hydroxide solution to the end-point described above. The results are listed in Table I.

Summary

The nitric acid oxidation of some aromatic hydrocarbons and derivatives is described.

The titration of several hydrocarbon picrates is reported and the advantages of this method of analysis are pointed out.

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

Synthetic Mydriatics. I

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

The great majority of substances which exhibit marked mydriatic activity, and especially those which find practical application as mydriatics, are of two types: esters of a hydroxy acid such as tropic, $C_6H_5CH(CH_2OH)COOH$, or mandelic, $C_6H_5CH(OH)COOH$, and an amino alcohol; aryl-alkylamines similar to epinephrine or ephedrine in structure.

We have discovered that the benzilic acid ester of β-piperidinoethyl alcohol,[3] $(C_6H_5)_2C(OH)CO\text{-}OCH_2CH_2NC_5H_{10}$, is a strong mydriatic. This observation shows that the alcoholic hydroxyl in the acid radical, which seems to be quite essential for strong mydriasis in the ester type, may be tertiary as well as secondary (mandelic acid) or primary (tropic acid).

Recently four other esters of benzilic acid—the tropyl,[4] the pseudotropyl,[5] the β-diethylamino-ethyl[6] and the γ-diethylamino-β,β-dimethylpropyl[7] ester—have been shown to be not only mydriatics but also local anesthetics and antispasmodics.[8]

The substituted ethyl and propyl esters of benzilic acid, which we prepared, are listed in Table II. Three compounds, β-piperidinoethyl benzilate hydrochloride, the ester methobromide and the methobromide of β-diethylaminoethyl benzilate, when tested on the rabbit's eye, were described by Dr. F. Bruce Fralick and Dr. Harold F. Falls, to whom we are indebted for all of the animal tests, as excellent mydriatics; the hydrochlorides of the β-diethylaminoethyl and the γ-piperidinopropyl ester of benzilic acid, as well as the methobromide of the latter, produced good mydriasis.

Some of the ester hydrochlorides were found to be so insoluble in water that satisfactory 1–2% solutions could not be prepared. In these instances the methobromides of the esters proved to be much more soluble. Furthermore, the quaternary compounds have been found to be much less irritant and are as active or even more active than the corresponding tertiary amine hydrochlorides.[9]

The esters were prepared by the methods of Horenstein and Pählicke,[10] according to which the potassium salt of the required acid was heated with the hydrochloride or hydrobromide of the basic-substituted alkyl halide, or the acid, dissolved in isopropyl alcohol, was allowed to react with the basic-substituted alkyl halide.

In view of the statement in the literature[11] that aminomethyl phenyl ketone produces mydriasis,[12] it seemed desirable to prepare and test a few amino ketones and some of the corresponding secondary alcohols. It was found that no, or only slight, mydriasis was obtained with 1–5% solutions of the hydrochlorides of the ketones and secondary alcohols listed below.

Ketones: aminomethyl phenyl,[13] diethylamino-

(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) Von Brucke and Jesserer [*Arch. expil. Path. Pharmacol.*, **190**, 516 (1938)] stated that this ester is an antispasmodic but no description of its preparation seems to have been published.

(4) Kreitmair, *Klin. Wschr.*, **15**, 676 (1936).

(5) Kroner, *ibid.*, **15**, 678 (1936).

(6) Halpern, *Arch. int. Pharmacodynam. Therap.*, **59**, 179 (1938).

(7) Fromherz, *Arch. expil. Path. Pharmacol.*, **173**, 113, 126 (1933).

(8) During the last few years a number of esters have been prepared primarily in the hope that they might be found to be antispasmodics; their mydriatic activity was discovered more or less incidentally during routine pharmacological tests. Among the very few studies which deal with the relationship between chemical structure and mydriatic activity those of Pyman [*J. Chem. Soc.*, **111**, 1109 (1917)] and of von Braun, Braunsdorf and Räth [*Ber.*, **55**, 1666 (1922)] deserve mention.

(9) As early as 1868, Crum, Brown and Fraser [*Trans. Roy. Soc. Edinburgh*, **25**, 708 (1868)] discovered that the mydriatic action of methylatropinium sulfate is about the same as that of atropine sulfate.

