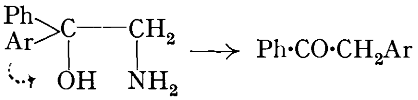
340. *The Mechanism of the Deamination of Amino-alcohols. Part I. Amino-alcohols derived from Phenyl α-Amino-β-phenylethyl Ketone.*

By Arthur K. Mills.

It was shown by McKenzie and Roger (J., 1924, **125**, 844) that a study of the deamination of amino-alcohols, Ph·CH(NH_2)·C(OH)PhR, derived from desylamine (McKenzie and Richardson, J., 1923, **123**, 79) could be used to compare the migrational aptitude of the phenyl group with that of other organic radicals. Since many of these deaminations led to unexpected results, McKenzie and Mills (*Ber.*, 1929, **62**, 1784) studied the reactions with optically active amino-alcohols, and they were then able to confirm the fact that in every case the reaction involved almost entirely the migration of the phenyl group, although the extension of the work to optically active material showed a very slight wandering of other aromatic groups—the anisyl and the α-naphthyl radical. McKenzie, Mills, and Myles (*Ber.*, 1930, **63**, 904) later showed that deamination of β-amino-αβ-diphenyl-α-*p*-tolylethyl alcohol caused in the same way almost entirely the migration of the phenyl group and only to an extremely small extent the migration of the *p*-tolyl group. These results were all the more surprising as not only had the dehydration of glycols and pinacols (Tiffeneau and Lévy, *Bull. Soc. chim.*, 1931, **49**, 1661; Bachmann and Shankland, *J. Amer. Chem. Soc.*, 1929, **51**, 306; Bailar, *ibid.*, 1930, **52**, 3596; Bachmann and Moser, *ibid.*, 1932, **54**, 1124) led to the supposition that the α-naphthyl, anisyl, and *p*-tolyl radicals had a greater tendency to migrate than the phenyl radical, but also the deamination of various amino-alcohols of the type CPhR(OH)·CH_2·NH_2 (R = α-naphthyl, anisyl, or *p*-tolyl) had caused no migration of the phenyl group.

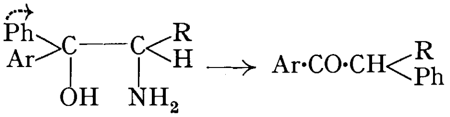
It thus became evident that two types of deamination of amino-alcohols led to entirely different results with regard to the comparative migrational aptitude of the phenyl group :



$$\mathrm{Ph}(\mathrm{Ar})\mathrm{C(OH)}\text{—}\mathrm{CH_2NH_2} \longrightarrow \mathrm{Ph{\cdot}CO{\cdot}CH_2Ar}$$

Type A.

Ar = α-naphthyl (Luce, *Compt. rend.*, 1925, **180**, 145), anisyl (Orékhoff and Roger, *ibid.*, p. 70), or *p*-tolyl (McKenzie, Mills, and Myles, *loc. cit.*).



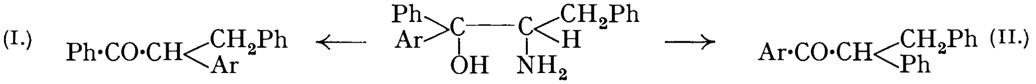
$$\mathrm{Ph}(\mathrm{Ar})\mathrm{C(OH)}\text{—}\mathrm{C(R)(H)NH_2} \longrightarrow \mathrm{Ar{\cdot}CO{\cdot}CH}{<}^{\mathrm{R}}_{\mathrm{Ph}}$$

Type B.

R = Ph. Ar = α-naphthyl, anisyl, or *p*-tolyl (McKenzie and Mills; McKenzie, Mills, and Myles, *locc. cit.*).

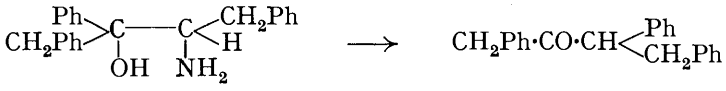
As it was only in the deamination of amino-alcohols of the type CPhAr(OH)·CHPh·NH_2 that this anomalous migration of the phenyl group occurred, it has been assumed that the normal reaction is the migration of the heavier radicals, as in type (A), and the migration of the phenyl group, as in type (B), has been considered abnormal. Such a decision cannot, however, be made until the deamination of amino-alcohols has been further examined. In order to study the factors governing rearrangement, a study has therefore been made of the deamination of a series of alcohols of the type CPhAr(OH)·CH(CH_2Ph)·NH_2, where the migration must occur towards a secondary carbon atom with a benzyl group attached. As the benzyl group has an extremely small saturation capacity (Tiffeneau and co-workers, *Bull. Soc. chim.*, 1931, **49**, 1776, 1788, 1840), the chemical nature of this series of amino-alcohols should approach closely to that which led to deaminations of type (A).

