addition of absolute ether to the cold solution there precipitated 20 g. (36.8%) of the ketone hydrochloride; m. p. 269–270° after recrystallization from a mixture of alcohol and ethyl acetate.

Anal. Calcd. for $C_{19}H_{22}ONCl$: Cl, 10.88. Found: Cl, 11.03.

β-Dimethylaminoethyl β-Naphthyl Ketone Hydrochloride.—From 17.0 g. of methyl β-naphthyl ketone, 8.4 g. of dimethylamine hydrochloride, 4.5 g. of trioxymethylene and 30 cc. of absolute alcohol there was obtained 18 g. (69%) of the ketone salt; m. p. 153–154° after recrystallization from a mixture of alcohol and ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}ONCl$: Cl, 13.44. Found: Cl, 13.46.

β-Piperidinoethyl β-Naphthyl Ketone Hydrochloride.—Eighteen grams (60%) of the basic ketone hydrochloride was obtained from 17.0 g. of methyl β-naphthyl ketone, 12.5 g. of piperidine hydrochloride, 4.5 g. of trioxymethylene and 30 cc. of absolute alcohol; m. p. 240–241° after recrystallization from a mixture of alcohol and ethyl acetate.

Anal. Calcd. for $C_{18}H_{22}ONCl$: Cl, 11.67. Found: Cl, 11.62.

β-Dimethylaminoethylphenylcarbinol Hydrochloride.—A solution of 8.5 g. of the ketone hydrochloride in 50 cc. of water was shaken with Raney nickel under an initial pressure of three atmospheres until the required amount of hydrogen had been absorbed. The mixture was filtered, the filtrate evaporated to dryness, the residue dissolved in alcohol and the carbinol salt precipitated with ether; yield 6.2 g. (73%); m. p. 135–136°.[19]

(19) The same melting point was reported by Mannich and Heilner (ref. 14, p. 360) who reduced the ketone salt with the aid of palladinized carbon.

β-Piperidinoethylphenylcarbinol Hydrochloride.—Reduced in the manner described above, 10.1 g. of the ketone salt yielded 7.3 g. (72%) of the carbinol hydrochloride after three recrystallizations from a mixture of alcohol and ethyl acetate; m. p. 138–139°.[20]

A mixture of 5 g. of the ketone hydrochloride, 75 cc. of water and 230 g. of 2% sodium amalgam was treated, portionwise, with 20 cc. of hydrochloric acid. After two hours the clear solution was decanted, made alkaline, extracted with ether, the solvent removed from the ether layer and the residue recrystallized from chloroform; m. p. 236–237°. This product seems to be 1,6-dipiperidino-3,4-diphenylhexandiol-3,4 which Mannich and Lämmering[21] obtained by reduction of the ketone with aluminum amalgam in moist ether.

β-Piperidinoethyl-β-naphthylcarbinol Hydrochloride.—This compound was obtained in 97% yield when 7.2 g. of the ketone hydrochloride, dissolved in 25 cc. of water was reduced with Raney nickel; m. p. 191–192° after precipitation from an alcoholic solution by ether.

Anal. Calcd. for $C_{18}H_{24}ONCl$: Cl, 11.60. Found: Cl, 11.51.

Summary

A number of amino-, piperidino- and morpholinoethyl and propyl esters of benzilic acid have been described.

Pharmacological examinations have shown that a number of them exhibit mydriatic activity.

(20) The same compound has been obtained by the use of a platinum oxide catalyst (ref. 15, p. 240).

(21) Mannich and Lämmering, *Ber.*, **55**, 3515 (1922).

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 20, 1941

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Synthetic Mydriatics. II

BY F. F. BLICKE AND CHARLES E. MAXWELL[1,2]

Since the β-piperidinoethyl ester of benzilic acid,[3] based on experiments with laboratory animals, seems to be an excellent mydriatic, it was of interest to determine the extent to which mydriatic activity could be retained when other acids were substituted for benzilic acid. Consequently a number of esters of β-piperidinoethyl alcohol were prepared which are listed in Table I.

We are indebted to Dr. F. Bruce Fralick and Dr. Harold F. Falls for the evaluation of our products which were tested as salts or methobromides on the rabbit's eye.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by Charles E. Maxwell in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Lilly Endowment Fellow.

(3) Blicke and Maxwell, THIS JOURNAL, **64**, 428 (1942).

Only two of the twenty esters which were examined proved to be strong mydriatics (Table I), namely, the esters of tropic (11) and dicyclohexylglycolic acid (12); the former was tested as the methobromide.

