bromic acid the value of K decreased markedly with time from 0.20 to 0.14 hour^{-1} at 36% ketone formation.

A solution containing 4.78 g. (5 ml.) of glycol in 100 ml. of water was refluxed for 5.75 hours. The characteristic odor of methyl isopropyl ketone became evident within one hour. A 25-ml. sample of the solution required 0.45 ml. of 0.141 N sodium hydroxide to neutralize the acid produced. Analysis for ketone indicated a yield of 1.2%. In another experiment where 1.2 g. of sodium carbonate was added at first, no ketone was formed.

Refluxing and stirring 16.63 g. (10 ml.) of trimethylethylene bromide with 200 ml. of water and 10 g. of sodium carbonate for six hours gave no detectable amount of ketone. The dibromide phase, however, disappeared in two hours.

Summary

The mechanism by which trimethylethylene bromide is converted into methyl isopropyl ketone has been studied. The reaction proceeds in steps through trimethylethylene bromohydrin and trimethylethylene glycol as evidenced by rate measurements on the hydrolysis of the bromide and bromohydrin and on the conversion of glycol to ketone.

Preliminary experiments with isobutylene bromide indicate that a similar mechanism holds for the hydrolysis of this compound.

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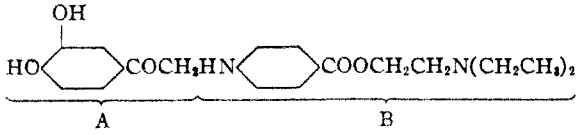
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. I. Some Amines of the "Eprocaine" Type[1]

BY RALPH HILL[1] AND GARFIELD POWELL

Among local anesthetics which have pressor action, a compound appears[2] under the name of "Eprocaine." It is a particularly simple combination of a well-known pressor residue (A) and an anesthetic residue (B), and is reported to have pressor and anesthetic activity.[2]



We have sought, in the work described below, a confirmation of the preparation and properties of "eprocaine" itself, and the synthesis of other compounds in which the residue A is unchanged and the residue B is varied to include other anesthetic residues which have been subjected to some physiological testing. "Eprocaine" itself has been studied, and also the di-*n*-propyl, di-isopropyl, di-*n*-butyl homologs on the aliphatic amino group. We have also prepared, for comparison, the compounds in which B is the "benzocaine" residue (ethyl *p*-aminobenzoate) and the homologs of this having *n*-propyl and *n*-butyl ester groups, together with derivatives. The ethyl ester[3] has previously been described (with a much lower melting point) but no mention has been made of derivatives or physiological testing.

"Eprocaine" was found to give a definite rise in blood pressure when injected intravenously into a pithed decerebrate cat anesthetized with nembutal. A 1% solution gave definite anesthesia, administered intracutaneously to the guinea pig, with evidence the next day of severe tissue damage at the point of injection.[4] On the second group of amines (with B as benzocaine and related residues), anesthetic testing was limited (because of the low solubility of the salts in water) to dusting on the exposed sciatic nerve of the frog. With benzocaine as control, absence of activity was indicated.[5]

Experimental

β-Diethylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate Hydrochloride, "Eprocaine."—Fifteen grams of procaine was dissolved in 75 cc. of boiling water and 11.8 g. of chloroacetylcatechol added. The mixture was refluxed for two hours and then concentrated *in vacuo* nearly to dryness. On addition of 75 cc. of alcohol the residue crystallized. Recrystallized from 85% alcohol it melted at about 205° with darkening; yield 73% from procaine.

Anal.[6] Calcd. for $C_{21}H_{27}O_5N_2Cl$: C, 59.9; H, 6.5; N, 6.6; Cl, 8.4. Found: C, 59.8; H, 6.4; N, 6.9; Cl, 8.7.

"Eprocaine" is only slightly soluble in hot alcohol, but quite soluble in water. With ferric chloride solution it gives an emerald green color, turning violet on careful addition of sodium carbonate solution. All compounds described in this paper derived from 3,4-dihydroxyphenacyl halides responded to this test, with addition of alcohol when needed for solubility purposes. The free base is precipitated by sodium hydroxide and is dissolved in excess. The base is soluble in alcohol, acetone, and hot water. insoluble in cold water and benzene.

Table I shows the results obtained in the preparation of homologs by the following general procedure, in each case using a corresponding amount of the proper ester. Four grams of ethyl *p*-aminobenzoate was dissolved in about 500 cc. of boiling water and 4.5 g. of chloroacetylcatechol added. The clear solution was boiled for four hours, keeping the volume constant by the addition of water. During this process the product separated out as white flocculent crystals. The crystals were filtered hot, washed with hot water, and recrystallized from alcohol.

Dibenzoate of β-Diethylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—A solution of 0.5 cc. of benzoyl chloride in 3 cc. of benzene was added to 0.5 g. of "eprocaine" dissolved in 20 cc. of water. One-half gram of sodium carbonate was added in portions with shaking and cooling. The product separated as a gummy mass which

(1) From a dissertation submitted by Ralph Hill in partial fulfillment of the requirements for the Ph.D. degree at Columbia University. Original manuscript received January 15, 1943.

(2) Osborne, *Science*, **85**, 105 (1935).

(3) Ishiwara, *Ber.*, **57**, 1126 (1924).

(4) Private report of M. G. Mulinos, Columbia University.

(5) Private report of Edwin J. Fellows, Temple University.

(6) For analyses reported in this paper we are indebted to Mr. Saul Gottlieb.