Phenyl α-amino-β-phenylethyl ketone hydrochloride, Ph·CO·CH(CH_2Ph)·NH_2,HCl, was acted upon by Grignard reagents to give the required amino-alcohols, which were then treated with nitrous acid. The composition of the resulting ketones showed whether the reaction was of type (A), forming (I), or of type (B), forming (II).



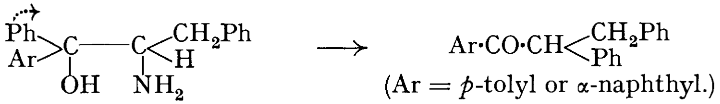
$$\text{(I.)}\ \mathrm{Ph{\cdot}CO{\cdot}CH}{<}^{\mathrm{CH_2Ph}}_{\mathrm{Ar}} \longleftarrow \mathrm{Ph}(\mathrm{Ar})\mathrm{C(OH)}\text{—}\mathrm{C(CH_2Ph)(H)NH_2} \longrightarrow \mathrm{Ar{\cdot}CO{\cdot}CH}{<}^{\mathrm{CH_2Ph}}_{\mathrm{Ph}}\ \text{(II.)}$$

As a preliminary experiment, β-*amino*-αβ-*dibenzyl*-α-*phenylethyl alcohol* was acted on by nitrous acid. In this case, where only the phenyl and the benzyl group could migrate, it was expected to find the migration of the phenyl group on account of its more aromatic character: the reaction actually took this course, the product being αγ-diphenyl-γ-benzylacetone :



$$\substack{\text{Ph}\\ \text{CH}_2\text{Ph}}{>}\underset{\text{OH}}{\text{C}}\text{---}\underset{\text{NH}_2}{\text{C}}{<}\substack{\text{CH}_2\text{Ph}\\ \text{H}} \longrightarrow \text{CH}_2\text{Ph}\cdot\text{CO}\cdot\text{CH}{<}\substack{\text{Ph}\\ \text{CH}_2\text{Ph}}$$

The reaction of β-*amino*-αγ-*diphenyl*-α-p-*tolyl*-n-*propyl alcohol* with nitrous acid was now studied : both the phenyl and the *p*-tolyl radical are liable to migrate and, as has been seen, it was impossible to make any predictions as to the final product. Actually, only *p*-tolyl αβ-diphenylethyl ketone was isolated in almost theoretical yield. The deamination of β-*amino*-αγ-*diphenyl*-α-(α-*naphthyl*)-n-*propyl alcohol* was carried out in a similar manner, and the product was α-*naphthyl* αβ-*diphenylethyl ketone.* The phenyl group had evidently migrated in both cases as in type (B) :



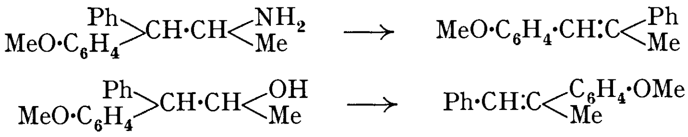
$$\substack{\text{Ph}\\ \text{Ar}}{>}\underset{\text{OH}}{\text{C}}\text{---}\underset{\text{NH}_2}{\text{C}}{<}\substack{\text{CH}_2\text{Ph}\\ \text{H}} \longrightarrow \text{Ar}\cdot\text{CO}\cdot\text{CH}{<}\substack{\text{CH}_2\text{Ph}\\ \text{Ph}}$$

(Ar = *p*-tolyl or α-naphthyl.)

In a recent paper (*Bull. Soc. chim.*, 1931, **49**, 1686) Tiffeneau indicates that in the deamination of some amino-alcohols of the type $CH_3\cdot CH(NH_2)\cdot C(OH)PhAr$ (Ar = *p*-tolyl or anisyl) the phenyl group migrates. It is therefore evident from these results that the normal deamination of amino-alcohols is that of type (B).

