[Contribution from the Department of Chemistry, University of Notre Dame]

# THE REARRANGEMENT OF BETA AMINO ALCOHOLS WITH HEAT AND ALKALI[1]

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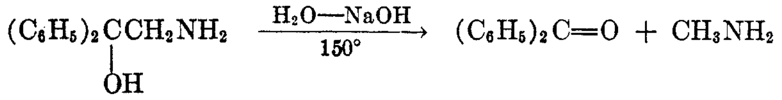
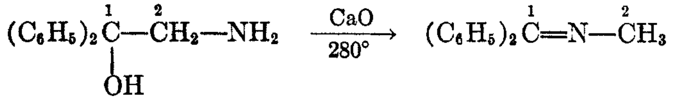
*Beta*-amino alcohols have been shown to undergo various rearrangements with acids (1, 2) but the effect of bases on these substances has been less thoroughly investigated. Bettzieche and Ehrlich (3) found that certain aryl-substituted amino alcohols yielded an aliphatic amine and a carbonyl compound when heated with aqueous alkali in a sealed tube:



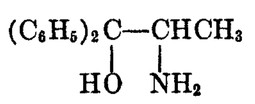
$$(C_6H_5)_2\underset{\displaystyle OH}{C}CH_2NH_2 \xrightarrow[150°]{H_2O—NaOH} (C_6H_5)_2C{=}O + CH_3NH_2$$

Stieglitz and Lenth (4) found that 1,1-diphenyl-2-aminoethanol gave methyliminobenzophenone when it was heated under anhydrous conditions with soda-lime or calcium oxide. In this rearrangement the nitrogen atom originally attached to carbon atom 2 has become attached to carbon atom 1 as well:



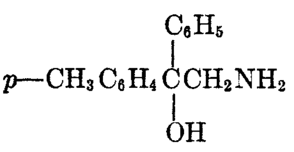
$$(C_6H_5)_2\underset{\displaystyle OH}{\overset{1}{C}}—\overset{2}{C}H_2—NH_2 \xrightarrow[280°]{CaO} (C_6H_5)_2\overset{1}{C}{=}N—\overset{2}{C}H_3$$

In connection with our work on the formation of *beta*-amino alcohols from Grignard reagents and oximes (5, 6) it seemed of interest to study this rearrangement further, and to determine, if possible, its mechanism. With this in mind we have investigated the action of calcium oxide on 1,1-diphenyl-2-amino-1-propanol (I), 1-phenyl-1-*p*-tolyl-2-aminoethanol (II), and 1,1,2-triphenyl-2-aminoethanol (III).



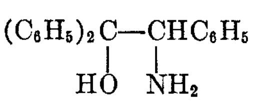
$$(C_6H_5)_2\underset{\displaystyle HO}{C}—\underset{\displaystyle NH_2}{C}HCH_3$$

I



$$p—CH_3C_6H_4\underset{\displaystyle OH}{\overset{\displaystyle C_6H_5}{C}}CH_2NH_2$$

II



$$(C_6H_5)_2\underset{\displaystyle HO}{C}—\underset{\displaystyle NH_2}{C}HC_6H_5$$

III

When amino alcohol I was heated with calcium oxide in an atmosphere of dry nitrogen at 265–285° it was partly rearranged to ethyliminobenzophenone. The yield of the ketimine was usually 50–75% of the theoretical amount, and some amino alcohol was always recovered. When the reaction was carried out at lower temperatures (130–230°) or in the absence of calcium oxide, no rearrangement occurred, and the alkamine was recovered almost quantitatively. The structure of the rearrangement product was established: (a) by hydrolysis to the ketone

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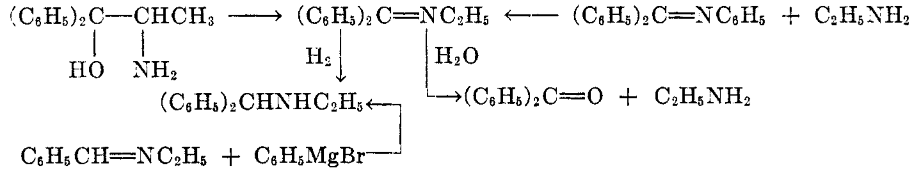
[1] A part of this work was presented before the Organic Division at the Baltimore meeting of the American Chemical Society, April, 1939.