The discovery of the activity of the last-mentioned ester is especially interesting since it demonstrates that an aromatic nucleus in the acid radical of the ester is not essential for mydriatic activity.

Experimental

Acetylbenzilic Acid.—A mixture of 50 g. of crude benzilic acid and 100 cc. of acetic anhydride was heated on a steam-bath for fourteen hours, 60 cc. of water added and the mixture stirred and cooled. The product, which weighed 39 g. (63%), was dried in a vacuum desiccator over sulfuric acid for several days; m. p. 104°.

TABLE I

ESTERS OF β-PIPERIDINOETHYL ALCOHOL (HYDROCHLORIDES)

Compounds 3, 6 and 8 were recrystallized from dioxane; 5, 10, 12, 15, 17 and 18 from a mixture of alcohol and ethyl acetate; 4 and 11 from a mixture of isopropyl alcohol and ethyl acetate; 9 from a mixture of alcohol and dioxane; 14 from amyl alcohol; 16 from amyl acetate; 1, 2, 7 and 13 were precipitated from an alcoholic solution by the addition of ether. Compounds 11, 14, 15, 16 and 17 produced a mild anesthesia when applied to the rabbit's cornea; compounds 3, 4, 7, 10, 12, 13 and 18 were practically inactive.

$RCOOCH_2CH_2NC_5H_{10}\cdot HCl$

	RCO—			M. p., °C.	Formula	% Halogen Calcd.	Found
1	C_6H_5COO—	C, D[a]	0[b]	170–171[c]	$C_{14}H_{20}O_2NCl$	13.14	13.17
2	α-$C_{10}H_7COO$—	D	0	169–170	$C_{18}H_{22}O_2NCl$	11.09	11.11
3	$C_6H_5CH_2COO$—	B	0	145–146[d]	$C_{15}H_{22}O_2NCl$	12.49	12.37
4	C_6H_5COCOO—	B	0	122–123	$C_{15}H_{20}O_3NCl$	11.91	11.90
5	$(C_6H_5)_2CHCOO$—	A	0	153–154	$C_{21}H_{26}O_2NCl$	10.13	9.97
6	$CH_3(CH_2)_5CH(OH)COO$—	C	0	141–143	$C_{15}H_{30}O_3NCl$	11.52	11.36
7	$C_6H_5CH(OH)COO$—	B, C	0	159–160	$C_{15}H_{22}O_3NCl$	11.84	11.85
8	$C_6H_{11}CH(OH)COO$[e]	C	0	180–181	$C_{15}H_{28}O_3NCl$	11.59	11.42
9	$C_6H_{10}(OH)COO$—[f]	C	0	201–202	$C_{14}H_{26}O_3NCl$	12.15	12.02
10	α-$C_{10}H_7CH(OH)COO$—	B	+	157–158	$C_{19}H_{24}O_3NCl$	10.14	10.15
11	$C_6H_5CH(CH_2OH)COO$—(CH_3Br)[g]	B	++++	127–128	$C_{17}H_{26}O_3NBr$	21.47	21.32
12	$(C_6H_{11})_2C(OH)COO$—[h]	B	+++	229–230	$C_{21}H_{38}O_3NCl$	9.13	9.15
13	$(C_6H_{11})_2C(OH)COO$—(CH_3Br)	..	++	216–217	$C_{22}H_{40}O_3NBr$	17.90	17.82
14	$(C_6H_5)_2C(OOCCH_3)COO$—(CH_3Br)	B	++	220–221	$C_{24}H_{30}O_4NBr$	16.78	16.78
15	$(C_6H_5)_2C(OCH_3)COO$—	B	0	178–179	$C_{22}H_{28}O_3NCl$	9.12	9.09
16	$(C_6H_5)_2C(Cl)COO$—	..	++	145–146	$C_{21}H_{25}O_2NCl_2$	18.03	17.97
17	$C_{12}H_8C(OH)COO$—[i]	B	++	345–348[j]	$C_{21}H_{24}O_3NCl$	9.49	9.50
18	$C_6H_5CH(OOCCH_3)COO$—(CH_3Br)	D	+	141–142	$C_{18}H_{26}O_4NBr$	19.97	20.16