Bailar and Bachmann and co-workers (*locc. cit.*) have recently studied the dehydration of *sym.*-pinacols and deduced a number for the "migrational aptitude" of various organic radicals compared with phenyl as unity : α-naphthyl 18 > *p*-tolyl 15 > phenyl 1. It is evident that these figures cannot be applied to migrations arising from the deamination of amino-alcohols. Bachmann and Moser (*loc. cit.*) state that "the migration aptitude of a group in a symmetrical benzopinacol has been shown to be a property characteristic of that group and is not dependent on the particular pinacol in which it is found." The author holds, however, that no evidence is yet forthcoming to show that organic groups have any definite characteristic such as a "migrational aptitude" and, therefore, that no attempt can be made to explain the mechanism of reactions by the application of such values. It seems more reasonable to assume that the comparative "migratory aptitudes" of organic radicals tend to differ for every compound, but that in very similar compounds—the tetra-substituted aromatic pinacols—the difference has not been measurable. Notice must be taken of the nature of the carbon atom towards which the migration occurs, and, where different dehydrating agents are used, of the possibility of the formation of different intermediate additive structures.

Lévy, Gallais, and Abragam (*Bull. Soc. chim.*, 1928, **43**, 868) give another example of the variable migration of organic groups, for in the deamination of β-anisyl-β-phenyl*iso*propylamine the phenyl group migrates more readily than the anisyl group, whereas the dehydration of the corresponding alcohol, β-anisyl-β-phenyl*iso*propyl alcohol, causes the migration of the anisyl group :



$$\substack{\text{Ph}\\ \text{MeO}\cdot\text{C}_6\text{H}_4}{>}\text{CH}\cdot\text{CH}{<}\substack{\text{NH}_2\\ \text{Me}} \longrightarrow \text{MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}\colon\text{C}{<}\substack{\text{Ph}\\ \text{Me}}$$

$$\substack{\text{Ph}\\ \text{MeO}\cdot\text{C}_6\text{H}_4}{>}\text{CH}\cdot\text{CH}{<}\substack{\text{OH}\\ \text{Me}} \longrightarrow \text{Ph}\cdot\text{CH}\colon\text{C}{<}\substack{\text{C}_6\text{H}_4\cdot\text{OMe}\\ \text{Me}}$$

These reactions show a close analogy with those already outlined in this paper, for the less negative aromatic radical again migrates during deamination and the more negative group during dehydration.

Experimental

Phenyl α-Amino-β-phenylethyl Ketone Hydrochloride.—Phenyl β-phenylethyl ketone was prepared in practically theoretical yield by the reduction of chalkone in ethyl-alcoholic solution with platinum-black as catalyst. The *iso*nitroso-compound was obtained by the method of Schneidewind (*Ber.*, 1888, **21**, 1326) but with the use of methyl alcohol, in which the ketone is more soluble. Dissolved in alcohol (120 c.c.) it (30 g.) was reduced with stannous chloride (156 g.) in 225 c.c. of concentrated hydrochloric acid and a little tin. After 3 days, the precipitate was filtered off, dried, washed with ether (which removed 6 g. of unattacked *iso*nitroso-compound), and in hot aqueous solution freed from tin as sulphide. *Phenyl α-amino-β-phenylethyl ketone hydrochloride* crystallised on cooling; recrystallised from 90% alcohol, it formed clusters of colourless needles (25 g.), m. p. 228—229° (decomp.) (Found : C, 68·9; H, 6·3; N, 5·2; Cl, 13·3. $C_{15}H_{15}ON,HCl$ requires C, 68·8; H, 6·2; N, 5·4; Cl, 13·6%).

β-Amino-αβ-dibenzyl-α-phenylethyl alcohol.—5 G. of the preceding hydrochloride were added gradually to the Grignard reagent prepared from 14·5 g. of benzyl chloride (6 mols.). The mixture was heated for 2 hours on a water-bath and then decomposed by ice and hydrochloric acid. The *β-amino-αβ-dibenzyl-α-phenylethyl alcohol hydrochloride* which separated was washed with ether and crystallised several times from absolute alcohol (yield, 5·5 g.), forming needles, m. p. 251—252° (decomp.) (Found : C, 74·6; H, 7·1; N, 4·0; Cl, 9·7. $C_{22}H_{23}ON,HCl$ requires C, 74·6; H, 6·8; N, 4·0; Cl, 10·0%). The amino-alcohol hydrochloride was dissolved in hot aqueous alcohol, and the solution made alkaline with ammonia. The *β-amino-αβ-dibenzyl-α-phenylethyl alcohol* obtained crystallised from aqueous alcohol in colourless rectangular prisms, m. p. 96—97° (Found : C, 83·3; H, 7·4; N, 4·6. $C_{22}H_{23}ON$ requires C, 83·2; H, 7·3; N, 4·4%).