(10) Horenstein and Pählicke, *Ber.*, **71**, 1654 (1938).

(11) Pitini, *Arch. internat. de pharmacodyn. et de Therapie*, **14**, 75 (1905).

(12) A 10% solution was required.

(13) Mannich and Hahn, *Ber.*, **44**, 1546 (1911). Used as hydrobromide.

methyl phenyl,[14] β-dimethylaminoethyl phenyl,[15] β-diisoamylaminoethyl phenyl, piperidinomethyl phenyl.[16]

Experimental

The alcohols were obtained by the processes indicated below. The chloride hydrochlorides were produced when the alcohol, dissolved in chloroform, was treated with thionyl chloride. When the basic chloride was required, the latter was liberated from an aqueous solution of the salt and used immediately.

The two procedures, A and B, used for the preparation of the esters are illustrated in the case of β-piperidinoethyl benzilate hydrochloride.

TABLE I

ALCOHOLS AND CHLORIDE HYDROCHLORIDES

		Alcohol B. p., °C.	Chloride hydrochloride M. p., °C.[a]
1	β-Aminoethyl	.....	.....[b]
2	β-Butylaminoethyl	.....[c]	.....[d]
3	β-Diethylaminoethyl	.....[e]	210–211[f]
4	β-Dibutylaminoethyl	.....[g]	.....[h]
5	β-(Methylcyclohexylamino)-ethyl	115–116 (13 mm.)[i]	.....[j]
6	β-(Dicyclohexylamino)-ethyl	165–167 (6 mm.)[k]	185–186[l]
7	β-Methylphenylamino)-ethyl	151–153 (15 mm.)[m]	.....[n]
8	β-Piperidinoethyl	196–199[o]	229–231[p]
9	β-Morpholinoethyl	220–222[q]	.....[r]
10	γ-Piperidinopropyl	.....	.....[s]
11	β-Piperidinoisopropyl	191–194[t]	203–204[u]
12	β,β-Dimethyl-γ-piperidino-propyl	.....[v]	.....[w]

