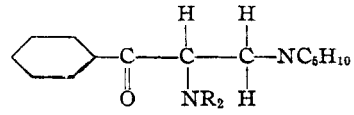
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS COLLEGE OF PHARMACY]

β-Piperidino-α-di-n-alkylaminopropiophenone Dihydrobromides

BY H. L. DAVIS

N-Piperidinomethyl phenyl ketone[1] and β-N-piperidinoethyl phenyl ketone[2] have been shown to possess local anesthetic activity. The following experiments were undertaken to prepare propiophenones having the structure



(R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11})

and to determine whether these compounds would have a vaso-pressor action and local anesthetic activity.

β-N-Piperidino-α-dimethylaminopropiophenone, β-N-piperidino-α-diethylaminopropiophenone and β-N-piperidino-α-di-n-propylaminopropiophenone were not isolated but were obtained as their dihydrobromides. The latter were formed by preparing an ether solution of the corresponding β-bromo-α-di-n-alkylaminopropiophenone, to which was added the required amount of piperidine, the precipitated piperidine hydrobromide was filtered off and an absolute alcohol solution of hydrogen bromide was added to the filtrate. The corresponding dihydrobromide precipitated immediately.

β-N-Piperidino-α-di-n-butylaminopropiophenone and β-N-piperidino-di-n-amylaminopropiophenone dihydrobromides could not be prepared. The addition of an absolute alcohol solution of hydrogen bromide to precipitate either dihydrobromide caused the separation of an oil from which only piperidine hydrobromide and the corresponding di-n-alkylamine hydrobromide could be isolated and which decomposed to a tarry mixture under vacuum distillation.

The β-bromo-α-di-n-alkylaminopropiophenones were separated and identified as their hydrobromides. These hydrobromides were prepared by treating β,α-dibromopropiophenone in absolute alcohol or in dry ether solution with the appropriate di-n-alkylamine, and the precipitated di-n-alkylamine hydrobromide was filtered off. After the addition of an absolute alcohol solution of hydrogen bromide to the filtrate, the hydrobromide of the corresponding β-bromo-α-di-n-alkylaminopropiophenone separated as a white, crystalline solid.

β-Bromo-α-dimethylaminopropiophenone hydrobromide and β-bromo-α-diethylaminopropiophenone hydrobromide formed 1,3-diphenylpyrazole when treated with phenylhydrazine.

A 2% solution of each of the three β-N-piperidino-α-di-n-alkylaminopropiophenones dihydrobromides was instilled into a rabbit's eye[3] and showed no observable local anesthetic action. A 1% solution of each of these three ketones was injected intravenously into a dog[3] and showed no vaso-pressor action and no observable toxicity.

Experimental Part

α,β-Dibromopropiophenone.—This ketone was prepared by following the method of Kohler[4] with these differences: the allyl alcohol was prepared by the method described in "Organic Syntheses."[5] The solution obtained after completion of the oxidation of the α,β-dibromopropyl alcohol was allowed to stand overnight and the α,β-dibromopropionic acid crystallized in small white crystals. The mixture was filtered through asbestos and yielded a product sufficiently pure for the preparation of the acid chloride, yield 81%. The method of E. Fischer[6] served best to prepare the acid chloride. By ether extraction of the aqueous solution obtained from the Friedel–Crafts reaction the α,β-dibromopropiophenone was obtained in 98% yield. Crystallized from alcohol this ketone melted 55–56°.[7]

Preparation of the Hydrobromides of the β-Bromo-α-di-n-alkylaminopropiophenones.—In absolute ether solution: two mols of the di-n-alkylamine was dissolved in an equal volume of dry ether. To 10 g. of α,β-dibromopropiophenone, dissolved in 35 cc. of dry ether, the di-n-alkylamine solution was added in portions with stirring, while the temperature was kept between 20 and 25°. When the reaction was completed (a short time after the temperature ceased to rise after the last addition), the precipitated di-n-alkylamine hydrobromide was filtered off and washed with ether which ran into the filtrate. To the latter was then added the calculated volume of a freshly prepared absolute alcohol solution of hydrogen bromide (0.32 g. per cc.). A white, crystalline solid separated immediately, and after an hour the solution was filtered.

