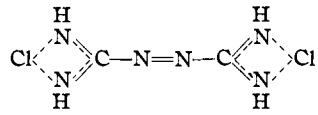
ture of such compounds is inadequate. Thus in the structural formula of azochloramid given above, the chlorine was arbitrarily bound to the imino group with the realization that such a picture as the following would probably convey a much closer idea of the properties of the compound.



Acknowledgment is made of many helpful suggestions received from Dr. Wm. Mansfield Clark of Baltimore, Dr. William Gump of Trudeau, Dr. Leonor Michaelis and Dr. Harry Sobotka of New York City. Dr. H. B. Glass has participated in some of the experimental work cited above.

Summary

1. A method of preparing N,N′-dichloroazodicarbonamidine from azo-dicarbonamidine or hydrazo-dicarbonamidine salts has been described. Solubility data together with other physical properties of the compound and reactions which can be used for its detection and estimation have been given.

2. Methods of reducing azochloramid to azo-dicarbonamidine or hydrazo-dicarbonamidine and the formation of a derivative of azo-dicarbonamidine containing a sulfonic group in anhydrized linkage have been described and evidence offered for the structure of the latter compound.

3. Some of the factors underlying the stability of N-chloro compounds have been discussed.

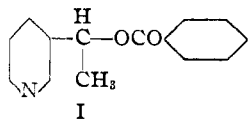
BELLEVILLE, N. J. RECEIVED APRIL 26, 1934

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

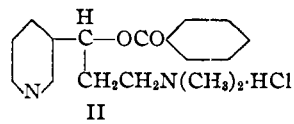
A Pyridyl Dimethylaminopropyl Benzoate[1]

BY JOHN M. SNELL AND S. M. MCELVAIN

In a previous paper[2] the benzoate and *p*-aminobenzoate of β-pyridylmethylcarbinol were described. Both of these compounds, in the form of their hydrochlorides, show extremely low intravenous toxicities to white rats and, while the *p*-aminobenzoate is inactive for surface anesthesia, the benzoate (I) produces a longer duration of anesthesia of the rabbit's cornea than does cocaine. This benzoate, however, causes considerable irritation of the rabbit's eye, an effect which, it seemed, might possibly be ascribed to the acidity of the salt of such a weak base. For this reason it was thought that the introduction of another basic group into the molecule would sufficiently neutralize the acidity of the salt to make it considerably less irritating. Work in this direction has resulted in the synthesis of β-pyridyl-β-dimethylaminoethylcarbinyl benzoate. It was isolated in the form of its monohydrochloride (II).

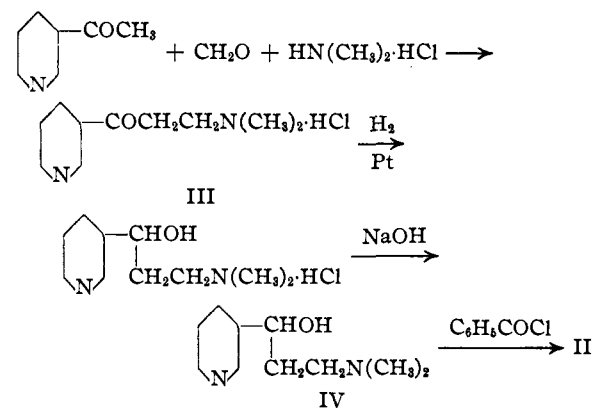


I



II

The compound II was prepared by the application of the Mannich reaction[3] to β-acetylpyridine, the reduction of the resulting amino ketone (III) to the corresponding carbinol (IV), and finally the benzoylation of this carbinol to produce the desired compound (II). These reactions are illustrated thus



Pharmacological Report.—The compound II is being studied pharmacologically by Mr. Charles L. Rose of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A preliminary report of its pharmaco-

(1) This work was supported in part by a grant from the Wisconsin Alumni Research Foundation.

(2) Strong and McElvain, THIS JOURNAL, **55**, 816 (1933).

(3) Mannich, *et al.*, *Arch. Pharm.*, **255**, 261 (1917); **265**, 589 (1927).

logical properties is given in the following table. For comparison the corresponding values for the β-pyridylmethylcarbinyl benzoate (I), procaine and cocaine are included in the table. The durations of anesthesia were determined by topical application of a solution of the anesthetic to the rabbit's cornea; the toxicity determinations were intravenous to white rats.

PHARMACOLOGICAL DATA

Compound	Av. duration of corneal anesthesia Min.	% Soln.	Intravenous toxicity (mg. kg.) M. L. D.	Irritation
I	43	1	100	Severe
II	13	1	38	Negligible
Procaine	0	2	40	Negligible
Cocaine	29	2	17.5	Negligible

It is apparent that the substitution of the $-CH_2N(CH_3)_2$ group for one of the hydrogen atoms of the methyl group of I lowers considerably the anesthetic efficiency and increases the intravenous toxicity. In spite of these undesirable changes in pharmacological properties, compound II compares quite favorably to procaine and cocaine as a local anesthetic. But it should be noted that the introduction of this additional basic group into I did have the intended effect of practically completely destroying the irritating properties associated with the latter structure.

