

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME]

AMINO ALCOHOLS. I. PHENYLPROPANOLAMINE AND PARA-TOLYLPYRROPIANOLAMINE

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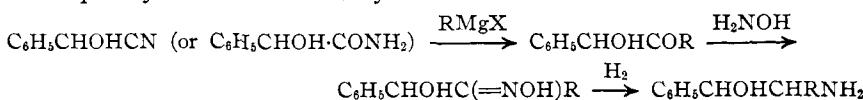
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The encouraging results from the pharmacodynamic investigations of ephedrine, particularly those of Chen,¹ have stimulated the interest of chemists in this compound as well as in its homologs and analogs.²

Since Smith³ isolated *nor-d-ψ*-ephedrine from ephedra species and in view of the fact that (3,4-dihydroxyphenol)-ethanolamine has in many respects a physiological activity not unlike that of (3,4-dihydroxyphenyl)-ethanolmethylamine, or adrenaline,⁴ it appeared that arylalkanolamines of the general types ArCHOHCHRNH₂ merited further study and investigation.

Various methods are recorded for the synthesis of compounds of this class. Phenylethanolamine has been prepared in low yields by reducing ω-amino-acetophenone⁵ or mandelonitrile⁶ with sodium amalgam; Alles claimed better results from phenylnitro-ethanol.^{2c} Phenylpropanolamine has been made by reducing α-aminopropiophenone with sodium or its amalgam;⁷ by reducing phenylnitro-ethanol with zinc dust and acetic acid;⁸ from isonitrosopropiophenone by catalytic means with palladinized gum arabic, but from 5.7 g. of isonitroso ketone in a solution of 85 cc. of alcohol, 57 cc. of water and 7.1 cc. of 30% hydrochloric acid, only 1.4 g. of phenylpropanolamine was isolated.⁹ A method of more general application was developed by Tiffeneau and Lévy¹⁰ who used the scheme



¹ Chen, *J. Pharmacol.*, **28**, 31 (1926).

² (a) Hyde, Browning and Adams, *THIS JOURNAL*, **50**, 2287 (1928); (b) Tiffeneau, *J. pharm. chim.*, [8] **7**, 228 (1928); (c) Alles, *J. Pharmacol.*, **32**, 121 (1927); (d) Manske and Johnson, *THIS JOURNAL*, **51**, 580 (1929).

³ Smith, *J. Chem. Soc.*, **125**, 51 (1928).

⁴ Oswald, "Chemische Konstitution und Pharmakologische Wirkung," Borntraeger, Berlin, 1924, pp. 361-363; Schultz, *Hygienic Lab. Bull.*, **55**, 31 (1909); Hugo-unenq and Florence, "Principes de Pharmacodynamie," Masson et Cie., Paris, 1928, p. 175.

⁵ Pictet and Gams, *Ber.*, **43**, 2385 (1910); Mannich and Thiele, *Arch. Pharm.*, **253**, 181 (1915).

⁶ Hess and Ubrig, *Ber.*, **48**, 1984 (1915).

⁷ Calliesz, *Arch. Pharm.*, **250**, 150 (1912); Eberhardt, *ibid.*, **255**, 143 (1917).

⁸ Nagai, U. S. Patent 1,356,877 [*C. A.* **15**, 412 (1921)].

⁹ Hunnius and Rabe, *Ber.*, **45**, 2166 (1912).

¹⁰ Tiffeneau and Lévy, *Bull. soc. chim.*, [4] **37**, 1247 (1925); *Compt. rend.*, **183**, 969 (1926).

the reduction of the alcohol-oxime being accomplished by means of sodium. This is a valuable method and by means of it various phenylalkanolamines, up to and including phenylhexanolamine, were made. However, the ultimate yields were not very large.

