11. *Synthetic Mydriatics.*

By A. H. Ford-Moore and H. R. Ing.

The preparation of some forty alkamine esters, mostly of benzilic acid, is described and the results of their testing as mydriatics are discussed.

Since the extensive study of synthetic tropeines by Jowett and Pyman (*7th Internat. Cong. Appl. Chem.*, 1909, IV*A*, 1, 335) and the work of von Braun, Braunsdorf, and Räth (*Ber.*, 1922, **55**, 1666) on the tropic esters of simple alkamines, little work has been published on synthetic mydriatics of the atropine type until recently, although a good deal of work has been done in France and U.S.A. on synthetic spasmolytics. Spasmolytic properties, however, appear to be less highly specific than mydriatic properties and more closely allied to local anæsthetic properties.

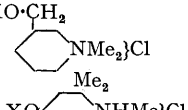
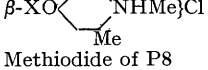
In 1942 Blicke and Maxwell (*J. Amer. Chem. Soc.*, 1942, **64**, 428, 431) reported that the benzilic esters of diethylamino- and piperidino-ethanols and their methobromides were excellent mydriatics when tested on the rabbit's eye in 1—2% solutions, but no quantitative comparison with atropine was made. Later Blicke and Kaplan (*ibid.*, 1943, **65**, 1967) found that the benzilic esters of simple alkamines were usually more potent mydriatics than the corresponding esters of mandelic acid or of any of the four isomeric phenylhydroxypropionic acids, including tropic acid.

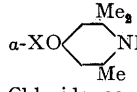
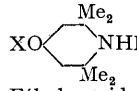
The mydriatic action of atropine is due to the drug antagonising acetylcholine released at the terminations of the parasympathetic (cholinergic) nerves to the circular muscle of the iris; stimulation of these nerves constricts the pupil and atropine prevents this effect. It occurred to us that acetylcholine might be antagonised by a suitable choline ester, and in fact both *tropylcholine chloride* and *benzilylcholine chloride* were found to have mydriatic properties, the latter being about a third as active as atropine in the mouse and about twice as active as the former. At the time (1942) these were the only mydriatic choline esters known to us, but Swan and White (*Proc. Soc. Exp. Biol. Med.*, 1943, **53**, 164) announced the discovery of mydriatic dialkylcarbamic esters of choline of which di-*n*-butylcarbamylcholine was the best. Recently Loew, Kaiser, and Anderson (*Fed. Proc.*, 1946, **5**, 190) have reported that the diphenylmethyl ether of choline has mydriatic properties.

Starting from benzilylcholine a search was made for more active benzilic esters of the same type. All our compounds were tested for mydriatic potency by Dr. Edith Bülbring and Mrs. Izabella Wajda in the Department of Pharmacology, Oxford, by comparing the effects of the synthetic substances and of atropine in groups of mice by direct measurement of the size of the pupil (Ing, Dawes, and Wajda, *J. Pharmacol.*, 1945, **85**, 85; cf. Pulewka, *Arch. exp. Path. Pharm.*, 1932, **168**, 307). Later Mr. G. S. Dawes compared the effects of the synthetic mydriatics and of atropine on the salivary secretion and blood pressure of the cat; his results are incorporated in the paper by Ing, Dawes, and Wajda (*loc. cit.*).

The synthetic benzilic esters are listed in Table I, together with their serial numbers and their relative molar potencies in terms of atropine sulphate = 100; the potencies of the more active compounds are also given on a dose–weight basis in parentheses. Molar potencies are more illuminating for studies on the structure and action of drugs, but for clinical purposes the relative potencies of equal doses are usually more useful; thus although E27 is intrinsically more active than E3, it presents no advantage over an equal dose of E3 because of its higher molecular weight. Atropine, E3, and E27 all have approximately the same activity in equal doses in mice,

TABLE I.

