Anal. The substance was rendered anhydrous by heating for two hours at 130 to 140°.[13] 2.8328 g. was thus obtained from 3.1430 g. of air-exposed material. Subs. (anhydrous), 0.3467: 10.5 cc. of 0.2 *N* HCl; 0.3892: 11.8 cc. of 0.2 *N* HCl. Calcd. for $C_{16}H_{12}O_4N_2S$ (free acid of Orange I): N, 8.54. Found: N, 8.50, 8.51.

The loss of water on drying at 130 to 140° (see above) corresponds to two molecules of water of crystallization. In the air this water is taken up again. The figure obtained for the nitrogen content confirms the non-existence of the N-alkyl derivatives of Slotta and Franke.[14]

Summary

1. The alkylation of Orange I takes a normal course.

2. The theoretical deductions of Slotta and Franke rest on a false foundation and are, therefore, of no value.

[13] Below this temperature the water of crystallization is but incompletely removed.

[14] The analytical figures given in this paper have been determined by Mr. Daniel Sassi.

SUMMIT, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SHARP AND DOHME, INC.]

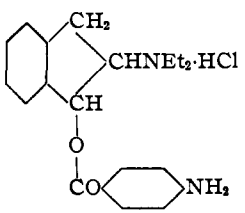
AMINO ALCOHOLS. VIII. BENZOIC ESTERS OF ARYLALKANOLAMINES

BY WALTER H. HARTUNG, JAMES C. MUNCH AND ERNEST B. KESTER

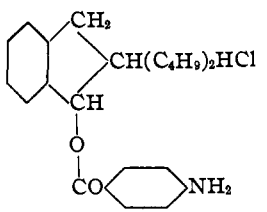
RECEIVED NOVEMBER 3, 1931 PUBLISHED APRIL 6, 1932

In the administration of local anesthetics such as procaine, epinephrine is often given simultaneously. The purpose of the latter is to constrict the blood vessels and thus prevent too rapid absorption of the desensitizing agent and to localize the anesthesia produced.[1] The ideal anesthetic would combine in a single molecule, and in proper ratio, both the desensitizing and vaso-constricting actions.

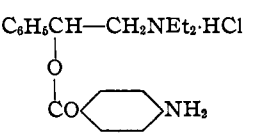
Attempts to prepare such a compound have previously been made. Marvel and du Vigneaud[2] prepared two α-hydroxyhydrindene derivatives (I and II) and phenylprocaine (III). None of the compounds had any pressor action, and I and II showed only a very slight anesthetic



I



II

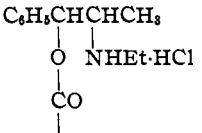


III

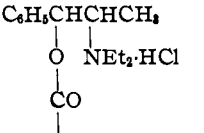
[1] Sollmann, "Manual of Pharmacology," Saunders, Philadelphia, 1926, 3d ed., p. 329; Hatcher and Eggleston, *J. Pharmacol.*, **8**, 385 (1916); Eggleston and Hatcher, *ibid.*, **13**, 433 (1919).

[2] Marvel and du Vigneaud, THIS JOURNAL, **46**, 2093 (1924).

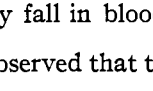
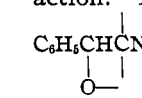
action. Kubota[3] found that allocaines S (IV) and A (V) are strongly anesthetic and that their effect on the circulatory system was to produce



Allocaine S
IV



Allocaine A
V

a primary fall in blood pressure followed by a rise to above normal. It will be observed that they contain the linkage  , an anesthesiophore group, and hence each might be expected to possess local anesthetic action. Each substance also contains a phenylethanolamine skeleton,  , a favorable condition for pressor activity; although there is still no available evidence regarding the pressor effect of the β-aminohydrindene residues of I and II. However, one would hardly expect these substances to have much (if any) effect on the circulation, even if no allowance is made for the effect on the pressor activity produced by benzoylation of the alcoholic hydroxyl, because the alkyl groups substituted on the amino nitrogen are of such a character and magnitude as to influence adversely the pressor action.[4] Chen, Wu and Henriksen and Schaumann conclude that, in general, the primary amines of the ephedrine type are more active and less toxic than the alkylated amines. Accordingly primary amines corresponding to III, IV and V ought to preserve maximum pressor activity unless it is destroyed by esterification.