In order to facilitate a more complete study of various arylalkanolamines, a search was first made for a more satisfactory method of making them, which centered itself on finding a suitable means for reducing isonitroso ketones, since the work of Slater¹¹ indicated that these intermediates could be prepared pure and in good yields. The process finally adopted has been described by one of us.¹² The isonitroso ketone was dissolved in absolute alcohol containing three equivalents of hydrogen chloride and shaken with palladinized charcoal in an atmosphere of hydrogen until saturated, whereby the ketonic group was reduced to a secondary alcohol and the oximino to a primary amine; the product was isolated as its hydrochloride, practically pure and in very good yield, by removing the catalyst, concentrating the alcoholic solution and diluting with excess ether. In the absence of hydrogen chloride the reduction was incomplete and the product was not the desired amino alcohol. Two compounds, phenylpropanolamine and *p*-tolylpropanolamine, have been prepared in this manner; others are under way and will be reported later.

Phenylpropanolamine has been known, but *p*-tolylpropanolamine, isomeric with ephedrine, is new. Pharmacologically both compounds produce effects paralleling those of ephedrine; they exert as great an effect on the blood pressure of an anesthetized dog as does the natural alkaloid and are also effective when administered orally. Their mydriatic action was found to be greater than that of either ephedrine or phenylethanolamine. Phenylethanolamine has no action when given by mouth.¹³ Both compounds had a potentiating effect when epinephrine was subsequently administered; that is, the effect of epinephrine was greatly increased.

The toxicity of phenylpropanolamine and *p*-tolylpropanolamine compared with that of natural ephedrine and phenylethanolamine¹⁴ given by Alles (ref. 2c) and Miller and Piness (ref. 13) is shown in the table.

It is seen that the phenyl derivative is less toxic and the tolyl more toxic than ephedrine. The pharmacological investigation is being continued and the results will be published later elsewhere.

Procedure

The isonitrosopropiophenone and *p*-tolyl- α -oximino-ethyl ketone were prepared from freshly distilled butyl nitrite and propiophenone and *p*-

¹¹ Slater, *J. Chem. Soc.*, **117**, 587 (1920).

¹² Hartung, THIS JOURNAL, **50**, 3370 (1928).

¹³ Miller and Piness, *J. Am. Med. Assocn.*, **91**, 1033 (1928).

¹⁴ Toxicity figures for ephedrine and phenylethanolamine given by Alles (ref. 2c) and Miller and Piness (ref. 13).

TABLE I
PHARMACOLOGICAL STUDIES

	Rats, intra-peritoneal	Minimum lethal dose, mg./kg.	Dogs, intra-peritoneal	Rabbits, intra-venous	Guinea pig, subcutaneous
Phenylpropanolamine	175	Over 500	75	600	
<i>p</i> -Tolylpropanolamine	50	Over 100	33	200	
Ephedrine	50	350	
Phenylethanolamine	30	1000	

methylpropiophenone, respectively; these were reduced as described above. The pure amino alcohols did not reduce Fehling's solution but formed with it a crystalline precipitate.¹⁵ The incompletely hydrogenated product, however, did reduce Fehling's solution, and this fact as well as the measure of the hydrogen absorbed could be used in determining the completeness of the catalytic reduction. This test is based on the observation that the oximino group is more easily reduced than the carbonyl, the remarks of Hunnius and Rabe to the contrary notwithstanding; and it is well established that in alkaline solution α -amino ketones are readily oxidized to pyrazine derivatives.¹⁶ Thus amino-acetone, in ammonia solution, is oxidized by mercuric chloride to dimethylpyrazine,¹⁷ *p*-methyl- α -amino-acetophenone to 2,5-di-*p*-tolylpyrazine;¹⁸ and α -aminopropiophenone is oxidized with methyl iodide to 3,6-diphenyl-2,5-dimethylpyrazine.¹⁹

Deamination by means of nitrous acid resulted in the formation of the original aryl alkyl ketones, identified as their semicarbazones. This is in harmony with the findings of Tiffeneau and Lévy,²⁰ who treated bases of the type ArCHOHCHRNH₂ with nitrous acid and obtained ketones of the type ArCOCH₂R. However, a peculiarity observed in connection with these deaminations was that unless the resulting product was first distilled, no semicarbazone could be isolated.