No.	Benzilic ester [X = $CPh_2(OH)\cdot CO$].	Potency.	Method of synthesis.	Crystallised from :	M. p.	Formula.	Found (%). C.	Found (%). H.	Required (%). C.	Required (%). H.	Notes.
C4	$CH_2(OX)\cdot CH_2\cdot NHMe_2\}Cl$	12·6	*a*	Ethanol or water	188—189°	$C_{18}H_{22}O_3NCl$	64·1	6·6	64·4	6·6	1
C1	$CH_2(OX)\cdot CH_2\cdot NMe_3\}Cl,\frac{1}{2}H_2O$	31	*b*	Ethanol–acetone	218	$C_{19}H_{24}O_3NCl,\frac{1}{2}H_2O$	63·6	7·1	63·6	7·0	2
E3	$CH_2(OX)\cdot CH_2\cdot NMe_2Et\}Cl$	104·4 (100)	*b*, *c*	,,	213	$C_{20}H_{26}O_3NCl$	66·1	7·2	66·0	7·2	3
E4	$CH_2(OX)\cdot CH_2\cdot NMe_2Pr^{\beta}\}Cl$	92·5 (85)	*b*	,,	199—200	$C_{21}H_{28}O_3NCl$	67·0	7·5	66·8	7·4	
E5	$CH_2(OX)\cdot CH_2\cdot NMe_2Pr^{\alpha}\}Br$	22	*c*	Ethanol–ethyl acetate	186—187	$C_{21}H_{28}O_3NBr$	59·9	6·5	59·7	6·6	
E6	$CH_2(OX)\cdot CH_2\cdot NMe_2\cdot C_3H_6\}Br$	28	*c*	Acetone	161—162	$C_{21}H_{26}O_3NBr$	60·2	6·3	60·0	6·2	
E7	$CH_2(OX)\cdot CH_2\cdot NMe_2Bu\}Br$	10·5	*c*	Ethanol–acetone	143—144	$C_{22}H_{30}O_3NBr$	60·0	7·1	60·5	6·9	
E11	$CH_2(OX)\cdot CH_2\cdot NMe_2Am\}Br$	13	*c*	Acetone	129—130	$C_{23}H_{32}O_3NBr$	61·4	7·2	61·3	7·2	
E25	$CH_2(OX)\cdot CH_2\cdot NMe_2\cdot CH_2\cdot CH_2Br\}Br$	30	*c*	Ethanol–acetone	173	$C_{20}H_{25}O_3NBr_2$	49·5	5·1	49·3	5·2	
E1	$CH_2(OX)\cdot CH_2\cdot NHEt_2\}Cl$	6·3	*a*	Ethanol–acetone	174—175	$C_{20}H_{26}O_3NCl$	—	—	—	—	4
E2	$CH_2(OX)\cdot CH_2\cdot NEt_2Me\}Cl$	64	*b*	,,	184—185	$C_{21}H_{28}O_3NCl$	66·6	7·4	66·6	7·5	5
E14	$CH_2(OX)\cdot CH_2\cdot NEt_3\}Br$	83 (66)	*c*	,,	220	$C_{22}H_{30}O_3NBr$	60·3	6·5	60·5	6·9	6
E15	$CH_2(OX)\cdot CH_2\cdot NEt_2Pr^{\alpha}\}Br$	22	*c*	,,	171	$C_{23}H_{32}O_3NBr$	61·6	7·1	61·3	7·2	
E16	$CH_2(OX)\cdot CH_2\cdot NHPr^{\beta}_2\}Cl$	9	*a*	Methyl ethyl ketone	147—148	$C_{22}H_{30}O_3NCl$	67·5	7·7	67·4	7·7	
E17	$CH_2(OX)\cdot CH_2\cdot NMePr^{\beta}_2\}I$	57·3	*c*	Ethanol or water	174—175	$C_{23}H_{32}O_3NI$	55·6	6·2	55·5	6·4	
E9	$CH_2(OX)\cdot CH_2\cdot NMeEtPr^{\alpha}\}Br$	27·6	*c*	Ethanol–acetone	189	$C_{22}H_{30}O_3NBr$	59·9	6·8	60·5	6·9	
E8	$CH_2(OX)\cdot CH_2\cdot CH_2\cdot NEt_2Me\}Cl$	60	*b*	,,	195	$C_{22}H_{30}O_3NCl$	67·6	7·6	67·4	7·7	
E10	$CH_2(OX)\cdot CH_2\cdot CH_2\cdot NEtMe_2\}Cl$	64	*b*	,,	181	$C_{21}H_{28}O_3NCl$	66·3	7·5	66·6	7·5	
E12	$CHMe(OX)\cdot CH_2\cdot NMe_2Et\}Br$	9·7	*c*	Ethanol	213	$C_{21}H_{28}O_3NBr$	60·0	6·5	59·7	6·6	
E26	$CHMe(OX)\cdot CMe_2\cdot CH_2\cdot NMe_2H\}Cl$	0	*d* (130°)	Methyl ethyl ketone	174—175	$C_{22}H_{30}O_3NCl$	66·6	7·7	67·4	7·9	
E27	$CH_2(OX)\cdot CMe_2\cdot CH_2\cdot NMe_2Et\}I$	142 (99)	*c*	Methyl acetate	136—137	$C_{23}H_{32}O_3NI$	55·6	6·5	55·3	6·5	
P1	$CH_2(OX)\cdot CH_2\cdot NH\cdot C_5H_{10}\}Cl$	0·6	*a*	Ethanol or acetone	170—171	$C_{21}H_{26}O_3NCl$	67·7	6·9	67·2	6·9	4, 4a
P2	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_5H_{10}\}Cl$	17·3	*b*	Ethanol–acetone	215	$C_{22}H_{28}O_3NCl$	67·8	7·2	67·9	7·3	5
P6	$CHMe(OX)\cdot CH_2\cdot NH\cdot C_5H_{10}\}Cl$	0	*a*	Ethanol–ether	167—168	$C_{22}H_{28}O_3NCl$	—	—	—	—	4
M1	$CH_2(OX)\cdot CH_2\cdot NH\cdot C_4H_8O\}Cl$	0	*a*	Ethanol–ethyl acetate	181	$C_{20}H_{24}O_4NCl$	—	—	—	—	4
M2	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_4H_8O\}Cl$	4·5	*b*	Ethanol	207—208	$C_{21}H_{26}O_4NCl$	64·1	6·7	64·3	6·7	5
M6	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_4H_8S\}Cl$	14	*b*	Ethanol–acetone	227 (decomp.)	$C_{21}H_{26}O_3NClS$.	61·8	6·5	61·8	6·6	
M7	$CH_2(OX)\cdot CH_2\cdot NMe\cdot C_4H_8SO_2\}Cl$	0	*b*	Ethanol	225 (decomp.)	$C_{21}H_{26}O_5NClS$	56·7	6·0	56·3	5·9	7
P7		65	*b*	Ethanol–acetone	238 (decomp.)	$C_{22}H_{28}O_3NCl$	67·5	7·0	67·8	7·2	
P8		16	*d* (160°)	Ethanol	244 (decomp.)	$C_{23}H_{30}O_3NCl$	68·2	7·5	68·4	7·4	
P9	Methiodide of P8	170 (116)	*c*	Ethanol or water	225 (decomp.)	$C_{24}H_{32}O_3NI$	—	—	—	—	8
P10	Methochloride of P8 + C_3H_8O	165 (120)	*c*	*iso*Propanol	224 (decomp.)	$C_{24}H_{32}O_3NCl,C_3H_8O$	67·7	8·3	67·8	8·4	9