[a] Salts 3 and 6 were dissolved in alcohol and precipitated by ether; 8 was recrystallized from a mixture of alcohol and ethyl acetate; 11 was recrystallized from amyl acetate. [b] We used the bromide hydrobromide ("Organic Syntheses," Vol. 18, p. 13). [c] Matthes, *Ann.*, **315**, 112 (1901). [d] The chloride boils at 113–116° (23 mm.). *Anal.* Calcd. for $C_6H_{14}NCl$: N, 10.33. Found: N, 10.34. [e] Incidentally the alcohol hydrochloride was prepared by passing hydrogen chloride into an ether solution of the alcohol; the precipitated salt was recrystallized from a mixture of acetone and alcohol; m. p. 135–136°. *Anal.* Calcd. for $C_6H_{16}ONCl$: Cl, 23.21. Found: Cl, 23.09. Horne and Shriner [THIS JOURNAL, **54**, 2928 (1932)] prepared this substance but did not report a melting point. [f] Gough and King [*J. Chem. Soc.*, 2436 (1928)] found the same melting point; Slotta [*Ber.*, **68**, 758 (1935)] reported 212°. [g] Barnett, Jenkins, Peet, Dreger and Adams, THIS JOURNAL, **59**, 2248 (1937). [h] The chloride boils at 114–115° (23 mm.). *Anal.* Calcd. for $C_{10}H_{22}NCl$: N, 7.31. Found: N, 7.15. [i] When a mixture of 99 g. of cyclohexylamine, 25 cc. of ethylene oxide and 9 cc. of water was treated according to the general procedure of Matthes (Ref. *c*) there was obtained 50 g. of β-(cyclohexylamino)-ethanol which boiled at 127–130° (15 mm.) [Wedekind and Bruch, *Ann.*, **471**, 91 (1928), found 119° (11 mm.)], 8 g. of cyclohexyldi-(β-hydroxyethyl)-amine which boiled at 175–178° (12 mm.) (the boiling point reported is 180–184° (14 mm.) [British Patent 297, **484**; *Chem. Zentr.*, **99**, I, 1683 (1929)] and 42 g. of unchanged cyclohexylamine. A mixture of 58 g. of β-(cyclohexylamino)-ethanol and 58 g. of formalin was heated on a steam-bath for twelve hours, sodium hydroxide added and the β-(methylcyclohexylamino)-ethanol extracted with ether; yield 51 g. Wedekind and Bruch [*Ann.*, **471**, 94 (1928)] found the boiling point to be 106° (10 mm.). [j] The chloride boils at 99–100° (11 mm.). *Anal.* Calcd. for $C_9H_{18}NCl$: N, 7.92. Found: N, 7.98. [k] When a mixture of 90.5 g. of dicyclohexylamine and 20 g. of ethylene chlorohydrin was heated for five hours at 150°, the base liberated with 40% sodium hydroxide solution and extracted with ether, there was obtained 30.8 g. of β-(dicyclohexylamino)-ethanol; b. p. 165–167° (6 mm.). The boiling point reported is 135° (2 mm.) [British Patent 351,605, *Chem. Zentr.*, **103**, I, 102 (1932)]. [l] The reported melting point is 186° (Ref. *k*). [m] From 53.5 g. of methylaniline and 40.0 g. of ethylene chlorohydrin there was obtained 42 g. of β-(methylphenylamino)-ethanol; b. p. 151–153° (15 mm.). Laun [*Ber.*, **17**, 676 (1884)] reported 218–219° (110 mm.). [n] The chloride boiled at 126–128° (8 mm.); von Braun and Kirschbaum [*Ber.*, **52**, 1719 (1919)] found 134° (13 mm.). [o] Twenty-seven grams of ethylene chlorohydrin was added to 58 g. of piperidine in a flask fitted with a reflux condenser. After the initial reaction had subsided, the mixture was heated for three hours on a steam-bath, dissolved in water, 40% sodium hydroxide solution added and the β-piperidinoethanol extracted with ether; yield 37 g.; b. p. 196–199°. Ladenburg, *Ber.*, **14**, 1877 (1881)] found 199°. [p] Dunlop [*J. Chem. Soc.*, **101**, 2002 (1912)] found 231°. [q] This alcohol was obtained in 85% yield by Knorr's general method [Knorr, *Ann.*, **301**, 9 (1898)] from morpholine, ethylene oxide and water; b. p. 220–222°. [r] The chloride boiled at 104–106° (29 mm.). Mason and Block [THIS JOURNAL, **62**, 1446 (1940)] reported 93–94° (12 mm.). *Anal.* Calcd. for $C_6H_{12}ONCl$: N, 9.36. Found: N, 9.28 [s] We used the bromide hydrobromide; m. p. 210–211°. Gabriel and Stelzner [*Ber.*, **29**, 2389 (1896)] found 212°. To obtain this substance, 73.5 g. of N-(γ-phenoxypropyl)-piperidine and 350 cc. of 48% hydrobromic acid were refluxed in an all glass apparatus for six hours, the mixture evaporated to dryness and the hydrobromide (70 g., 76%) dissolved in alcohol and precipitated with ether. N-(γ-Phenoxypropyl)-piperidine was prepared in 84% yield in the following manner: 72.0 g. of γ-phenoxypropyl bromide ("Organic Syntheses," **9**, 72) was added to 56.5 g. of piperidine and, after the initial reaction had subsided, the mixture was heated for three hours on a steam-bath, water added, the mixture acidified and unchanged bromide extracted with benzene. The aqueous layer was made strongly alkaline, the oily layer separated and the water extracted with ether. The product boiled at 152–154° (5 mm.); von Braun [*Ber.*, **42**, 2041 (1909)] reported 172° (13 mm.); yield 64 g. [t] Laun [*ibid.*, **17**, 682 (1884)] found 194°. [u] Wenker [THIS JOURNAL, **60**, 158 (1938)] found 204°. [v] Mannich, Lesser and Silten, *Ber.*, **65**, 384 (1932). [w] Mannich and Baumgarten, *ibid.*, **70**, 213 (1937).

(14) Adams and du Vigneaud [THIS JOURNAL, **46**, 2098 (1924)] described the base. This product was tested as the lactate.