Experimental

Propiophenone and *p*-tolylethyl ketone were prepared by the regular Friedel-Crafts reaction of propionyl chloride on benzene and toluene, respectively.

Isonitrosopropiophenone was prepared from propiophenone and butyl nitrite. Slater²¹ used methyl nitrite, a gas; butyl nitrite, a liquid, was found more convenient. In a 1-liter 3-necked, round-bottomed flask, fitted with stirrer, reflux and delivery tube for hydrogen chloride, was placed a solution of 80 g. of propiophenone (0.6 mole) in 400 cc. of ether; hydrogen chloride was passed through the stirred solution at the rate of 2-3 bubbles per second, stirring and addition of acid being continued throughout the reaction; then freshly distilled butyl nitrite, b. p. 75-81°, was added through the

¹⁵ Cf. Chen, *J. Am. Pharm. Assocn.*, **18**, 110 (1929).

¹⁶ Houben-Weyl, "Die Methoden der Organischen Chemie," 3d ed., Georg Thieme, Leipzig, 1923, Vol. III, p. 402.

¹⁷ Gabriel and Pinkus, *Ber.*, **26**, 2206 (1893).

¹⁸ Reudenburg, *ibid.*, **46**, 3555 (1913).

¹⁹ Eberhardt, *Arch. Pharm.*, **258**, 107 (1920).

²⁰ Tiffeneau and Lévy, *Compt. rend.*, **183**, 970 (1926).

reflux condenser in 2-3-cc. portions until a total of 61.8 g. (0.6 mole) was added. After addition of the first portion the reaction mixture slowly became a yellow-brown and after several more minutes a light yellow color, after which a second portion was added; now the color change took place more rapidly, whereupon a third portion was added, etc. The mixture gradually warmed up and the ether began to reflux gently. The total time required for the addition of the nitrite was about ninety minutes. Stirring and bubbling of hydrogen chloride were continued for another fifteen minutes and the mixture then was allowed to stand overnight, during which time it became quite dark. The next day the ethereal solution was slowly stirred into dilute sodium hydroxide containing pieces of ice and the ethereal layer was repeatedly extracted with cold alkali until no more product was obtained. The alkaline extracts were slowly stirred into concentrated hydrochloric acid containing sufficient ice to keep the reacting mixture cold. In this manner white crystals of isonitrosopropiophenone were obtained; these were recrystallized from toluene and melted at 106.0-106.5°,²¹ yield, 71 g., or 72.5% of the theoretical. When treated with hydroxylamine (hydrochloride) in alkaline solution for several hours it formed, on acidifying, a voluminous precipitate which was recrystallized from alcohol and melted at 230.5-231.0°; this agrees with the melting point given for phenylmethylglyoxime by Gudeman and Borsche²² who prepared it from $C_6H_5C(=NOH)COCH_3$.

p-Tolyl-α-oximino-ethyl ketone was prepared after the manner described for isonitrosopropiophenone, except that 88.8 g. of *p*-tolylethyl ketone (0.6 mole) was substituted for the propiophenone; yield, 78.5 g. of the twice recrystallized isonitroso ketone, or 74% of the theoretical. The crystals, from toluene, were white flakes and melted at 125°.

Anal. Calcd. for $C_{10}H_{11}O_2N$: N, 7.91. Found: (Kjeldahl) N, 7.90.

p-Tolylmethylglyoxime, prepared as was the phenyl homolog, decomposed at 230° (uncorr.), as recorded by Gudeman and Borsche.²²

Phenylpropanolamine.—With catalyst prepared as previously described¹² from 0.5 g. of palladium chloride and 3 g. of charcoal, it was possible to reduce two portions of 9.8 g. of isonitrosopropiophenone (0.06 mole), dissolved in 150 cc. of absolute alcohol containing 7.0 g. of hydrogen chloride, to phenylpropanolamine in from 145 to 190 minutes with yields of the isolated hydrochloride from 9.4 g. to 11.0 g., or 84 to 98% of the theoretical. After recrystallization from absolute alcohol the salt melted at 191°, which is the value given by Callies⁷ and Eberhardt.⁷

