the amino-group, would probably also be a contributory factor, although to a less degree than the ethyl and benzyl groups. The peculiar influence of the phenyl group has already been referred to by Mlle. Lévy in other connexions (*Bull. Soc. chim.*, 1923, **33**, 1655; 1926, **39**, 67).

It is also noteworthy that the best yield of glycol was obtained from that amino-alcohol in which the hydrocarbon residues attached to the tertiary carbon atom were purely aliphatic.

EXPERIMENTAL.

Deamination of β-Amino-αα-diethyl-β-phenylethyl Alcohol.—*r*-Phenylaminoacetic acid was converted into the hydrochloride (1 mol.) of its ethyl ester, which was then acted on by magnesium ethyl bromide (10 mols.). The resulting amino-alcohol (2 g.) was dissolved in 50% acetic acid, and an aqueous solution of sodium nitrite (2·2 g.) was gradually added, the temperature being maintained at 0°. Over-night, the oil had partly solidified; the product was extracted with ether, the extract washed with sodium bicarbonate, and the ether dried and expelled. The solid (1·6 g.) was crystallised thrice from light petroleum (b. p. 60—80°), from which it separated in needles containing no nitrogen, and melting at 89—89·5° (Found: C, 74·0; H, 9·4. Calc. for $C_{12}H_{18}O_2$: C, 74·2; H, 9·3%). The product gave an orange coloration with concentrated sulphuric acid, and was α-phenyl-ββ-diethylethylene glycol, which has m. p. 89° according to Tiffeneau and Lévy (*loc. cit.*).

The mother-liquors yielded a small quantity of oil which may have contained some ketone from semipinacolinic deamination, although no semicarbazone was actually obtained from it.

To eliminate the possibility of the acetic acid having caused the elimination of the amino-group by hydrolysis, a control experiment on the above lines was carried out in which the addition of the sodium nitrite was omitted. No glycol was isolated.

Deamination of β-Amino-β-phenyl-αα-dibenzylethyl Alcohol.—The amino-alcohol was prepared by the action of magnesium benzyl chloride on ethyl phenylaminoacetate hydrochloride. An aqueous solution of sodium nitrite (2·3 g.) was gradually added to the solution of the amino-alcohol (3 g.) in glacial acetic acid (30 g.), the solution being kept at 0° and stirred vigorously. The viscous product did not solidify entirely when kept over-night, and, after the addition of water, it was extracted with ether, the ether extract washed with sodium carbonate, and dried with sodium sulphate. The resulting oil was dissolved by heating with light petroleum (b. p. 60—80°). After the crystals (A) which gradually separated had been removed, the filtrate was evaporated to dryness, and the oil dissolved in ethyl alcohol; crystals (B) which separated were united with (A) and crystallised from ethyl alcohol; 0·6 g. of benzyl αβ-diphenylethyl ketone (m. p. 74—74·5°) was then obtained. The ethyl-alcoholic solution from which (B) had been withdrawn gradually deposited a higher-melting solid, which after crystallisation from rectified spirit gave α-phenyl-ββ-dibenzylethylene glycol, m. p.

115—116°. Yield, 0·5 g. For comparison, the glycol was prepared by the action of magnesium benzyl chloride on ethyl *dl*-mandelate, and there was no depression of the melting point when samples from both sources were mixed.

In another experiment, conducted under somewhat similar conditions with dilute acetic acid (15%, 180 c.c.), 5 g. of the amino-alcohol were acted on by a solution of 4 g. of sodium nitrite. The yield of pure glycol was in this case 1·1 g.

Deamination of β-Amino-α-ethyl-αβ-diphenylethyl Alcohol.—Ten g. of desylamine hydrochloride (1 mol.), prepared by the reduction of benzil β-monoxime with stannous chloride according to Pschorr and Brüggemann (*Ber.*, 1902, **35**, 2740), were added in instalments within 2 hours to the Grignard reagent prepared from 57 g. of ethyl iodide (9 mols.). The temperature was maintained at about 0° during the addition. Over-night, the mixture was boiled gently for 2½ hours, and then decomposed by ice and dilute hydrochloric acid. The acid layer was separated and made alkaline with ammonia; the free amino-alcohol then separated as an oil. The latter was triturated with ice-cold concentrated hydrochloric acid, and the solid hydrochloride (11 g.) was collected and crystallised from dilute hydrochloric acid–ethyl alcohol.

β-*Amino-α-ethyl-αβ-diphenylethyl alcohol hydrochloride*,

$$NH_2\cdot CHPh\cdot CEtPh\cdot OH,HCl,$$

crystallises in rosettes of feathery needles, m. p. 224—226° (Found : Cl, 12·6. $C_{16}H_{19}ON,HCl$ requires Cl, 12·8%). It gives a transient pink coloration with concentrated sulphuric acid.

A solution of sodium nitrite (2 g.) was gradually added to a solution of the hydrochloride (2·2 g.) in dilute hydrochloric acid, and the resulting oil was extracted with ether. Yield : 2 g. This was acted on by semicarbazide hydrochloride and sodium acetate; 1·3 g. of the solid semicarbazone were then obtained. After crystallisation from rectified spirit, rectangular needles of the semicarbazone of diphenylbutanone separated. These melted at 195—196°, and there was no depression of the melting point on admixture with the semicarbazone of diphenylbutanone prepared by the dehydration of ethylhydrobenzoin with concentrated sulphuric acid.

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