P11	α-XO{  NMe$_2$}I	196 ?		*c*	Water	239 (decomp.)	$C_{24}H_{32}O_3NI$	56·8	6·3	56·6	6·3	
P12	Chloride, corresponding to P11	143	(104)	*c*	*iso*Propanol	212 (decomp.)	$C_{24}H_{32}O_3NCl,C_3H_8O$	67·4	8·5	67·8	8·4	10
P13	XO{  NHMe}Cl	0		*d* (140°)	Ethanol–acetone	253 (decomp.)	$C_{24}H_{32}O_3NCl$	68·8	7·7	69·0	7·7	
P14	Ethobromide of P13	0		*c*	Ethanol	255 (decomp.)	$C_{26}H_{36}O_3NBr$	63·0	7·3	63·5	7·6	

The methods of synthesis (column 4) are listed in the experimental section. Potencies (column 3) are relative molar potencies (atropine sulphate = 100) on the eye of the mouse; the figures in parentheses are potencies on a dose–weight basis (atropine sulphate = 100).

1. Previously made by Blicke and Kaplan (*loc. cit.*) who record m. p. 183—185°.
2. Found (anhydrous): C, 65·1; H, 6·9. $C_{19}H_{24}O_3NCl$ requires C, 65·2; H, 6·9%.
3. Method *b* gives 75% yield; method *c*: dimethylaminoethyl benzilate heated with excess of ethyl chloride in acetone at 100° for 8—12 hours; the product crystallized from the reaction mixture, any unchanged tertiary base being recovered from the mother liquor.
4. Previously made by Blicke and Maxwell (*loc. cit.*); (4a) who record m. p. 175—176°.
5. Corresponding bromide made by Blicke and Maxwell.
6. The *chloride*, m. p. 235°, is more soluble in water, less soluble in alcohol, and has the same potency (Found: C, 67·4; H, 7·8. $C_{22}H_{30}O_3NCl$ requires C, 67·4; H, 7·7%).
7. M7 could not be obtained by oxidising M6 with hydrogen peroxide; β-chloroethylthiomorpholine dioxide was obtained from divinyl sulphone and ethanolamine, followed by thionyl chloride, and was converted into its methiodide.
8. Sparingly soluble in water (Found: I, 25·0. $C_{24}H_{32}O_3NI$ requires I, 24·9%).
9. Soluble in water; *iso*propanol of crystallization not lost at 100° in a vacuum (Found: Cl, 7·6. $C_{24}H_{32}O_3NCl$ requires Cl, 7·4%).
10. Began to lose *iso*propanol of crystallization at 150°, effervesced at 159°, resolidified, and finally melted at 212° (decomp.).