The free base was obtained by treating an aqueous solution of the hydrochloride with alkali; on cooling, the liberated amino alcohol solidified and after recrystallization from water melted at 103°, which agrees with the melting point given by Hunnius and Rabe.⁹

When isonitrosopropiophenone was reduced in the absence of hydrogen chloride, the reduction proceeded very slowly and not to completion: *e. g.*, 3.3 g. of isonitroso ketone in 75 cc. of absolute alcohol absorbed in six hours 1280 cc. of hydrogen (calculated for reduction to phenylpropanolamine, 1350 cc.), but from the product there was isolated only 1.3 g. of material which melted at 108-110°; when this was mixed with known phenylpropanolamine, the melting point ranged from 70 to 80°. This product was not identified.

p-Tolylpropanolamine was obtained as the hydrochloride by reducing the *p*-tolyl-α-oximino-ethyl ketone under the conditions described for phenylpropanolamine. The hydrochloride, after recrystallization from absolute alcohol, melted at 205°.

²¹ The melting point given in Beilstein's "Handbuch," 4th ed., Vol. VII, p. 678, varies from 108 to 115°.

²² Gudeman and Borsche, *Ber.*, **40**, 740 (1907).

Anal. Calcd. for $C_{10}H_{15}ON \cdot HCl$: Cl, 17.59; N, 6.95. Found: Cl (as AgCl), 17.49, 17.62; N (Kjeldahl), 7.04.

The free base, isolated as was phenylpropanolamine, melted at 112°.

Anal. Calcd. for $C_{10}H_{15}ON$: N, 8.48. Found: N (Kjeldahl), 8.53, 8.63.

Deamination.—A solution was prepared of 6 g. of *p*-tolylpropanolamine hydrochloride (0.03 mole) in 200 cc. of water and 15 cc. of acetic acid; it was cooled to 7° and to it was slowly added a solution of 6.2 g. of sodium nitrite (0.09 mole) in 35 cc. of water; the mixture was allowed to stand at room temperature for twenty-four hours, was neutralized with sodium carbonate and extracted with ether. From about one-third of the extract the ether was allowed to evaporate spontaneously and the residue was treated in the regular way to form semicarbazone; there was no evidence of its formation. The remainder of the ethereal solution was dried and distilled. The high-boiling product formed a semicarbazone melting at 191°; mixed with known semicarbazone of *p*-tolylethyl ketone there was no change in the melting point.

Phenylpropanolamine was deaminated under similar conditions. From a fourth of the ethereal extract the ether was evaporated on the steam-bath; the residue formed no semicarbazone. From a second fourth the ether was evaporated, the residue heated to boiling but not distilled and treated to form semicarbazone; after standing for ten days a very small yield of crystals was obtained, insufficient to recrystallize. The remainder of the ethereal solution was distilled; that boiling at 210–220° formed a semicarbazone that melted at 177.5°, the semicarbazone of propiophenone.

Thus it appears that the deaminated product must be distilled before it will form a semicarbazone.

Summary

1. Phenylpropanolamine and *p*-tolylpropanolamine have been prepared by reducing the appropriate isonitroso ketones catalytically.
2. The method appears to be of general application and is being extended.
3. The two compounds discussed show physiological activity paralleling that of ephedrine. Further pharmacological studies are being made.

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THE ALIPHATIC DIOLEFINS. II. THE PREPARATION AND SOME PHYSICAL CONSTANTS OF Δ -1,5-HEXADIENE

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In connection with some previous work on Δ -1,5-hexadiene,² it was noticed that great confusion existed among the physical constants recorded in the literature. Accordingly, the hydrocarbon was made from two different sources and the following accurate concordant constants were determined: boiling point, d_t/d_p , melting point, density and refractive index.

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² Cortese, *Ber.*, **62**, 504 (1929).