[a] Method of preparation. [b] Mydriatic activity: 0 = inactive; + = poor; ++ = moderate; +++ = good; ++++ = excellent. [c] Von Braun, Braunsdorf and Rath [*Ber.*, **55**, 1666 (1922)] found 171–172°. [d] Leffler and Brill [THIS JOURNAL, **55**, 367 (1933)] reported 139°. [e] Radical of hexahydromandelic acid. [f] Radical of 1-hydroxyhexahydrobenzoic acid. [g] Methobromide. [h] Radical of dicyclohexylglycolic acid. The acid was prepared according to Gauerke and Marvel, THIS JOURNAL, **50**, 1180 (1928). [i] Radical of 9-hydroxyfluorene-9-carboxylic acid. [j] The ester base melted at 136–137° after recrystallization from benzene. According to the German Patent 657,526 (*C. A.*, **32**, 6043 (1938)) the base melts at 136°; it is said to be of therapeutic value.

Diphenylmethoxyacetic Acid.—A mixture of 24.6 g. of diphenylchloroacetic acid, 50 cc. of methyl alcohol and 3 cc. of concentrated sulfuric acid was refluxed for three hours, poured into water, the ester layer separated and the aqueous layer extracted with ether.

The crude methyl diphenylmethoxyacetate was refluxed for twelve hours with 8.4 g. of potassium hydroxide which had been dissolved in a mixture of methyl alcohol and water. After evaporation to dryness on a steam-bath, the residue was dissolved in water and the solution acidified. The precipitated, oily acid, which soon solidified, was dissolved in very dilute sodium carbonate solution, shaken with charcoal, filtered and the filtrate acidified; yield 23.3 g. (95%); m. p. 100–101° after recrystallization from a mixture of benzene and petroleum ether.

Most of the esters listed in Table I were prepared according to methods A,[3] B,[3] C or D: (A) the potassium salt of the acid was heated with β-piperidinoethyl chloride hydrochloride; (B) the acid and β-piperidinoethyl chloride were heated in isopropyl alcohol; methods C and D are illustrated below.

(C) **β-Piperidinoethyl Mandelate Hydrochloride (7).**—A mixture of 2.9 g. (0.02 mole) of β-piperidinoethyl chloride, 5.2 g. (0.02 mole) of silver mandelate and 60 cc. of benzene was refluxed for sixteen hours, filtered and the filtrate treated with hydrogen chloride. The ester hydrochloride precipitated as an oil which solidified when rubbed under ether; yield 4.2 g. (71%).

(D) **β,β-Dimethyl-γ-dimethylaminopropyl Acetylmandelate Hydrochloride.**—To 3.2 g. (0.025 mole) of β,β-dimethyl-γ-dimethylaminopropyl alcohol,[4] dissolved in 10 cc. of chloroform, there was added 5.0 g. (0.025 mole) of acetylmandelyl chloride[5] dissolved in 10 cc. of the same solvent. After one hour at ordinary temperature, the ester hydrochloride was precipitated by ether as an oil which soon crystallized. The product was precipitated twice from an alcoholic solution by ether; yield 5.8 g. (68%); m. p. 182–183°.[6]

This compound did not produce mydriasis.

β,β-Dimethyl-γ-diethylaminopropyl 1-Hydroxyhexahydrobenzoate Hydrochloride.—A mixture of 3.5 g. of β,β-dimethyl-γ-diethylaminopropyl chloride,[7] 60 cc. of benzene and 3.6 g. of potassium 1-hydroxyhexahydrobenzoate was refluxed for twelve hours, filtered and the filtrate treated with hydrogen chloride to precipitate the hydrochloride; yield 4.5 g.; m. p. 174–175° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{16}H_{32}O_3NCl$: Cl, 11.01. Found: Cl, 10.85.

This compound is not a mydriatic.

(4) Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).

(5) "Organic Syntheses," Vol. 4, p. 1.

(6) The melting point reported (U. S. Patent 1,932,341; *C. A.*, **28**, 578 (1934)) is 179°.

(7) Mannich and Baumgartner, *Ber.*, **70**, 210 (1937).

β-Piperidinoethyl Diphenylchloroacetate Hydrochloride (16).—(a) Five and six-tenths grams of β-piperidinoethyl benzilate hydrochloride[3] was mixed with 3 cc. of thionyl chloride and after twelve hours the product was precipitated with petroleum ether. The material was dissolved in ethyl acetate, precipitated with ether and finally recrystallized from dioxane; yield 4.0 g. (69%).

(b) To 6.7 g. of β-piperidinoethyl benzilate, dissolved in 20 cc. of benzene, there was added 3.9 g. of acetyl chloride. After the mixture had been refluxed for one and one-half hours the product was precipitated with petroleum ether and recrystallized from amyl acetate; yield 6.1 g. (85%).