TABLE II.

No.	Compound.	Potency.	Method of synthesis.	Crystallized from:	M. p.	Formula.	Found (%). C.	Found (%). H.	Required (%). C.	Required (%). H.
C2	CMePh(OH)·CO_2·CH_2·CH_2·NMe_3}Cl,H_2O	0	*b*	Ethanol–acetone	170° *	$C_{14}H_{22}O_3NCl,H_2O$	54·7	8·1	54·9	7·9
C3	CHPh(CH_2·OH)·CO_2·CH_2·CH_2·NMe_3}Cl,$\frac{1}{2}H_2O$	12·5	*b*	Methanol–ethyl acetate	178—179	$C_{14}H_{22}O_3NCl,\frac{1}{2}H_2O$	56·9	7·6	56·7	7·7
P3	CMePh(OH)·CO_2·CH_2·CH_2·$NMe·C_5H_{10}$}Cl	0	*b*	Ethanol–acetone	164—165	$C_{17}H_{26}O_3NCl$	61·8	8·2	62·3	7·9
M3	CHPh(CH_2Cl)·CO_2·CH_2·CH_2·NH·C_4H_8O}Cl	0	*d*	,,	149	$C_{15}H_{21}O_3NCl_2$	54·3	6·5	53·9	6·3
M4	C_6H_4 C_6H_4>C(OH)·CO_2·CH_2·CH_2·NH·C_4H_8O}Cl	0	*a*	Ethanol	195—196	$C_{20}H_{22}O_4NCl$	64·0	6·2	64·1	5·9
M5	CMePh(OH)·CO_2·CH_2·CH_2·NH·C_4H_8O}Cl	0	*a*	,,	192 (decomp.)	$C_{16}H_{24}O_4NCl$	58·1	7·4	58·3	7·3
E13	CPh$_2$(OH)·CO·NH·CH_2·CH_2·NMe_2Et}Br	11	*c*	Ethanol–acetone	227	$C_{20}H_{27}O_2N_2Br$	58·8	6·6	59·0	6·7
E21	CPh$C_{10}H_7$β(OH)·CO_2·CH_2·CH_2·NMe_2Et}Cl	0	*b*	,,	221 (decomp.)	$C_{24}H_{28}O_3NCl$	69·6	6·7	69·7	6·8
E22	CPh$C_{10}H_7$α(OH)·CO_2·CH_2·CH_2·NMe_2Et}Cl	5	*b*	Ethanol–ethyl acetate	194—195	$C_{24}H_{28}O_3NCl$	69·5	6·8	69·7	6·8

* Began to lose water at 163°.

but **E3** has the advantage over E27 that it can be prepared from more readily accessible materials.

The mydriatic effect of E3 in the mouse, the cat, and man is more transient than that of atropine and is, in this respect, more comparable with that of homatropine; E3 also produces paralysis of accommodation in man.

In the homologous series $CH_2(OX)\cdot CH_2\cdot NMe_2R\}Hal$. [X = $CPh_2(OH)\cdot CO$ and R = an alkyl group], a sharp maximum in mydriatic activity occurs when R = Et, and it is interesting to note that the most active mydriatic discovered by Swan and White (*Amer. J. Ophthal.*, 1944, **27**, 933) was the dibutylcarbamic ester of the same alkamine (X = $NBu_2\cdot CO$; R = Et). The relatively high activity of E4 (R = Pr^{β}) is abruptly diminished by the introduction of a second *iso*propyl group (E17); the *n*-propyl group (E5) is less effective than the *iso*propyl group. In the series $CH_2(OX)\cdot CH_2\cdot NEt_2R\}Hal$. the maximum again occurs when R = Et.