(15) Mannich and Heilner, *Ber.*, **55**, 359 (1922).

(16) Blicke and Blake, THIS JOURNAL, **52**, 235 (1930); we found the melting point of the hydrochloride to be 220–221° instead of 210–211°.

TABLE II

ESTERS OF BENZILIC ACID (HYDROCHLORIDES AND METHOBROMIDES)

$(C_6H_5)_2C(OH)—COO—R·HCl$ (or CH_3Br)

C_6H_{11} = cyclohexyl; NC_4H_8O = morpholino; NC_5H_{10} = piperidino. Tested on the rabbit's cornea, compounds 2, 4, 6, 11, 13, 17 and 19 were found to be inactive as local anesthetics; compounds 3, 7, 8 and 9 showed some activity while compound 20 proved to be a strong anesthetic. Compounds 1 and 10 were recrystallized from alcohol; 2 and 5 from ethyl acetate; 7 and 17 from amyl acetate; 3, 6, 9, 11, 12, 13, 15 and 19 from a mixture of alcohol and ethyl acetate; 4, 8, 14, 16 and 18 were precipitated from an alcoholic solution by the addition of ether.

	R	I[a]	II[b]	M. p., °C.		% Halogen Calcd.	% Halogen Found
1	$—CH_2CH_2NH_2$	A, B	−−	170–171	$C_{16}H_{17}O_3N$	(5.16	5.13 N)
2	$—CH_2CH_2NH(C_4H_9)·HCl$	B	0	121–122	$C_{20}H_{26}O_3NCl$	9.75	9.70
3	$—CH_2CH_2N(C_2H_5)_2·HCl$	A	+++	174–175[c]	$C_{20}H_{26}O_3NCl$	9.75	9.80
4	$—CH_2CH_2N(C_2H_5)_2·CH_3Br$[d]		++++	169–170	$C_{21}H_{28}O_3NBr$	18.92	18.81
5	$—CH_2CH_2N(C_4H_9)_2·HCl$	B	0	126–127	$C_{24}H_{34}O_3NCl$	8.44	8.35
6	$—CH_2CH_2N(C_4H_9)_2·CH_3Br$		0	138–139	$C_{25}H_{36}O_3NBr$	16.70	16.81
7	$—CH_2CH_2N(CH_3)(C_6H_{11})·HCl$	B	−−	154–155	$C_{23}H_{30}O_3NCl$	8.78	8.68
8	$—CH_2CH_2N(CH_3)(C_6H_{11})·CH_3Br$		+	153–154	$C_{24}H_{32}O_3NBr$	17.28	17.19
9	$—CH_2CH_2N(C_6H_{11})_2·HCl$	B	0	197–198	$C_{28}H_{38}O_3NCl$	7.51	7.48
10	$—CH_2CH_2N(CH_3)(C_6H_5)$	B	−−	78–79	$C_{23}H_{23}O_3N$	(3.88	3.84 N)
11	$—CH_2CH_2N(CH_3)(C_6H_5)·CH_3Br$		0	179–180	$C_{24}H_{26}O_3NBr$	17.51	17.53
12	$—CH_2CH_2NC_4H_8O·HCl$	B	+	180–181	$C_{20}H_{24}O_4NCl$	9.38	9.31
13	$—CH_2CH_2NC_4H_8O·CH_3Br$		++	203–204	$C_{21}H_{26}O_4NBr$	18.32	18.22
14	$—CH_2CH_2NC_5H_{10}·HCl$	A, B	++++	175–176	$C_{21}H_{26}O_3NCl$	9.69	9.64
15	$—CH_2CH_2NC_5H_{10}·CH_3Br$		++++	202–203	$C_{22}H_{28}O_3NBr$	18.40	18.42
16	$—CH_2CH_2CH_2NC_5H_{10}·HBr$	A	+++	168–169	$C_{22}H_{28}O_3NBr$	18.40	18.42
17	$—CH_2CH_2CH_2NC_5H_{10}·CH_3Br$		+++	168–169	$C_{23}H_{30}O_3NBr$	17.82	17.86
18	$—CH(CH_3)CH_2NC_5H_{10}·HCl$	A	−−	167–168	$C_{22}H_{28}O_3NCl$	9.09	9.09
19	$—CH(CH_3)CH_2NC_5H_{10}·CH_3Br$		0	176–177	$C_{23}H_{30}O_3NBr$	17.82	17.78
20	$—CH_2C(CH_3)_2·CH_2NC_5H_{10}·HCl$	A	++	170–171	$C_{24}H_{32}O_3NCl$	8.48	8.57