In the preparation of the dimethylamino ketone the

(1) Blicke and Blake, THIS JOURNAL, **52**, 236 (1930).

(2) Mannich and Lammering, *Ber.*, **55**, 3515 (1922); Mannich and Curtas, *Arch. Pharm.*, **264**, 750 (1926).

(3) The pharmacological tests were made by Professor W. J. R. Camp of the Department of Pharmacology of the University of Illinois College of Medicine and by Mr. Frank Mayer of this College.

(4) Kohler, *Amer. Chem. J.*, **42**, 383 (1909).

(5) "Organic Syntheses," Vol. I, p. 15 (1921).

(6) Fischer, *Ber.*, **37**, 2508 (1904).

(7) Kohler reported 58°.

solution was kept between 0 and 5° during the addition of the amine solution and the remainder of the preparation completed as rapidly as possible. The other di-*n*-alkylamines react much more slowly, a five-minute reaction time was allowed for the diethylamine, and the time of nine minutes for the remaining amines. Di-*n*-propylamine reacted the slowest.

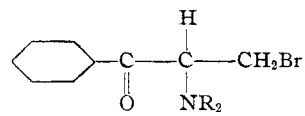
The preparation of these hydrobromides in absolute alcohol solution was carried out using essentially the same conditions and procedure as in the preparation in dry ether solution. The dialkylamine solution was added in portions during two minutes, while the reaction mixture was stirred and maintained between 20 and 25°. One more minute was allowed for completion of the reaction. Then the calculated volume of a freshly prepared absolute alcohol solution of hydrogen bromide (0.41 g. per cc.) was added rapidly and the solution allowed to stand in ice-water. The product formed a white, crystalline solid.

For the preparation of the dimethylamino ketone 1.75 mol of amine was used. The dimethylamine solution must be added during twenty seconds, forty seconds more allowed for the reaction to be completed and the hydrogen bromide solution added quickly at the end of this time. If longer reaction time is allowed and if 2 mols of dimethylamine is used a white, difficultly soluble, amorphous powder is formed and contaminates the product. Crystallized from methanol the powder melted at 220°, and was not further examined.

These hydrobromides formed white clusters of long, colorless needles, the dimethyl and diethyl compounds from absolute ethyl alcohol, the di-*n*-propyl compound from benzene, the di-*n*-butyl compound from a mixture of four volumes of benzene and one volume of petroleum ether, and the di-*n*-amyl compound from a mixture of equal parts of benzene and hexane.

The dimethylamino ketone hydrobromide crystallized from chloroform with 1 mole of chloroform of crystallization. The square, thick, colorless plates lost chloroform slowly on standing and became opaque; 0.641 g. was filtered from chloroform, the crystals dried by filter paper and air-dried for twenty minutes. Heated at 110° until no further appreciable loss in weight occurred, 0.167 g. was lost. Calcd. for $C_{11}H_{15}ONBr_2 - 1CHCl_3$, 26.16%. Found, 26.05%.

TABLE I

HYDROBROMIDES OF: 

R =	Nitrogen, % Calcd.	Found	Bromine, % Calcd.	Found
CH_3	4.15	4.12	47.41	47.53
C_2H_5	3.83	3.80	43.77	43.85
n-C_3H_7	3.56	3.54	40.65	40.76
n-C_4H_9	3.32	3.28	37.94	37.78
n-C_5H_{11}	3.11	3.09	35.57	35.48

	M. p., °C.	Yield in % Alcohol	Ether
CH_3	165–166	54.85	82.92
C_2H_5	161–162	54.08	78.92
n-C_3H_7	140–141	36.32	74.44
n-C_4H_9	128–129	Small	67.54
n-C_5H_{11}	127.5–129	Small	50.71

The di-*n*-alkylamine hydrobromides, precipitated in the preparations, were each identified by mixed melting points with the known hydrobromide prepared from the appropriate di-*n*-alkylamine.