Summary

Twenty esters of β-piperidinoethyl alcohol were prepared and tested for mydriatic activity.

Two esters were found to be strong mydriatics, namely, the β-piperidinoethyl esters of tropic and dicyclohexylglycolic acid.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 22, 1941

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chemistry of Vitamin E. XXXI. 3,5-Dinitrobenzazide as a Reagent for Preparation of Derivatives of Tocopherols[1]

BY LEE IRVIN SMITH AND JOSEPH A. SPRUNG

Although *p*-nitrophenyl isocyanate has been used for preparation of solid derivatives of tocopherols,[2] the most common reagent is cyanic acid, which gives sparingly soluble allophanates with these substances.[2a,3] It usually requires several days for the allophanates to crystallize, and the preparation and handling of the large amounts of cyanic acid required is tedious and unpleasant.

In 1934 Sah and Ma[4] found that phenols, when heated in dry toluene with 3,5-dinitrobenzazide, were smoothly converted into the corresponding phenylurethans. Since the reagent is readily converted into 3,5-dinitrophenyl isocyanate when its solution in toluene is heated, the isocyanate is obviously an intermediate. But the azide is a stable solid, easy to prepare quickly and in quantity either by action of nitrous acid upon the hydrazide[5] or by action of sodium azide upon a solution of the acid chloride in acetic acid.[6]

It appeared worth while to try 3,5-dinitrobenzazide as a reagent for preparation of solid derivatives of tocopherols. The results have shown that the reagent is an excellent one for this purpose. The reaction requires but an hour, and the derivatives crystallize well and in yields of 70–90%. Recrystallization from alcohol is sufficient to give a pure product. All of the pure 3,5-dinitrophenylurethans crystallized as waxy yellow needles, although they gave perfectly colorless solutions in alcohols. This behavior is apparently characteristic of the 6-hydroxychroman structure, for it was exhibited by the simple pentamethyl-6-hydroxychroman as well as by those chromans having a long, aliphatic side chain (tocopherols).

The melting points of the 3,5-dinitrophenylurethans of α-, β- and γ-tocopherol are, respectively, 145–147°, 153–155° and 143–145°. A mixture of the urethans of α- and γ-tocopherols melted at 140–145°. This is a very small depression of the melting point, but this phenomenon appears to be characteristic of derivatives of the tocopherols, especially α- and γ-, for the allophanates of these substances also give very small melting point depressions when mixed.

In order to test the suitability of the 3,5-dinitrophenylurethans as derivatives for isolation purposes, a gram of α-tocopherol was converted into the urethan. After one crystallization from alcohol, the derivative weighed 1.13 g. (76%) and melted at 142–144°. Hydrolysis of this material gave back 0.64 g. of α-tocopherol. The dinitrophenyl residue was recovered as 3,5-dinitrophenol, m. p. 126–127°, instead of 3,5-dinitroaniline.[7]

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Experimental[8]

3,5-Dinitrobenzazide.—The method of Blanksma and Verberg was used. The dinitro acid (50 g.) and phosphorus

(1) Paper XXX, THIS JOURNAL, **63**, 1887 (1941).

(2) (a) Evans, Emerson and Emerson, *J. Biol. Chem.*, **113**, 319 (1936); (b) Karrer and Fritzsche, *Helv. Chim. Acta*, **22**, 260 (1939).

(3) (a) Drummond and Hoover, *Biochem. J.*, **31**, 1852 (1937); (b) Todd, Bergel and Work, *ibid.*, **31**, 2257 (1937); (c) Emerson, Emerson, Mohammad and Evans, *J. Biol. Chem.*, **122**, 99 (1937); (d) Karrer, Fritzsche and Escher, *Helv. Chim. Acta*, **22**, 661 (1939); (e) Karrer, Koenig, Ringier and Salomon, *ibid.*, **22**, 1139 (1939).

(4) Sah and Ma, *J. Chinese Chem. Soc.*, **2**, 229 (1934).

(5) Sah and Ma, *ibid.*, **2**, 41, 162 (1934).

(6) Blanksma and Verberg, *Rec. Trav. Chim.*, [4] **53**, 989 (1934).

(7) Sidgwick and Taylor, *J. Chem. Soc.*, **121**, 1854 (1922).

(8) Microanalyses by E. E. Renfrew and C. H. Stratton.