TABLE I

Compound formed	Ester reacting	M. p., °C.	Yield, % of theoret.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	Ia	220–221[a] with darkening		$C_{17}H_{17}O_5N$	68.5	5.4	68.6	5.2
II	IIa	210–211	60	$C_{18}H_{19}O_5N_2$	65.8	5.5	66.0	5.8
III	IIIa	196–196.5	58	$C_{19}H_{21}O_5N$	66.5	6.1	66.7	6.2
IV	IVa	Abt. 225 with darkening	69	$C_{23}H_{31}O_5N_2Cl$	61.3	6.9	61.5	7.1
V[b]	Va	223–224	66	$C_{23}H_{31}O_5N_2Cl$	61.3	6.9	61.3	7.1
VI[b]	VIa	227–230	55	$C_{25}H_{35}O_5N_2Cl$	62.7	7.3	62.6	7.5

I is ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate from Ia: ethyl *p*-aminobenzoate
II is propyl *p*-(3,4-dihydroxyphenacylamino)-benzoate from IIa: propyl *p*-aminobenzoate
III is butyl *p*-(3,4-dihydroxyphenacylamino)-benzoate from IIIa: butyl *p*-aminobenzoate
IV is β-diisopropylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate hydrochloride from IVa: β-diisopropylaminoethyl *p*-aminobenzoate
V is β-di-*n*-propylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate hydrochloride from Va: β-di-*n*-propylaminoethyl *p*-aminobenzoate
VI is β-di-*n*-butylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate hydrochloride from VIa: β-di-*n*-butylaminoethyl *p*-aminobenzoate hydrochloride.

[a] Literature m. p. 201°; see ref. 3. [b] Recrystallized from dilute acetic acid containing a little hydrochloric acid.

solidified after an hour of shaking. The solid was filtered off, washed with benzene, air dried, and recrystallized from alcohol. The melting point was 150–150.5°.

Anal. Calcd. for $C_{35}H_{34}N_2O_7$: C, 70.7; H, 5.7. Found: C, 70.7; H, 5.6.

The corresponding acetyl derivative appears to be unstable to water.

Dibenzoate of β-Di-*n*-propylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—This was prepared in the same manner as the above and recrystallized from alcohol; m. p. 154–154.5°.

Anal. Calcd. for $C_{37}H_{38}N_2O_7$: C, 71.3; H, 6.2. Found: C, 71.6; H, 6.4.

Diacetate of Ethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—Three grams of ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate was suspended in 200 cc. of water to which ice had been added, and solution was effected by addition of 4.1 cc. of 20% sodium hydroxide solution (slight excess of three equivalents), and 2.8 cc. of acetic anhydride was added rapidly with stirring. A gelatinous precipitate formed. Sufficient acetic acid was added to give a clear solution on boiling. On cooling the product separated in crystalline form. The crystals were filtered, washed with 50% acetic acid followed by water, and recrystallized from alcohol; m. p. 179–181°.

Anal. Calcd. for $C_{21}H_{21}O_7N$: C, 63.1; H, 5.3. Found: C, 63.1; H, 5.5.

The Triacetates of Ethyl, Propyl, and Butyl *p*-(3,4-Dihydroxyphenacylamino)-benzoates.—These all were prepared by a procedure similar to the following, given for the ethyl ester, with results shown in Table II. One-half gram of ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate was suspended in 20 cc. of acetic anhydride, and two drops of concentrated sulfuric acid added. The mixture was warmed slightly and the suspended solid gradually dissolved. The solution was allowed to stand for an hour, and was then poured into about 125 cc. of water. As the excess acetic anhydride hydrolyzed, the product separated out as a white solid. It was recrystallized from dilute acetic acid.

Hydrolysis of β-Di-*n*-propylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—A quantity of this compound was dissolved in an excess of 0.1 *N* sodium hydroxide solution and allowed to stand at room temperature for several hours. On acidification with dilute hydrochloric acid, crude *p*-(3,4-dihydroxyphenacylamino)-benzoic acid separated as a white amorphous solid. This was washed free from chloride with water, by centrifuging and decanting the washings. The product was recrystallized first from dilute acetic acid and then from alcohol. It decomposed at 241° when placed in a melting point tube at 230° and heated at the rate of 3° per minute. The product was soluble in sodium bicarbonate with evolution of carbon dioxide. It gave an emerald green color with ferric chloride solution.

TABLE II

Compound	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl ester	143–144	$C_{23}H_{23}O_8N$	62.6	5.2	62.7	5.5
Propyl ester	129–131	$C_{24}H_{25}O_8N$	63.3	5.5	63.3	5.7
Butyl ester	120	$C_{25}H_{27}O_8N$	64.0	5.8	64.2	5.9

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.7; H, 4.5. Found: C, 62.5; H, 4.6.

Hydrolysis of the ester linkage thus proceeds normally without affecting the phenacylamino group.

Summary

Diethylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate, "eprocaine," and related esters in which the alcohol group is ethyl, propyl, butyl, β - diisopropylaminoethyl, β - di - *n* - propylaminoethyl, and β-di-*n*-butylaminoethyl were prepared by interaction of the suitable *p*-aminobenzoic ester with chloracetylcatechol. Dibenzoyl derivatives of the β-diethylaminoethyl and β-di-*n*-propylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoates were prepared, and also the di- and tri-acetates of ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate, as well as the triacetates of the propyl and butyl esters.

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