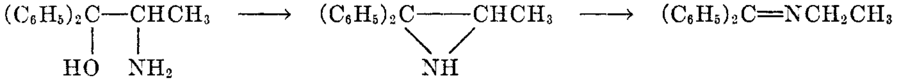
and amine; (b) by comparison of physical properties with ethyliminobenzophenone synthesized from ethylamine and benzophenone anil; (c) by reduction to the corresponding saturated amine; and (d) by comparison, through derivatives, of this amine with the amine synthesized from benzylidenethylamine and phenylmagnesium bromide. This proof was considered necessary in view of the oily nature of the ketimine and the saturated amine.



In a similar way it was established that amino alcohol II, 1-phenyl-1-*p*-tolyl-2-aminoethanol, was rearranged by calcium oxide at 260° to methylimino-*p*-methylbenzophenone. In this case rearrangement occurred more easily, and no alkamine was ever recovered. When the reaction was carried out at lower temperatures or in the absence of calcium oxide no rearrangement occurred.

Amino alcohol III, 1,1,2-triphenyl-2-aminoethanol, on heating with calcium oxide at 250° yielded an oil which was shown to be benzyliminobenzophenone.

It seemed to us that the rearrangement probably involved a dehydration of the amino alcohol to an ethylenimine, and that this substance, under the influence of the heat and alkali, undergoes a ring cleavage between the two carbon atoms.



This mechanism is supported by the fact that Coleman and Waugh (7) found that 2,3-diphenylethylenimine is rearranged to benzylidenbenzylamine by heat, while Erlenmeyer (8) had previously shown that the corresponding amino alcohol, 1,2-diphenyl-2-aminoethanol, also yields benzylidenbenzylamine on heating.

If the first step in the rearrangement is dehydration of the amino alcohol, it would help to explain the strenuous conditions found necessary in our work, for tertiary amino alcohols have been shown to be resistant to dehydration by neutral and alkaline dehydrating agents (9). The ethylenimine should, therefore, be more easily rearranged than the amino alcohol. Since the ethylenimine corresponding to amino alcohol I has recently been made readily available (10) rearrangement studies were carried out on it. The results showed that 2,2-diphenyl-3-methylethylenimine rearranged to ethyliminobenzophenone when heated, with or without calcium oxide, and that the rearrangement occurred at a much lower temperature than with the amino alcohol.

## EXPERIMENTAL

A. *1,1-Diphenyl-2-amino-1-propanol and 2,2-diphenyl-3-methylethylenimine.* 1. *Rearrangement of the amino alcohol.* A mixture of 3 g. of the amino alcohol (5), m.p. 103–104°, and 1.5 g. of freshly powdered calcium oxide was heated in a small retort in a stream of dry nitrogen at 270° (oil-bath temperature) for seventy-five minutes. The cooled reaction mixture was extracted several times with anhydrous ether. Distillation of the material remaining after evaporation of the ether yielded 1 g. of an oil, b.p. 154–159°/10 mm., $n_D^{20}$ 1.5976, and 0.75 g. of the amino alcohol, b.p. 160–170°/10 mm., m.p. 102°. In one run the oil solidified and then melted at 58–59°. Sommelet (11) records the melting point 61–62° for ethyliminobenzophenone prepared from benzophenone dichloride.

When the amino alcohol was heated with calcium oxide at temperatures of 130–230° no rearrangement occurred, and the alkamine was recovered almost quantitatively.