Deamination. To a solution of 2·0 g. of the amino-alcohol in 80 c.c. of 25% acetic acid, cooled in ice–salt, a solution of 2·0 g. of sodium nitrite in 20 c.c. of water was added during 2 hours with mechanical stirring. After 12 hours, the slightly oily product was collected, washed with water, and crystallised from rectified spirit; colourless needles (1·8 g.) were obtained, m. p. 74—74·5° alone or mixed with benzyl αβ-diphenylethyl ketone obtained from the deamination of β-amino-β-phenyl-αα-dibenzylethyl alcohol (J., 1927, 575).

*β-Amino-αγ-diphenyl-α-*p*-tolyl-*n*-propyl Alcohol.*—From 5 g. of phenyl α-amino-β-phenylethyl ketone hydrochloride and the Grignard reagent prepared from 19·7 g. of *p*-tolyl bromide (6 mols.), by the method already described, *β-amino-αγ-diphenyl-α-*p*-tolyl-*n*-propyl alcohol hydrochloride* (4·2 g.) was obtained; it crystallised from rectified spirit in fine needles, m. p. 218—219° (decomp.) (Found : C, 74·5; H, 6·9; N, 3·9. $C_{22}H_{23}ON,HCl$ requires C, 74·6; H, 6·8; N, 4·0%). It was converted into *β-amino-αγ-diphenyl-α-*p*-tolyl-*n*-propyl alcohol*, which crystallised from rectified spirit in spheres of fine needles, m. p. 134—135° (Found : C, 83·1; H, 7·5; N, 4·6. $C_{22}H_{23}ON$ requires C, 83·2; H, 7·3; N, 4·4%).

Deamination. From 1·1 g. of the amino-alcohol, in dilute acetic acid, and a solution of sodium nitrite (1·0 g.) in water, after 2 hours' stirring at 0°, a white solid (1·0 g.) separated, which crystallised from aqueous alcohol in fine needles (0·9 g.), m. p. 89—90° alone or mixed with *p*-tolyl diphenylethyl ketone prepared by the action of sodium ethoxide and benzyl chloride on benzyl *p*-tolyl ketone (Turner, J., 1915, **107**, 1460).

*β-Amino-αγ-diphenyl-α-(α-naphthyl)-*n*-propyl Alcohol.*—5 G. of phenyl α-amino-β-phenylethyl ketone hydrochloride were slowly added to the Grignard reagent prepared from 23·8 g. of α-naphthyl bromide (6 mols.). The mixture was left over-night, heated on a water-bath for 2 hours, and decomposed with ice and hydrochloric acid. A red oil was precipitated which changed to a white solid after a day; this was washed with ether and crystallised several times from aqueous alcohol and then from rectified spirit, 4·3 g. of β-amino-αγ-diphenyl-α-(α-naphthyl)-*n*-propyl alcohol hydrochloride being obtained in rectangular prisms, m. p. 229—230° (decomp.). The amino-alcohol hydrochloride was converted into *β-amino-αγ-diphenyl-α-(α-naphthyl)-*n*-propyl alcohol*, which crystallised from absolute alcohol in rectangular prisms, m. p. 165—166° (Found : C, 84·8; H, 6·7; N, 4·0. $C_{25}H_{23}ON$ requires C, 84·95; H, 6·6; N, 4·0%).

Deamination. An aqueous solution of sodium nitrite (1·0 g.) was slowly added at 0° to the amino-alcohol (1·5 g.) dissolved in dilute acetic acid. A thick yellowish pasty mass separated and was extracted with ether. The resulting oil (1·4 g.) was crystallised from rectified spirit and then from light petroleum (b. p. 70—90°), forming rhombohedral crystals (1·0 g.), m. p. 68—69°, alone or mixed with *α-naphthyl αβ-diphenylethyl ketone* synthesised from α-naphthyl benzyl ketone (Found : C, 89·3; H, 5·9. $C_{25}H_{20}O$ requires C, 89·2; H, 6·0%).

Synthesis of α-Naphthyl αβ-Diphenylethyl Ketone.—4 G. of carefully purified naphthyl benzyl ketone (Luce, *Compt. rend.*, 1925, **180**, 145) were added to sodium (1 atom) dissolved in 20 c.c. of absolute alcohol and the mixture was refluxed for 5 minutes on a water-bath. Benzyl chloride (1 mol.) was then added, and the whole refluxed for 3 hours until neutral and poured into water. The oil which separated was extracted with ether and crystallised from rectified spirit and light petroleum (b. p. 70—90°), α-naphthyl αβ-diphenylethyl ketone (4·2 g.) being obtained, m. p. 68—69°.

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CHEMISCHES INSTITUT DER UNIVERSITÄT, HEIDELBERG.
THE UNIVERSITY, ABERDEEN.

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