BF_4^- tetrahedra and Rb^+ or NH_4^+ ions. A regular BF_4^- tetrahedron with B-F = 1.43 Å., is assumed in order to determine the eleven parameters of the structure. The rubidium ions are first placed approximately by neglecting the scattering of the other much lighter atoms; these are then assigned parameter values which lead to a generally acceptable agreement between calculated and observed intensities of x-ray reflections. An identical assignment of parameter values in ammonium fluoborate leads to only fair agreement between calculated and observed intensities; these are much improved by the introduction of small distortions which may be interpreted as a tendency toward the formation of hydrogen bonds between nitrogen and fluorine.

STANFORD UNIVERSITY, CALIF.

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[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORY OF THE UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. VII. Procaine Analogs, Part I

BY DAVID E. ADELSON, L. G. MACDOWELL AND C. B. POLLARD

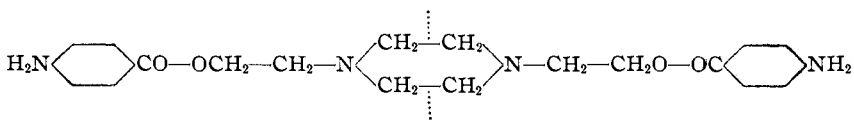
Considerable work has been done in the field of alkyl *p*-aminobenzoates to ascertain the relationship between chemical constitution and physiological action. Such investigations have included the preparation of procaine analogs containing dissimilar alkylamino groups,[1] aliphatic and aryl aliphatic acids in the place of *p*-aminobenzoic acid[2] and unsaturated groups in the side chain of the acids.[2] Other studies have shown the effect of increase in the length of the carbon chain of the alkyl group and the effect of branched-chain alkyl derivatives in the procaine series.[3] Soderman and Johnson[4] and Roberts and Johnson[5] have studied procaine analogs containing different aromatic acids. Numerous other investigations, far too extensive to list here, have been carried out to determine the effect of increasing molecular weight on the anesthetic properties of compounds of the procaine type.

The purposes of the present investigation were (1) to study the effect of cyclic diamines, such as piperazine, and various types of aliphatic secondary amines on the therapeutic properties of the procaine molecule, (2) to determine the effects thus produced by the increased nitrogen content of the molecule and (3) to devise a simple method for obtaining piperazino-1,4-bis-(β-ethanol) in good yield.

(1) Brill, THIS JOURNAL, **54**, 2484 (1932).
(2) Brill and Bulow, *ibid.*, **55**, 2059 (1933); Brill and Cook, *ibid.*, **55**, 2062 (1933).
(3) Adams, Rideal, Burnett, Jenkins and Dreger, *ibid.*, **48**, 1758 (1926).
(4) Soderman and Johnson, *ibid.*, **47**, 1390 (1925).
(5) Roberts and Johnson, *ibid.*, **47**, 1396 (1925).

Pyman[6] has prepared the latter compound in 41% yield from piperazine and 2-chloroethanol. The present workers have prepared piperazino-1,4-bis(β-ethanol) in quantitative yield by a method analogous to that used by Horne and Shriner[7] in the preparation of β-diethylaminoethanol.

It is apparent that the di-*p*-aminobenzoate of piperazino-1,4-bis-(β-ethanol) is in reality a "double" procaine molecule. If the molecule is split into symmetrical halves as indicated by the dotted lines, it is logical to consider the molecule as



being composed of two similar parts, each of which has a smaller molecular weight than procaine. The percentage of nitrogen in procaine is 11.86, whereas the di-*p*-aminobenzoate of piperazino-1,4-bis-(β-ethanol) contains 13.59% N. Hence the new molecule contains more nitrogen per unit molecular weight than procaine and in addition possesses a cyclic diamino linkage. It will be interesting to learn the modifications which these two effects will produce in the therapeutic properties of procaine.

Experimental

Piperazino-1,4-bis-(β-ethanol).—Twenty-one grams of anhydrous piperazine[8] was dissolved in an equal weight of boiling methanol contained in a flask fitted with a condenser. A stream of ethylene oxide was passed into the solution until the theoretical quantity had been absorbed.

(6) Pyman, *J. Chem. Soc.*, **93**, 1793 (1908).
(7) Horne and Shriner, THIS JOURNAL, **54**, 2925 (1932).
(8) Pollard, Bain and Adelson, *ibid.*, **57**, 199 (1935).

The heat of reaction was sufficient to keep the solution at reflux temperature. Upon cooling the addition compound crystallized out, yield 42 g. (98%). Piperazine-1,4-bis-(β-ethanol) crystallizes from amyl acetate in large prisms which melt at 135–135.5°.