The propanolamine derivatives E8 and E10 were both less active and less toxic than their ethanolamine analogues. The introduction of a β-methyl group into E3, as in E12, leads to a sharp drop in activity, a result which recalls the decline in cholinergic preperties in passing from acetylcholine to acetyl-β-methylcholine. The high activity of E27 is interesting because Fromherz (*Arch. exp. Path. Pharm.*, 1933, **173**, 116) examined an analogous compound $CH_2(OX)\cdot CMe_2\cdot CH_2\cdot NEt_2Me\}SO_4Me$, which produced mydriasis in cats in 0·1% solution (atropine, 0·001%; *loc. cit.*, p. 126); the tertiary base hydrochloride, $CH_2(OX)\cdot CMe_2\cdot CH_2\cdot NEt_2H\}Cl$, was about half as active, and the tropic ester of the tertiary base was scarcely mydriatic at all.

The piperidinoethanol compounds P1 and P2, which Blicke and Maxwell classed as " excellent " mydriatics, proved to be relatively feeble and much less active than E2, which these authors examined as the bromide and also classified as " excellent ". The morpholino- and thiomorpholino-compounds (M1, M2, M6, and M7) were even more feeble in their action.

Fromherz (*loc. cit.*) and Blicke and Kaplan (*loc. cit.*) noted that benzilic esters of alkamines were better mydriatics than the corresponding tropic esters, and we have already noted a similar result for benzilyl- and tropyl-choline; an even more striking example of the efficacy of benzilic acid in mydriatic esters is provided by the compounds P8 to P10. Eucatropine is the mandelic ester of the β-isomeride of 4-hydroxy-1 : 2 : 2 : 6-tetramethylpiperidine, and P8 is the corresponding *benzilic* ester; in the mouse eucatropine hydrochloride has a molar potency of 0·4 whereas that of P8 is 16; eucatropine methiodide has a potency of 2·8, and the *metho*-salts of P8 have 165—170. The α-isomeride of 4-hydroxy-1 : 2 : 2 : 6-tetramethylpiperidine also yields a mydriatic benzilic ester, the *methochloride* (P12), having a molar potency of 143; the *methiodide* (P11) was sparingly soluble in water, and too few mice were used for the figure in Table I to be reliable. The benzilic ester of the symmetrical 4-hydroxy-1 : 2 : 2 : 6 : 6-pentamethylpiperidine (P13) was inactive.

Although P10 is more potent than E3 in the mouse, its mydriatic effect is also more transient; in man it proved to be a very weak mydriatic and uncertain in action; like eucatropine it is not a cycloplegic drug (personal communication by Professor Ida Mann).

One of the most striking results of a study of the benzilic esters listed in Table I is that the salts of tertiary bases are much less active than their metho-salts; thus the compounds C4, E1, E16, P1, M1, and P8 are markedly less active than their respective metho-salts C1, E2, E17, P2, M2, and P10. Fromherz (*loc. cit.*) and Blicke and Maxwell (*loc. cit.*) noted a similar effect, and the point has been fully discussed by Ing, Dawes, and Wajda (*loc. cit.*).

Mydriatic activity appears to be more specifically associated with the nature of the acyl group than with that of the alkamine; this is illustrated by the results listed in Table II. Several α-hydroxy-α-phenylpropionic esters (C2, P3, M5) had no activity although the benzilic analogues C1 and P2 were active. Replacement of the benzilic ester group in E3 by the benzilamido-group (E13) reduced the activity to a tenth.

An attempt to find an asymmetric analogue of E3 in order to discover whether compounds of this type display any stereochemical specificity comparable with that of the belladonna alkaloids was unsuccessful; the *phenyl-β-naphthylglycollic* ester was inactive and the *phenyl-α-naphthylglycollic* ester only feebly active.

These results on modifications of the benzilyl group are in striking contrast with those which have been obtained by numerous authors on spasmolytic alkamine esters in which the nature of the acyl group can be varied widely without drastic loss of activity.

The preparation of the alkamine esters presented no special difficulty. The method of Horenstein and Pählicke (*Ber.*, 1938, **71**, 1654)—*i.e.*, by heating the chloroalkylamine salt of an organic acid—proceeded very easily when the N atom was quaternary, but required higher

temperatures when the N atom was tertiary or the Cl atom attached to a secondary carbon. The benzilic esters of 4-hydroxy-1 : 2 : 2 : 6-tetramethylpiperidines were prepared by heating the dry hydrochlorides of the latter with diphenylchloroacetyl chloride, a method which we owe to Dr. F. E. King; the α-chlorine atom of the product is readily hydrolysed in aqueous solution. A similar method was used to prepare the ββ-dimethylpropanolamine derivatives E26 and E27.