[a] Method of preparation. [b] Mydriatic activity: 0 = inactive; + = poor; ++ = moderate; +++ = good; ++++ = excellent. [c] The same melting point has been reported (Ref. 8). [d] Methobromide.

β-Piperidinoethyl Benzilate Hydrochloride.—(A) A mixture of 31.9 g. (0.12 mole) of potassium benzilate[17] and 22.5 g. (0.12 mole) of β-piperidinoethyl chloride hydrochloride was heated for two hours at 140°. The material was extracted with hot alcohol, the extract concentrated, cooled and ethyl acetate added whereupon the ester hydrochloride precipitated; yield of crude product 44 g. (99%).

(B) The hydrochloride of β-piperidinoethyl chloride was dissolved in water, a saturated solution of sodium carbonate added, the base extracted with ether, the solution dried with fused sodium sulfate and the ether removed in a current of dry air. The product was used immediately.

To 7.4 g. (0.05 mole) of the basic chloride there was added 11.4 g. (0.05 mole) of benzilic acid, dissolved in 50 cc. of isopropyl alcohol. The mixture was refluxed for twelve hours, the solvent removed under diminished pressure on a steam-bath and the residue washed with ethyl acetate; yield 13 g. (70%). The crude product was purer than that obtained by process A.

β-Piperidinoethyl Benzilate Methobromide.—A solution of 3.4 g. (0.01 mole) of the ester in 25 cc. of absolute alcohol was poured into a magnesium citrate bottle, cooled to 0° and 10 cc. of methyl bromide added. After several hours at ordinary temperature about two-thirds of the alcohol was removed and the methobromide precipitated with absolute ether; yield 4.0 g. (94%).

The hydrobromide and the methobromide of γ-piperidinopropyl benzilate both melt at 168–169° and even though the mixed melting point was 152–157°, the methobromide was hydrolyzed in order to establish its identity. A mixture of 4.58 g. of the methobromide, 1.68 g. of potassium hydroxide and 10 cc. of absolute alcohol was refluxed for three hours, the precipitated potassium benzilate (2.73 g. or 97%) filtered, dissolved in water and the solution acidified; 2.21 g. of benzilic acid was obtained.

The alcoholic filtrate was neutralized with hydrobromic acid, evaporated to dryness, the residue treated with hot alcohol and the undissolved potassium bromide removed by filtration. Upon addition of ethyl acetate to the filtrate 2.11 g. (95%) of the methobromide of γ-piperidinopropyl alcohol precipitated; m. p. 138–139°.

The hitherto unknown methobromide was obtained when a mixture of 14.3 g. of γ-piperidinopropyl alcohol, 19.0 g. of methyl bromide and 50 cc. of absolute alcohol was allowed to remain at ordinary temperature for three hours and ether then added; the precipitated product weighed 22.5 g. (93%) and melted at 138–139° after recrystallization from acetone which contained a small amount of alcohol.

Anal. Calcd. for $C_9H_{20}ONBr$: Br, 33.56. Found: Br, 33.51.

β-Diisoamylaminoethyl Phenyl Ketone Hydrochloride.[18]—A mixture of 13.8 g. of acetophenone, 23 g. of diisoamylamine hydrochloride, 3.4 g. of trioxymethylene and 20 cc. of absolute alcohol was heated for two hours on a steam-bath; the trioxymethylene dissolved gradually. Upon

(17) Benzilic acid was prepared by oxidation of benzoin with potassium bromate ("Organic Syntheses," Coll. Vol. I, p. 82).

(18) Prepared by the general method of Mannich and Heilner, *Ber.*, **55**, 359 (1922).

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 $C_{16}H_{22}ONCl$: 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).

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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°.