Anal. Calcd. for $C_8H_{18}N_2O_2$: N, 16.09. Found: N, 16.07.

Di-*p*-nitrobenzoate of Piperazino-1,4-bis-(β-ethanol).—This compound is prepared in 50% yield from the above by treatment with *p*-nitrobenzoyl chloride in cold alkaline solution. Recrystallization from xylene gives small yellow granules which melt at 158–158.5°.

Anal. Calcd. for $C_{22}H_{24}N_4O_8$: N, 11.86. Found: N, 11.74.

Di-*p*-aminobenzoate of Piperazino-1,4-bis-(β-ethanol).—Reduction of the di-*p*-nitrobenzoate with a large excess of powdered iron[3] followed by extraction with hot xylene yields this compound. It is purified by solution in dilute hydrochloric acid followed by reprecipitation with dilute alkali and recrystallization from xylene as silky needles, m. p. 203–204°.

Anal. Calcd. for $C_{22}H_{28}N_4O_4$: N, 13.59. Found: N, 13.55.

The tetrahydrochloride of the di-*p*-aminobenzoate of piperazino-1,4-bis-(β-ethanol) is prepared by dissolving the free base in dilute acid and evaporating the solution *in vacuo* at room temperature. The crystals thus formed are very hygroscopic and must be oven-dried prior to analysis. The compound is stable in boiling water.

Anal. Calcd. for $C_{22}H_{32}N_4O_4Cl_4$: N, 10.04. Found: N, 9.83.

Summary

1. Piperazino-1,4-bis-(β-ethanol) has been prepared in good yield. From it have been synthesized the di-*p*-nitrobenzoate, the di-*p*-aminobenzoate and the tetrahydrochloride of the latter.

2. The therapeutic properties of the tetrahydrochloride of the di-*p*-aminobenzoate of piperazino-1,4-bis-(β-ethanol) will be investigated.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, VIRGINIA MILITARY INSTITUTE]

Normal Fatty Acid Amides of Ethylenediamine

BY N. BEVERLEY TUCKER[1]

The purpose of the work herein reported was to record the physical properties, chiefly the melting points, of the normal fatty acid diamides of ethylenediamine. The amides were all prepared alike, *i. e.*, the diamine was boiled for forty-eight hours with the calculated double molar quantity of the ethyl ester of the desired acid. The resulting solid product was recrystallized to constant melting point, the lower members to the butyric from a mixture of ethyl acetate and alcohol, others from absolute alcohol. The first six members of the series were examined under the polarizing microscope, and their solubilities in three solvents were measured. Results are summarized in the tables.

The diacetyl,[2] dipropionyl and dibutyryl[3] derivatives, as well as several related compounds, have been reported.[3,4]

TABLE I

MELTING POINTS AND SOLUBILITIES

(Melting points were measured with complete stem immersion to eliminate stem correction)

Derivative	M. p.	Solubility at 25°C. in g./100 cc. Water	Abs. EtOH	Et. acetate	N, % Calcd.	Found
C_2	173–173.5	68.3	13.1	0.25	19.4	...
C_3	189.0	40.8	13.8	.26	16.27	16.22
C_4	191–191.3	4.78	13.7	.28	14.00	13.69
C_5	183.0	0.35		.48	12.28	...
C_6	177–177.3	.02	6.48		10.94	11.18
C_7	171.5	Too small	2.49	.11	9.80	9.82

Melting points of higher members of the series: C_8, 169–169.5; C_{10}, 164.0; C_{11}, 160.5; C_{12}, 159.0; C_{13}, 156–156.4; C_{14}, 154.5; C_{15}, 153.0; C_{16}, 148.5; C_{17}, 149.5–150.

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Results of Experiments

In the tables, derivatives of ethylenediamine of the general formula $C_2H_4(NHCOR)_2$, where R is straight chain, are designated as the C_n derivative, where n = the total number of carbon atoms in the acid.

Grateful acknowledgment is made of the assistance of Professor E. Emmet Reid. The writer also wishes to thank Professor Edward Steidtmann for assistance in measuring crystal properties.

(2) Hofmann, *Ber.*, **21**, 2332 (1888).

(3) Klingenstein, *ibid.*, **28**, 1173 (1895); Chattaway, *J. Chem. Soc.*, **87**, 381 (1905).

(4) Windaus, Dörries and Jensen, *Ber.*, **54**, 2745 (1921); Rosenmund, U. S. Patents 1,926,014 and 1,926,015.