Preparation of 1,3-Diphenylpyrazole.—To 3.4 g. of β-bromo-α-dimethylaminopropiophenone hydrobromide in 30 cc. of absolute alcohol was added 1.1 g. of phenylhydrazine in 5 cc. of absolute alcohol. To 3 g. of β-bromo-α-diethylaminopropiophenone hydrobromide in 20 cc. of absolute alcohol was added 1.77 g. of phenylhydrazine in 5 cc. of absolute alcohol. The solutions were allowed to stand overnight. They were then warmed to 40°, water added till the clear solution became slightly cloudy and allowed to stand several days. The pyrazole crystallized in long needles and the solution was filtered. After several repetitions of this addition of water there was obtained from the dimethylamino compound a yield of 0.78 g. (35.13%), and from the diethylamino compound a yield of 0.22 g. (11.28%). Crystallized from 65% alcohol, the pyrazole formed long, slender, white needles which melted 86–87° and mixed with pyrazole prepared by the method of Auwers and Schmidt[8] the melting point was not depressed.

Anal.[9] Calcd. for $C_{15}H_{12}N_2$: C, 81.77; H, 5.49; N, 12.73. Found: C, 81.92; H, 5.49; N, 12.72.

From the mixture of the diethylamino compound and phenylhydrazine there also separated 0.91 g. of a solid which crystallized from 65% alcohol in long, flat, transparent, orange needles, m. p. 152–153°.

Anal.[10] C, 76.79; H, 5.53; N, 17.85; Rast m. w. 302.6 and 310.4.

Preparation of 1-(*p*-Bromophenyl)-3-phenylpyrazole.—To a hot solution of 5.7 g. of β-bromo-α-dimethylaminopropiophenone hydrobromide in 30 cc. of absolute alcohol was added 20 cc. of a hot 50% alcohol solution of *p*-bromophenylhydrazine hydrochloride, and to the mixture a hot solution of 4.6 g. of crystalline sodium acetate in 30 cc. of water was added immediately. Crystals formed in the orange solution while still hot. When cold a slightly sticky, orange-red, crystalline mass was obtained on filtering, which, air-dried, weighed 3.55 g. After crystallization from 70% alcohol the pale-yellow, very thin, transparent needles melted at 137–138°.

Anal.[9] Calcd. for $C_{15}H_{11}N_2Br$: C, 60.20; H, 3.70; N, 9.36; Br, 26.72. Found: C, 60.51; H, 3.80; N, 9.13; Br, 26.50.

Preparation of the Dihydrobromides of the β-Piperidino-α-di-*n*-alkylaminopropiophenones.—An ether solution of the appropriate β-bromo-α-di-*n*-alkylaminopropiophenone was prepared as described. One mol of piperidine in an equal volume of ether was added to the ether solution of the amino ketone in portions with stirring while the solution was kept between 15 and 20°. Precipitation of piperidine hydrobromide started at once and was soon completed. The solution was filtered and a second mol of piperidine added in like manner. This solution stood

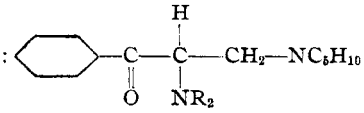
(8) *Ber.*, **58B**, 528 (1925).
(9) Microanal. by Kurt Eder, University of Chicago.
(10) Microanal. by T. S. Ma, University of Chicago.

several hours and the piperidine hydrobromide was filtered off. To the filtrate an absolute alcohol solution of hydrogen bromide (at least 0.3 g. per cc.) was added until no further precipitation occurred. The product precipitated as a finely divided, white solid, or as a golden oil which solidified to a finely divided, white solid on standing at 0°.