2. *Hydrolysis of the rearrangement product.* One gram of the above oil was shaken for a few minutes at room temperature with 50 ml. of 6 *N* hydrochloric acid. The solution, originally clear, quickly became turbid, and a purple oil rose to the top. This oil was taken up in ether, the ether solution was dried and evaporated. The material remaining solidified after seeding with benzophenone, and then melted at 48°. The oxime prepared from this product melted at 140° and did not depress the melting point of known benzophenone oxime.

When the aqueous acid solution was made basic, a small amount of amino alcohol separated (m.p. 100°, benzamide, m.p. 188°). The filtrate was distilled into dilute hydrochloric acid. Evaporation of this distillate gave a hygroscopic hydrochloride from which a picrate was prepared. The picrate melted at 164° and did not depress the melting point of ethylamine picrate (m.p. 165°).

3. *Reduction of the rearrangement product.* One gram of the "rearrangement oil" was dissolved in 150 ml. of boiling absolute alcohol and treated with 6 g. of sodium. The cooled solution was poured into water, extracted with ether, and the dried extract distilled after removal of the ether. There was obtained 0.75 g. of an amine, b.p. 142°/8 mm., $n_D^{20}$ 1.5680. This amine was converted into a hydrochloride, m.p. 240°, a phenylthiourea, m.p. 149–149.5°, and an *alpha*-naphthylurea, m.p. 181–182°.

4. *Ethyliminobenzophenone.* Benzophenone anil was made in 50% yield by the general method of Reddelein (12) from 10 g. of benzophenone, 5 drops of 40% hydrobromic acid, and 11 g. of aniline. Ten grams of the anil and a few crystals of aniline hydrobromide were heated at 230° for forty-five minutes while a stream of dry ethylamine was passed through the mixture. During this time 3.0 g. of aniline distilled out (calculated, 3.6 g.). The cooled residue was extracted repeatedly with dry ether, and the ether extract on distillation yielded 5 g. of a light yellow oil, b.p. 144°/7 mm., $n_D^{20}$ 1.5895. It resisted all attempts at crystallization.

*Anal.* Calc'd for $C_{15}H_{15}N$: C, 86.1; H, 7.23; N, 6.70.
Found: C, 86.2; H, 7.49; N, 6.81.

One gram of the ketimine was shaken with 25 ml. of 6 *N* hydrochloric acid at room temperature. The acid-insoluble oil formed was shown to be benzophenone; the acid solution yielded ethylamine picrate.

Two grams of the ketimine was reduced with 10 g. of sodium in 100 ml. of absolute alcohol. The amine, isolated in 1 g. yield, boiled at 155–157°/12 mm., $n_D^{20}$ 1.5698.

5. *Benzohydrylethylamine.* A solution of 13.3 g. (0.1 mole) of benzylidenethylamine (b.p. 125–126°/95 mm.) in two volumes of dry ether was added over a period of forty-five minutes to a Grignard reagent prepared from 3 g. of magnesium and 20 g. of bromobenzene. The reaction mixture was refluxed for two hours, and was then hydrolyzed with ice and ammonium chloride. There was obtained 15 g. of amine, b.p. 143–148°/8 mm., $n_D^{20}$ 1.5656.

*Anal.* Calc'd for $C_{15}H_{17}N$: C, 85.24; H, 8.12; N, 6.63.
Found: C, 85.01; H, 8.43; N, 6.76.

Busch and Leefheim (13) have also prepared this amine; they report the boiling point 175°/20 mm., and obtained a hydrochloride, m.p. 248°.

6. *Rearrangement of 2,2-diphenyl-3-methylethylenimine.* A mixture of 3 g. of the ethylenimine (10) and 1.5 g. of calcium oxide was heated in a stream of nitrogen at 250–260° for one and one-half hours. The product, obtained in 2.2 g. yield, had b.p. 144–147°/10 mm., $n_D^{20}$ 1.5868. The same compound was obtained when the ethylenimine was heated in the absence of calcium oxide, at temperatures of 175–205°.