E3 has been used in the Oxford Eye Hospital and elsewhere during the last two years with some success. Clinical reports on its use have been published by Mann (*Brit. J. Ophthal.*, 1946, **30**, 8) and by Riddell (*ibid.*, p. 1). It is proposed to give E3 the name Lachesine (from Λαχεσις, one of the Fates, whose sister Ἄτροπος gave her name to atropine).

Experimental.

[Analyses (all micro-) are by Weiler and Strauss. Melting points are uncorrected.]

Benzilic Esters.—The methods of preparation are indicated by letters *a*, *b*, *c*, and *d* in Table I.

(*a*) An intimate mixture of the chloroalkyldialkylamine hydrochloride and potassium benzilate was heated at 140—160° for 3—4 hours and the cooled melt extracted with hot ethanol. The alcohol extract was evaporated and the product stirred with acetone and separated. In a few cases the chloroalkylamine and benzilic acid were heated in boiling chlorobenzene, from which the benzilic ester hydrochloride separated.

(*b*) The chloroalkyltrialkylammonium chloride (or iodide) was heated in boiling ethanol with potassium (or silver) benzilate for 1 hour. The solution was filtered from metal halide, evaporated, and the residue heated at 100° until it solidified completely; it was stirred with acetone, collected, and recrystallised.

Methods *a* and *b* yield homogeneous products; any chloroalkylammonium benzilate which has failed to undergo the Horenstein and Pählicke rearrangement remains in the acetone used to wash the product.

(*c*) The tertiary aminoalkyl benzilate was heated with an alkyl halide without a solvent or in acetone. Methochlorides were usually obtained by digesting the methiodide with silver chloride in methanol.

(*d*) The dry tertiary amino-alcohol hydrochloride (prepared in ethanol but not usually isolated) was heated with diphenylchloroacetyl chloride at the temperature indicated in parentheses until the evolution of hydrogen chloride ceased (3—5 hours). The melt was dissolved in hot water, cooled, diluted, and the ester precipitated by the addition of dilute ammonia solution.

Miscellaneous Esters.—These (Table II) were prepared by analogous methods; *i.e.*, (*a*) from the chloroalkylamine hydrochloride and the potassium salt of the acid; (*b*) from the chloroalkyltrialkylammonium halide and the potassium (or silver) salt of the acid in ethanol; (*c*) from the tertiary base and the alkyl halide; (*d*) from the amino-alcohol and the acid chloride.