The dimethylamino- derivative was crystallized from absolute methanol, the diethylamino- compound from an absolute butanol solution saturated at 70°, and the di-*n*-propylamino- compound by dissolving it in three volumes of absolute butanol (1 g. per 10 cc.) at 65° and adding two volumes of petroleum ether. The dimethylamino-, diethylamino- and di-*n*-propylamino- derivatives, when they crystallized rapidly from solution, formed finely divided white powder. When crystallization was slow, colorless, thick, hexagonal plates were formed.

From the oil obtained as a final product in the attempt to prepare the di-*n*-butylamino- and the di-*n*-amylamino- derivatives, only the corresponding di-*n*-alkylamine hydrobromide and piperidine hydrobromide could be isolated. When subjected to vacuum distillation the oil darkened rapidly and formed a tar.

TABLE II

DIHYDROBROMIDES OF: 

R =	M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found	Yield, %
CH_3	190–191	6.63	6.68	37.86	37.76	58.54
C_2H_5	164–165	6.22	6.19	35.51	35.38	73.28
n-C_3H_7	154–155	5.85	5.71	33.41	33.34	54.97

Summary

Five new β-bromo-α-di-*n*-alkylaminopropiophenone hydrobromides have been prepared.

Three new β-N-piperidino-α-di-*n*-alkylaminopropiophenone dihydrobromides have been prepared.

The β-N-piperidino-α-di-*n*-alkylaminopropiophenone dihydrobromides do not show vasopressor or local anesthetic activity.

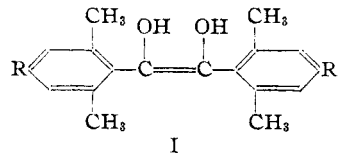
CHICAGO, ILLINOIS RECEIVED JANUARY 27, 1941

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Enediols. VII.[1] Bromostilbenediols

BY REYNOLD C. FUSON, S. L. SCOTT AND R. V. LINDSEY, JR.[2]

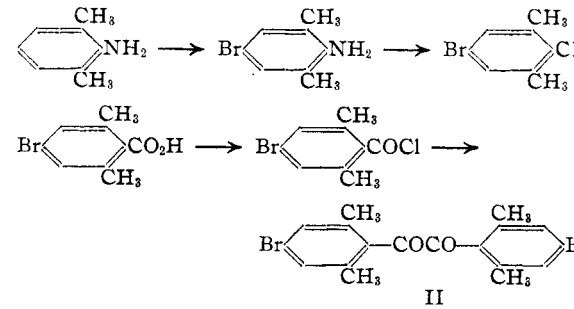
When it was discovered that 1,2-dimesitylacetylene glycol (I, R = CH_3) was stable,[3] a program of exploratory research was instituted to



I

study the relation of the various structural features of the molecule to its remarkable behavior. One problem was to determine the effect of substituents in the aromatic rings. However, the types of substituents, which can be so introduced and which at the same time can be tolerated under the experimental conditions necessary to produce an enediol, are greatly limited. One of the simplest of these is the bromine atom. The present report deals with its incorporation into various enediol molecules.

The first bromo enediols to be prepared were those derived from 4,4′-dibromo-2,6-xylil (II). The latter was made from 2,6-xylidine according to the following scheme.



II

The hydrolysis of the nitrile was facilitated by the presence of the halogen atom. Yields of 70 to 80% of the acid were obtained by heating the nitrile for three hours at 170–180° with 70% sulfuric acid. Addition of sodium nitrite to the diluted sulfuric acid hydrolysis mixture, according to the method of Gattermann, Fritz and Beck,[4] gave an almost quantitative yield of the bromo acid.

The bromine atoms had a similarly marked effect on the properties of the enediols. Whereas the enediols from 2,6-xylil (I, R = H) could be

(1) For the preceding communication in this series see Fuson and Kelton, THIS JOURNAL, **63**, 1500 (1941).

(2) Abbott Research Fellow, 1940–1941.

(3) Fuson and Corse, THIS JOURNAL, **61**, 975 (1939); Thompson, *ibid.*, **61**, 1281 (1939).

(4) Gattermann, Fritz and Beck, *Ber.*, **32**, 1122 (1899).