The rearrangement product on treatment with 6 *N* hydrochloric acid yielded benzophenone and ethylamine.

Reduction of 2.1 g. of the rearrangement product with 7 g. of sodium and 100 ml. of absolute alcohol gave 1.75 g. of amine, b.p. 141–143°/9 mm., $n_D^{20}$ 1.5683.

A comparison of the rearrangement and reduction products in this series is given in Table I.

TABLE I

REARRANGEMENT OF 1,1-DIPHENYL-2-AMINO-1-PROPANOL AND 2,2-DIPHENYL-2-METHYLETHYLENIMINE

| SOURCE | COMPOUND | | | | |
|---|---|---|---|---|---|
| | Ethyliminobenzophenone | Benzohydrylethylamine | Amine HCl M.p., °C. | Amine phenylthiourea M.p., °C. | Amine α-naphthylurea M.p., °C. |
| Benzylidenethylamine + $C_6H_5MgBr$ | | B.p. 143–8/8 mm.<br>$n_D^{20}$ 1.5656 | 246–247 | 150–151 | 183.5–185 |
| Benzophenone + ethylamine | B.p. 144°/7 mm.<br>$n_D^{20}$ 1.5895 | B.p. 155°/12 mm.<br>$n_D^{20}$ 1.5698 | 246–247 | 150–151 | 182–183 |
| Ethylenimine | B.p. 142°/8 mm.<br>$n_D^{20}$ 1.5889 | B.p. 143°/8 mm.<br>$n_D^{20}$ 1.5683 | 240 | 149 | 183–184 |
| Amino alcohol | B.p. 139°/5 mm.<br>$n_D^{20}$ 1.5976 | B.p. 142°/8 mm.<br>$n_D^{20}$ 1.5680 | 240 | 149–150 | 181–182 |

TABLE II

REARRANGEMENT OF 1-PHENYL-1-*p*-TOLYL-2-AMINOETHANOL

| SOURCE | COMPOUND | | | | |
|---|---|---|---|---|---|
| | Methylimino-*p*-methylbenzophenone | *p*,N-Dimethylbenzohydrylamine | Amine Hydrochloride M.p. °C. | Amine Phenylthiourea M.p. °C. | Amine α-Naphthylurea M.p. |
| Benzylidenmethylamine + *p*-tolylmagnesium bromide | | B.p. 169–172°/16 mm.<br>$n_D^{20}$ 1.5700 | 186.5–187 | 140–140.5 | 171.5–172.5 |
| *p*-Methyl benzophenone + $MeNH_2$ | B.p. 165–169°/12 mm.<br>$n_D^{20}$ 1.5965 | B.p. 144–148°/8 mm.<br>$n_D^{20}$ 1.5715 | 184–186 | 138–139 | 170–171 |
| Amino alcohol | B.p. 169–171°/13 mm.<br>$n_D^{20}$ 1.5965 | B.p. 148–150°/9 mm.<br>$n_D^{20}$ 1.5706 | 185–186 | 139.5–140 | 171.5–172.5 |

B. *1-Phenyl-1-p-tolyl-2-aminoethanol.* 1. *Rearrangement of the amino alcohol.* A mixture of 3 g. of the amino alcohol (2) and 1.5 g. of calcium oxide was heated at 260° in a stream of dry nitrogen for one hour. A viscous yellow oil was isolated in 2 g. yield, b.p. 140–143°/5 mm., $n_D^{20}$ 1.5965. Hydrolysis of this oil with 6 *N* hydrochloric acid yielded *p*-methylbenzophenone, m.p. 58° after recrystallization from 95% ethyl alcohol, which did not depress the melting point of an authentic sample of the ketone (m.p. 58°). An amine hydrochloride, m.p. 223°, was also isolated from the hydrolysis; this did not depress the melting point of methylamine hydrochloride, m.p. 225°. The platinichloride of the amine melted at 224–225°.