Wolfheim[5] has prepared the benzoic ester of phenylethanolamine (VI) but he made no mention of its physiological properties. In the light of our results we should expect it to be both a pressor and anesthetic. Recently Tiffeneau described the benzoic ester of phenylbutanolamine (VIII) as approaching cocaine in anesthetic potency, results which we have verified.[6] Tiffeneau made no mention of other physiological properties and probably it would not be a pressor, since the unesterified phenylbutanolamine is relatively inactive on the circulatory system.[4b,7]

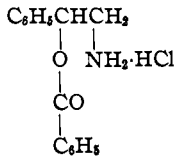
[3] Kubota, *J. Pharmacol.*, **12**, 361 (1919).

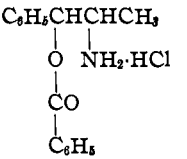
[4] (a) Barger and Dale, *J. Physiol.*, **41**, 19 (1910); (b) Chen, Wu and Henriksen, *J. Pharmacol.*, **36**, 363 (1929); (c) Schaumann, *Arch. exptl. Path. Pharmakol.*, **157**, 114 (1930); (d) Ehrhart, *Metallbörse*, **20**, 1800 (1930).

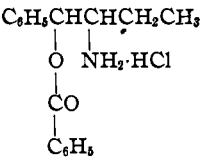
[5] Wolfheim, *Ber.*, **47**, 1440 (1914).

[6] Lévy, "Essais et Dosages Biologiques des Substances Medicamenteuses," Masson et Cie, Paris, 1930, p. 132.

[7] Hartung, Munch, Deckert and Crossley, THIS JOURNAL, **52**, 3317 (1930).


VI


VII


VIII

To determine the effect of esterification of the alcoholic hydroxyl group of an active pressor, we prepared and examined the benzoic ester of phenylpropanolamine (VII). Pharmacological tests with this compound indicate that as an anesthetic it approaches cocaine in potency, and also that it produces a rise in blood pressure when given intravenously to anesthetized dogs. So far as the authors are aware this is the first compound with a demonstrated pressor and anesthetic action. The only other compound which might be considered as having a similar pharmacodynamic behavior is cocaine.[8] Given in small doses, it selectively stimulates the vaso-motor center and also sensitizes the sympathetic nervous system to the action of the epinephrine in circulation.[9] Large doses paralyze the center, causing a marked fall in blood pressure and leading to collapse.

In Table I is given a summary of the behavior of the benzoic ester of phenylpropanolamine hydrochloride; other active substances are included to permit ready comparison.

TABLE I

COMPARATIVE PHYSIOLOGICAL BEHAVIOR

Compound as HCl salt	M. L. D. mg./kg. intravenous to rabbits	Local anesthesia: Dogs subcutaneous mg./dog	Local anesthesia: Rabbit cornea minutes duration after 1 mg.	Relative pressor action
Benzoic ester of phenylpropanolamine	20	20	13	1
Phenylpropanolamine	75	0	0	10+
Cocaine	7.7[b]	6[a]	30	See text
Procaine	30[b]	70[a]	30	

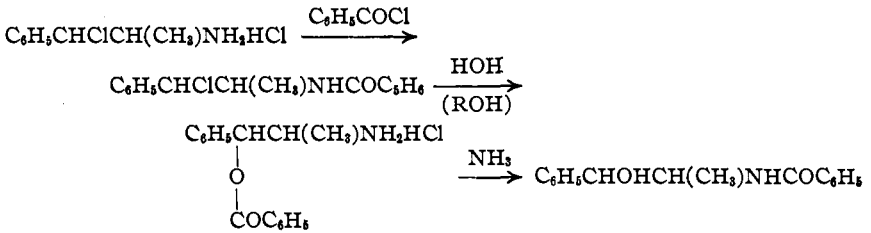
[a] Munch, "Bioassays," Williams and Wilkins Co., Baltimore, Md., 1931, p. 65.
[b] Roth, Hygienic Lab. Bull., **109**, 43 (1917).

Synthesis

The benzoic ester of phenylpropanolamine hydrochloride was prepared after the method described by Wolfheim[5] for the synthesis of esters of phenylethanolamine. This procedure is indicated as follows

[8] Sollmann, Ref. 1, p. 333.

[9] Meyer and Gottlieb, "Experimental Pharmacology," Lippincott, Philadelphia, 1926, p. 139; Paulsson, "Heffters Handbuch der Experimentelle Pharmakologie," Julius Springer, Berlin, 1920, Vol. II, p. 138.



Phenyl-1-amino-2-chloro-1-propane, as its hydrochloride, has already been described.[10]

Phenyl-1-chloro-1-benzoylamino-2-propane.—Eight and one half grams of the phenylaminochloropropane hydrochloride was shaken with a mixture of 17 g. of benzoyl chloride, 90 ml. of water, 90 ml. of ether and 90 ml. of a 10% solution of sodium hydroxide. After the reaction had ceased the ethereal layer was drawn off and allowed to evaporate; the crystalline residue was purified by forcing it out of benzene solution with excess ligroin; in this manner 10.2 g. (calcd. 11.3 g.) of the N-benzoyl product was obtained. It began to sinter at 122° and melted at 125° (corr.).