The Basic Moieties.—Tertiary chloroalkylamine hydrochlorides were prepared by the method used by Gough and King (*J.*, 1928, 2436) for diethylchloroethylamine hydrochloride. Quaternary chloroalkylammonium chlorides were prepared (i) by addition of methyl iodide to the tertiary base and subsequent digestion of the product with silver chloride, or (ii) by keeping the quaternary hydroxyalkylammonium chloride with a chloroform solution of thionyl chloride for several hours and evaporating the clear solution so obtained. The following compounds were prepared: trimethyl-β-chloroethylammonium chloride, prisms from ethanol, m. p. 241° (Found: C, 38·1; H, 8·4. Calc. for $C_5H_{13}NCl_2$: C, 38·0; H, 8·2%); dimethyl-β-chloroethylamine hydrochloride (Slotta and Behnisch, *Ber.*, 1935, **68**, 754); *dimethylethyl-β-hydroxyethylammonium picrate*, yellow needles, m. p. 251° (Found: C, 41·5; H, 5·27. $C_{12}H_{18}O_8N_4$ requires C, 41·6; H, 5·24%); *dimethylethyl-β-chloroethylammonium chloride*, hygroscopic prisms from ethanol–acetone, m. p. 231° (decomp.) (Found: C, 41·85; H, 8·85. $C_6H_{15}NCl_2$ requires C, 41·86; H, 8·72%); *picrate*, orange needles from methanol, m. p. 200° (Found: C, 39·3; H, 4·7. $C_{12}H_{17}O_7N_4Cl$ requires C, 39·5; H, 4·7%); *dimethyl-β-hydroxyethylisopropylammonium chloride*, hygroscopic prisms from *iso*butanol (Found: C, 49·8; H, 10·8. $C_7H_{18}ONCl$ requires C, 50·1; H, 10·7%); *β-chloroethylisopropylamine hydrochloride*, fine needles from acetone or methyl ethyl ketone, m. p. 180—181° (Found: C, 38·1; H, 8·25. $C_5H_{13}NCl_2$ requires C, 38·0; H, 8·23%); *β-chloroethyldiisopropylamine hydrochloride*, diamond-shaped prisms from acetone, m. p. 110° (Found: C, 47·9; H, 9·5. $C_9H_{19}NCl_2$ requires C, 48·0; H, 9·5%); *dimethyl-β-chloropropylamine hydrochloride*, hygroscopic needles m. p. 196° (Found: C, 37·9; H, 8·3. $C_5H_{13}NCl_2$ requires C, 38·0; H, 8·2%); *methyl dimethylamino-tert.-butyl ketone hydrobromide*, less hygroscopic than the hydrochloride, m. p. 174° (decomp.) (Found: C, 43·0; H, 8·1. $C_8H_{18}ONBr$ requires C, 42·9; H, 8·1%); *picrate*, yellow needles from methanol, m. p. 150° (Found: C, 45·6; H, 5·5. $C_{14}H_{20}O_8N_4$ requires C, 45·2; H, 5·4%); *3-chloro-1-dimethylamino-2 : 2-dimethyl-n-butane picrate*, from ethanol, m. p. 160° (Found: C, 43·3; H, 5·4. $C_{14}H_{21}O_7N_4Cl$ requires C, 42·8; H, 5·4%); *3-dimethylamino-2 : 2-dimethylpropanol hydrobromide*, obtained by reduction of the corresponding aldehyde (Mannich, Lesser, and Silten, *Ber.*, 1932, **65**, 381) by means of aluminium *iso*propoxide, formed plates from *iso*propanol, m. p. 158—159° (Found: C, 40·4; H, 8·3. $C_7H_{18}ONBr$ requires C, 39·6; H, 8·5%); β-chloroethylpiperidine (Dunlop, *J.*, 1912, **101**, 2002) gave a *methiodide*, m. p. 176—177°, from ethanol (Found: N, 4·6. $C_8H_{17}NClI$ requires N, 4·8%); piperidine-3-carbinol (Sandborn and Marvel, *J. Amer. Chem. Soc.*, 1928, **50**, 565) was methylated with formic acid and formalin and the product treated with thionyl chloride followed by methyl iodide to give 1 : 1-*dimethyl-3-chloromethylpiperidinium iodide*, which crystallised from ethanol in prisms, m. p. 176—177° (Found: C, 33·4; H, 5·5. $C_8H_{17}NClI$ requires C, 33·2; H, 5·8%).

Reduction of vinyldiacetonamine (21 g.) by means of aluminium *iso*propoxide and crystallisation of the product from benzene gave the β-alkamine (17 g.), m. p. 159—161°, and from the mother liquor a mixture (m. p. 120—123°; 3·5 g.) of the α- and β-alkamines. The β-alkamine was methylated with

formalin and formic acid and the *N*-methyl-β-alkamine purified by sublimation in a vacuum; m. p. 77—78° (Harries, *Annalen*, 1897, **294**, 352, records m. p. 70—72°). The β-alkamine (5 g.), boiled in amyl alcohol (100 c.c.) containing sodium (10 g.) for 30 hours, gave the α-form (3·6 g.), m. p. 137—138°. *N-β-Hydroxyethylthiomorpholine methochloride*, from *N*-methylthiomorpholine and ethylene chlorohydrin, crystallised from ethanol, m. p. 258° (decomp.) (Found: C, 42·4; H, 8·3. $C_7H_{16}ONClS$ requires C, 42·3; H, 8·2%); *N-β-chloroethylthiomorpholine methochloride* crystallised from ethanol–acetone and decomposed at 232—235° without melting (Found: C, 38·6; H, 6·9. $C_7H_{15}NCl_2S$ requires C, 38·9; H, 7·0%).

β-Dimethylaminoethylamine formed a *monobenzilate*, m. p. 152°, from ethanol (Found: C, 68·7; H, 7·6. $C_{16}H_{24}O_3N_2$ requires C, 68·3; H, 7·6%) and a *dibenzilate*, m. p. 168—169°, from ethanol (Found: C, 70·3; H, 6·67. $C_{30}H_{36}O_6N_2$ requires C, 70·5; H, 6·65%). The former was heated at 185° for 2 hours and a further ½ hour in a vacuum to remove volatile products; the product was extracted with benzene, from which *dimethylaminoethyl benzilamide hydrogen benzilate* separated; m. p. 126°, from chloroform–light petroleum (Found: C, 72·3; H, 6·4; N, 5·1. $C_{30}H_{34}O_5N_2$ requires C, 73·0; H, 6·5; N, 5·3%). The free *amide* crystallised from benzene–light petroleum, m. p. 124° (Found: C, 72·5; H, 7·4. $C_{18}H_{22}O_2N_2$ requires C, 72·5; H, 7·4%), and gave E 13 with ethyl bromide.