*Anal.* Calc'd for $C_2H_{12}Cl_6PtN_2$: Pt, 41.30. Found: Pt, 41.33.

The "rearrangement oil" (1.5 g.) was reduced with 4 g. of sodium in 100 ml. of boiling absolute alcohol. There was obtained 0.75 g. of an oil, b.p. 148–150°/9 mm., $n_D^{20}$ 1.5706. This material was converted into a hydrochloride, m.p. 185–186°, a phenylthiourea, m.p. 139.5–140°, and an α-naphthylurea, m.p. 171.5–172.5°.

2. *Synthesis of methylimino-p-methylbenzophenone.* *p*-Methylbenzophenone anil was prepared by the general method of Reddelein (12). A mixture of 10 g. of the anil (b.p. 205°/9 mm.) and 0.5 g. of aniline hydrobromide was heated in a stream of dry methylamine at 200–210° until 3 g. of aniline distilled out. The imine was obtained in 5 g. yield as a yellow viscous oil, b.p. 165–169°/13 mm., $n_D^{20}$ 1.5965.

*Anal.* Calc'd for $C_{15}H_{15}N$: N, 6.70. Found: N, 6.40.

The imine on hydrolysis with 6 *N* hydrochloric acid yielded *p*-methylbenzophenone and methylamine hydrochloride.

Reduction of 5.2 g. of the imine with 10 g. of sodium in 100 ml. of absolute alcohol yielded 4 g. of amine, b.p. 144–148°/8 mm., $n_D^{20}$ 1.5715.

3. *Synthesis of p-N-dimethylbenzohydrylamine.* A solution of 20 g. of benzylidenmethylamine in an equal volume of dry ether was added dropwise to a Grignard reagent prepared from 38 g. of *p*-bromotoluene, 5 g. of magnesium and 150 ml. of ether. The reaction mixture was refluxed for one hour and was then worked up in the usual way. There was obtained 18 g. of amine, b.p. 169–172°/16 mm., $n_D^{20}$ 1.5700.

*Anal.* Calc'd for $C_{15}H_{17}N$: C, 85.24; H, 8.12; N, 6.63.
Found: C, 85.33; H, 8.51; N, 6.69.

The hydrochloride of this amine melted at 186–187° after recrystallization from ether-alcohol mixture.

*Anal.* Calc'd for $C_{15}H_{18}ClN$: Cl, 14.34. Found: Cl, 14.25.

The α-naphthylurea melted at 171.5–172.5° after recrystallization from 95% alcohol.

*Anal.* Calc'd for $C_{26}H_{24}N_2O$: N, 7.37. Found, N, 7.36.

Semper and Lichtenstadt (14) reported this amine as a reduction product of the N-methyl ether of *p*-methylbenzophenone oxime; they did not isolate the free base, and give the melting point 199–201° for the hydrochloride.

A comparison of the derivatives from the rearrangement of 1-phenyl-1-*p*-tolyl-2-aminoethanol with the synthetic derivatives is shown in Table II.

C. *Rearrangement of 1,2,2-triphenyl-2-aminoethanol.* A mixture of 2.0 g. of the amino alcohol and 1 g. of calcium oxide was heated in a stream of nitrogen at 260° for one hour; there was obtained 1.8 g. of oil. This oil partially solidified on seeding with known benzophenone benzylimide (15). Hydrolysis of the "rearrangement oil" with dilute hydrochloric acid yielded benzophenone, identified as the oxime, m.p. 143°, and benzylamine, identified as the picrate, m.p. 197°.

## SUMMARY

1. The rearrangement of three aryl-substituted *beta* amino alcohols with heat and calcium oxide has been investigated. The amino alcohols have been shown to rearrange to ketimines; in two cases the rearrangement product was identified by synthesis and by reduction to a saturated, secondary amine.

2. A mechanism has been suggested for the rearrangement, and has been partially confirmed by a study of the rearrangement of 2,2-diphenyl-3-methylethylenimine.

NOTRE DAME, IND.

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