Anal. Calcd. for $C_6H_5CHClCH(CH_3)NHCOC_6H_5$: N, 5.12. Found: N (Kjeldahl), 4.81.

Benzoic Ester of Phen lpropanolamine Hydrochloride.—The most satisfactory procedure for rearranging the N-benzoyl derivative just described was to dissolve 5.8 g. of it in a solution of 40 ml. of *sec.*-butyl alcohol and 5 ml. of water; this solution was then heated in a beaker on an electric hot-plate until it had evaporated to about half its original volume and was then diluted with excess ether (isopropyl ether was found highly satisfactory); this forced out 3.4 g. of crystals. By evaporating the mother liquors and repeatedly boiling the residues in the dilute *sec.*-butyl alcohol and forcing out with ether, it was possible to obtain an ultimate yield of 72% of the ester. The crystals were purified by forcing out of an absolute alcoholic solution with ether; m. p. 208° (corr.).

Anal. Calcd. for $C_6H_5CH(OCOC_6H_5)CH(CH_3)NH_2 \cdot HCl$: Cl, 12.16. Found: Cl (as AgCl), 11.86.

This ester is stable in solution only in the form of its salt. An aqueous solution of the hydrochloride treated with ammonia causes the benzoyl group to shift from the oxygen to the nitrogen, and the N-benzoyl derivative of phenylpropanolamine precipitates, m. p. 142-143°.[11] This new rearrangement was to be expected, for Wolfheim observed a parallel behavior with his ester.

After the experimental work had been completed it was observed that Kanao[12] had already described a benzoic ester of phenylpropanolamine. He obtained his product by boiling N-benzoyl-nor-*dl*-ephedrine, m. p. 143° (the N-benzoyl derivative of phenylpropanolamine) with concentrated hydrochloric acid, which caused the benzoyl group to shift from the nitrogen to the oxygen, and the resulting ester (as hydrochloride) melted at 220°. When this was treated with ammonia the benzoyl shifted back onto the nitrogen, just as one would expect, and the N-benzoyl compound reformed. However, this time it did not melt at 143°, as did the original

[10] Hartung and Munch, THIS JOURNAL, **53**, 1875 (1931).

[11] Schmidt, *Arch. Pharm.*, **255**, 147 (1917).

[12] Kanao, *J. Pharm. Soc. Japan*, **48**, 1070 (1928); German abstract, *ibid.*, p. 145.

material, but at 128°. By comparing the ester and the final N-benzoyl substance with known products Kanao was able to identify both as derivatives of nor-*dl*-ψ-ephedrine. In other words, in all this process phenylpropanolamine had undergone a shift in configuration and into the pseudo form. From his results Kanao was led to believe that the ester can exist only when the amino alcohol is in this configuration. While we have as yet made no studies with the possible stereoisomers of our compounds, it would appear that our ester is of the nor-ephedrine type, for not only has it a melting point different from that found by Kanao, but the amide resulting from the rearrangement of the ester (m. p. 142–143°) is the N-benzoyl derivative of nor-*dl*-ephedrine.

Summary

1. The synthesis of the benzoic ester of phenylpropanolamine hydrochloride has been described. This synthesis presumably does not result in isomerization into the pseudo configuration.

2. This ester is structurally related to pressors and anesthetics.

3. Benzoylation of the alcoholic hydroxyl conferred anesthetic properties but caused a decrease to a tenth or less of the pressor potency.

4. This is the first compound to possess a demonstrated pressor and anesthetic action.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

NITROSO COMPOUNDS. I. (PRELIMINARY PAPER.) THE PREPARATION AND REDUCTION OF CERTAIN NITROSO KETONES

BY JOHN G. ASTON, DAVID F. MENARD AND M. GLENN MAYBERRY

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Introduction

The present paper deals with the preparation of α-nitroso ketones of the type, $(CH_3)_2C(NO)COCH_2R$, by the action of ethyl nitrite upon the corresponding ketones. The reduction of these α-nitroso ketones has also been studied with quite unexpected results.

The direct nitrosation of ketones upon an α-methylene group is a general reaction

$$RCH_2COR' + R''ONO \xrightarrow[C_2H_5ONa]{HCl} RC(=NOH)COR' + R''OH$$

The product of nitrosation in such cases is invariably the oxime.[1]

[1] Claisen and Manasse, *Ber.*, **22**, 526 (1889); Ponzio and DeGaspari, *J. prakt. Chem.*, [2] **58**, 392 (1896).