The Acidic Moieties.—The phenylnaphthylglycollic acids were prepared from the corresponding naphthyl benzyl ketones; the α-naphthyl ketone was prepared by the method of Cook and Hewitt (*J.*, 1934, 376) and the β-naphthyl ketone by a similar reaction in nitrobenzene solution. The ketones were converted into *iso*nitrosoketones and the diketophenylnaphthylethanes converted into the glycollic acids by keeping them in ether solution with methyl-alcoholic potash.

α-Naphthyl isonitrosobenzyl ketone, yellow needles from benzene, m. p. 130—131° (Found: N, 4·9. $C_{18}H_{13}O_2N$ requires N, 5·1%). *Diketophenyl-α-napthylethane*, m. p. 102—103°, from ethanol (Found: C, 82·8; H, 4·6. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%). *Phenyl-α-naphthylglycollic acid* crystallised from 50% (v/v) acetic acid in a hydrated form which began to lose water at 109° and melted with effervescence at 117°; on cooling the melt solidified and then melted at 146—147° (Found: C, 68·7; H, 6·0. $C_{18}H_{14}O_3,2H_2O$ requires C, 68·8; H, 5·7%). The anhydrous acid, m. p. 147—148°, was obtained by evaporating a benzene solution of the hydrated acid. With concentrated sulphuric acid the acid gave a greenish-yellow colour turning green.

β-Naphthyl isonitrosobenzyl ketone formed hexagonal plates from methanol, m. p. 159—160° (Found: N, 4·8. $C_{18}H_{13}O_2N$ requires N, 5·1%). *Diketophenyl-β-naphthylethane* formed needles from light petroleum, m. p. 88—89° (Found: C, 82·9; H, 4·7. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%). *Phenyl-β-naphthylglycollic acid* crystallised from benzene, m. p. 145—146°, and gave a greenish-blue colour turning mauve with concentrated sulphuric acid (Found: C, 77·6; H, 5·1. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·0%).

Esters.—The following basic esters are new. *Dimethylaminoethyl benzilate*, prisms from light petroleum, m. p. 91—92° (Found: C, 72·2; H, 7·1. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1%). Its *hydrogen benzilate* is formed (50% yield) by heating potassium benzilate and dimethylchloroethylamine hydrochloride in aqueous or alcoholic solution for 1 hour; prisms, sparingly soluble in alcohol, m. p. 159—160° (Found: C, 72·5; H, 6·3. $C_{32}H_{33}O_6N$ requires C, 72·8; H, 6·3%). *Diethylaminoethyl benzilate*, prisms from light petroleum, m. p. 54° (Found: C, 73·5; H, 7·7. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·7%). *Methyl-n-propylaminoethyl benzilate hydrochloride*, m. p. 154°, from ethanol (Found: C, 66·3; H, 7·5. $C_{20}H_{26}O_3NCl$ requires C, 66·0; H, 7·2%). *γ-Dimethylamino-ββ-dimethylpropyl benzilate*, long prisms from light petroleum, m. p. 66—67° (Found: C, 73·6; H, 7·9. $C_{21}H_{27}O_3N$ requires C, 73·9; H, 7·9%). *Piperidinoethyl benzilate*, prisms from light petroleum, m. p. 71—72° (Found: C, 74·1; H, 7·4. $C_{21}H_{25}O_3N$ requires C, 74·3; H, 7·4%).

β-4-Benzilyloxy-1 : 2 : 2 : 6-tetramethylpiperidine, crystallized first from methanol and finally from acetone, formed needles, m. p. 155—156° (Found: C, 75·2; H, 8·0. $C_{23}H_{29}O_3N$ requires C, 75·2; H, 7·9%). The corresponding *α-form* of this ester crystallised from acetone in prisms, m. p. 137—138° (Found: C, 75·0; H, 8·0. $C_{23}H_{29}O_3N$ requires C, 75·2; H, 7·9%). *4-Benzilyloxy-1 : 2 : 2 : 6 : 6-pentamethylpiperidine* crystallised from light petroleum, m. p. 94° (Found: C, 75·4; H, 8·5. $C_{24}H_{31}O_3N$ requires C, 75·6; H, 8·2%).

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