Experimental

β-Pyridyl-β-dimethylaminoethyl Ketone Hydrochloride (III).—A mixture of 40 g. of freshly distilled β-acetylpyridine,[2] 8 g. (0.1 mole) of dimethylamine hydrochloride, 3 g. (0.1 mole) of paraformaldehyde and 15 cc. of absolute alcohol was heated on the steam-bath under a reflux condenser with occasional shaking until all the paraformaldehyde had dissolved. The time required was two to three hours. The clear brown solution was cooled and treated with absolute ether until quite turbid, then allowed to stand overnight in a cold place. The crystals which separated were filtered off with suction and washed with acetone. A yield of 5.5–6 g. of the keto-amine hydrochloride was obtained in the form of light yellow crystals which were sufficiently pure for reduction. Recrystallized from 95% ethyl alcohol, the compound formed white needles melting sharply at 163.5–164°. Calcd. for $C_{10}H_{15}ON_2Cl$: C, 55.93; H, 6.90; Cl, 16.55. Found: C, 55.60; H, 7.17; Cl, 16.79.

The dihydrochloride of this amino ketone melts at 178.5–180°. Calcd. for $C_{10}H_{16}ON_2Cl_2$: Cl, 28.29. Found: Cl, 28.30.

The free base was found to be unstable, splitting off dimethylamine and leaving a non-volatile tar when an attempt was made to distil it.

The filtrate from the crude product was diluted with 200 cc. of ordinary ether. After standing for some time the ether solution was decanted from the oily precipitate and distilled. In this manner 27 g. of β-acetylpyridine was recovered. The yield of product (III) based on the β-acetylpyridine which was not recovered was 24% of the theoretical.

β-Pyridyl-β-dimethylaminoethylcarbinol (IV).—A solution of 22 g. (0.1 mole) of the crude keto-amine salt (III) was made in 100 cc. of water, and the solution filtered from the small amount of insoluble wax-like solid. The clear solution was added to a suspension of platinum black prepared by shaking about 0.3 g. of Adams platinum oxide catalyst and 10–15 cc. of water in an atmosphere of hydrogen. (The platinum oxide does not reduce readily in the presence of the amine salt.) The solution and catalyst were then shaken under 1–3 atmospheres of hydrogen until the hydrogen pressure in the apparatus remained constant. The time required for the reduction was five to six hours and about 1.3 equivalents of hydrogen were absorbed. The solution was then decidedly alkaline. Apparently some reduction of the pyridine ring occurred, and the resulting basic piperidine derivative inactivated the catalyst. The platinum was recovered by filtration, and the water was removed from the filtrate by evaporation on the steam-bath. The residue was dissolved in 95% alcohol and the resulting solution evaporated to dryness on the steam-bath. The glassy non-crystalline residue was dissolved in absolute alcohol, filtered to remove any remaining platinum, and treated with the calculated amount of a standard solution of sodium hydroxide in absolute alcohol required to liberate the free base. The precipitated sodium chloride was filtered off and washed with absolute alcohol. The filtrate and washings were distilled until the alcohol was removed. The distillate contained some dimethylamine, doubtless from decomposition of some unreduced keto-amine. The residue contained some water and alcohol which caused excessive frothing when vacuum distillation was attempted. In order to remove these materials an equal volume of toluene was added to the residue and distilled from it. The residue was then distilled under reduced pressure; 8 g. of yellow viscous liquid distilled over between 110 and 145° (2 mm.) and about 8 g. of tarry residue remained in the flask. The distillate was carefully fractionated through a small Widmer column and the portion coming over below 140° (3 mm.) discarded. About 5 g. of pale yellow viscous liquid distilled over at 140–143° (3 mm.). The yield was 36% of the theoretical. This carbinol readily forms a hydrate, and a small amount of water renders it completely insoluble in ether or benzene.

The monohydrochloride was not obtained crystalline, but the dihydrochloride, formed by saturating an anhydrous ether solution of the free base with anhydrous hydrogen chloride, formed white hygroscopic needles melting at 148–149°. It may be recrystallized from absolute alcohol or better from *n*-butyl alcohol. Calcd. for $C_{10}H_{18}ON_2Cl_2$: Cl, 28.06. Found: Cl, 28.10%.

β-Pyridyl-β-dimethylaminoethylcarbinyl Benzoate Hydrochloride (II).—Attempted benzoylations of both the aminocarbinol and its dihydrochloride in toluene, chloroform, and excess benzoyl chloride were quite unsuccessful. A small yield of the benzoate was obtained by carrying out the reaction in hexone (methyl isobutyl ketone). The following procedure was found to be the most satisfactory.

A solution of 1.8 g. (0.01 mole) of the carbinol base (IV) in 10 cc. of absolute ether and a similar solution of 1.4 g. (0.01 mole) of freshly distilled benzoyl chloride were poured together in a large Pyrex test-tube. An insoluble white addition compound was immediately formed, the heat of reaction causing the ether to boil. The test-tube was placed in a steam-bath and the ether boiled off. The residue darkened slightly and melted to a viscous liquid. Heating in the steam-bath was continued for one hour under reduced pressure, for three hours under atmospheric pressure. Moisture was excluded by means of a calcium chloride tube. The contents of the tube, now a solid crystalline mass, were dissolved in boiling hexone containing a little absolute alcohol. On cooling the solution a mass of white crystals slowly formed. The crystals were filtered off and recrystallized twice from pure hexone, the gummy insoluble portion being discarded. One gram of the pure benzoate hydrochloride was thus obtained. It melted at 162.5–163°. An additional 0.25 g. was obtained by concentrating and cooling the mother liquors and recrystallizing the product that separated. The yield of pure benzoate hydrochloride, calculated from carbinol base used, was 39% of the theoretical.

This hydrochloride is very soluble in water, ethyl alcohol, and *n*-butyl alcohol but only slightly soluble in acetone. It may be recrystallized from pure acetone or acetone containing a little ethyl alcohol, but is best purified by recrystallizing from hexone. It is not hygroscopic.

An apparently polymorphic form of this hydrochloride melting at 151.5–152.5° was obtained the first time it was prepared. The presence of a trace of the high melting form raised the melting point to 163°. The low-melting form was converted into the high melting form by recrystallization from hexone and seeding with a trace of the high melting form. Calcd. for $C_{17}H_{21}N_2O_2Cl$: C, 63.63; H, 6.60; Cl, 11.08. Found: C, 63.77; H, 6.66; Cl, 10.99.

Summary

The preparation and properties of β-pyridyl-β-dimethylaminoethylcarbinyl benzoate hydrochloride and certain incidental compounds are described.

This benzoate is an effective local anesthetic and its pharmacological properties are compared to those of procaine, cocaine and the previously described β-pyridylmethylcarbinyl benzoate hydrochloride.

MADISON, WISCONSIN RECEIVED APRIL 30, 1934

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reduction of Cyanides

BY L. A. WALTER AND S. M. MCELVAIN

In an attempt to reduce α-phenyl-ϑ-phenoxybutyl cyanide to the corresponding amine with sodium and alcohol[1] an excellent yield of ϑ-phenylbutyl phenyl ether with only a trace of the expected primary amine was obtained. This halogen-like behavior of the cyanide group suggested a further study of the reduction of cyanides in order to ascertain the effect of structure on the extent of the two competing reactions

$$\text{RCN} + \text{reduction (Na in } C_2H_5OH) \begin{cases} \nearrow \text{RH} + \text{NaCN} & (1) \\ \searrow \text{RCHNH}_2 & (2) \end{cases}$$

The present paper reports the results obtained from the reduction of nine cyanides of varying structure. The amount of reaction (1) was determined by a Volhard titration of an aliquot of the water-soluble portion of the reaction mixture; in a few cases the cleavage product (RH) was isolated and found to correspond in amount to the cyanide ion found by titration. The extent of reaction (2) was determined by isolating and weighing the primary amine. In each reduction the ratio of cyanide to sodium was 0.25 mole to 1.5 atoms.

(1) Adams and Marvel, THIS JOURNAL, **42**, 315 (1920).

The results obtained are summarized in Table I.

TABLE I

PRODUCTS FROM THE REDUCTION OF CYANIDES

Run	RCN, R is	Yield of NaCN, %	Yield of RH, %	Yield of RCH_2NH_2, %
1	n-C_4H_9	16	..	76
2	$(CH_3)_2CH$	24	..	63
3	$(CH_3)_3C$	33	..	60
4	n-C_3H_7, n-C_4H_9, CH	6	..	64[a]
5	n-C_3H_7, $(n$-$C_4H_9)_2$, C	10	7	54[a]
6	C_6H_5	84	..	7
7	$C_6H_5CH_2$	88	..	10
8	C_6H_5, $C_6H_5O(CH_2)_3$, CH	91	89[b]	5
9	$(CH_3)_2$, $C_5H_{10}N$, C[c]	61	33[d]	23[a]

[a] This amine is described in Table II. [b] ϑ-Phenylbutyl phenyl ether, see Table II. [c] In addition to the products shown in the table a 21% yield of piperidine and an 11% yield of isobutylamine were obtained. Considering the yield of the latter compound it is apparent that 95% (61 + 23 + 11) of the original cyanide was accounted for. [d] Isopropylpiperidine, *cf.* Drake and McElvain, THIS JOURNAL, **55**, 1155 (1933), Ref. 5.