1. R. ACHER, C. FROMAGEOT, and M. JUTISZ. Biochim. et Biophys. Acta, **5**, 81 (1950).
2. A. W. JOHNSON and D. J. MCCALDIN. J. Chem. Soc. 3470 (1957).
3. W. GRASSMANN and K. VON ARNIM. Ann. **519**, 192 (1935).
4. G. BARGER, R. ROBINSON, and T. S. WORK. J. Chem. Soc. 711 (1937).
5. H. RAPOPORT, H. BALDRIDGE, and E. J. VOLCHECK. J. Am. Chem. Soc. **75**, 5290 (1953).
6. L. FOWDEN. Biochem. J. **64**, 323 (1956).
7. A. C. HULME and W. ARTHINGTON. Nature, **173**, 588 (1954).
8. A. J. CLARKE and P. J. MANN. Biochem. J. **71**, 596 (1959).
9. L. FOWDEN. Private communication.
10. A. VIRTANEN and S. KARI. Acta Chem. Scand. **8**, 1290 (1954).
11. G. URBACH. Nature, **175**, 170 (1955).
12. R. MUNIER and M. MACHEBOEUF. Bull. soc. chim. biol. **33**, 846 (1951).

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SOME NEW BENZILIC ACID DERIVATIVES

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Morrison, Konigstein, and Cohen (1) have synthesized a series of esters of benzilic acid (I) related in structure to benadryl and trasentin. Klosa (2) has also reported that 2-dimethylaminoethyl esters of alkoxydiphenylacetic acid (II) possess strong analgesic and sedative action. In this communication we wish to describe the synthesis of some new benzilic acid derivatives similar in structure to both I and II. These compounds (III–VI) are listed in Table I. The intermediates required for their preparation are listed in Table II.

TABLE I

$$(C_6H_5)_2\overset{\displaystyle O-CH_2CH_2R}{\overset{|}{C}}-COOCH_2CH_2R_1$$

Compound	R	R_1	Yield, %	M.p. or b.p.	Formula	Analysis* Calculated C	H	N	Found C	H	N
III	Cl	$-N(CH_3)_2$.HCl	51	145–148°	$C_{20}H_{25}NO_3Cl_2$	60.32	6.33	3.52	61.3	6.61	3.72
IV	H	$-N$(pyrrolidine).HCl	64	166–168°	$C_{22}H_{28}NO_3Cl$	67.76	7.21	3.59	67.72	7.24	3.59
V	H	N(morpholine).HCl	80	172–174°	$C_{22}H_{28}NO_4Cl$	65.08	6.95	3.45	64.82	7.06	3.45
VI	$-N$(pyrrolidine)	$N(C_2H_5)_2$	74	195–197/1 mm	$C_{26}H_{36}N_2O_3$	73.55	8.55	6.60	73.11	8.44	6.75

*Calc.: for III Cl, 17.80. Found: Cl, 17.92.

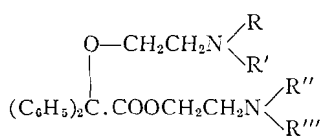
When an attempt was made to prepare dimethylaminoethyl diphenyl(2-hydroxyethoxy) acetate hydrochloride (VII) by the reaction of ethylene glycol with dimethylaminoethyl chlorodiphenylacetate hydrochloride, ring closure to form the cyclic lactone VIII occurred. Alkaline hydrolysis converted VIII to the corresponding acid IX.

TABLE II

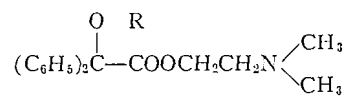
Intermediates $(C_6H_5)_2C(R)—COOR'$

R	R'	M.p. or b.p.	Yield, %	Formula	Analysis: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
OH	$CH_2CH_2N(CH_3)_2$ HCl	150–160°[a]	57							
OH	CH_2CH_2N(pyrrolidine) .HCl	174–175°[b]	78							
OH	CH_2CH_2N(morpholine) .HCl	178–180°[c]	61							
Cl	$CH_2CH_2N(CH_3)_2$ .HCl	184–186°[d]	83							
Cl	CH_2CH_2N(pyrrolidine) .HCl	165–167°	88	$C_{20}H_{23}NO_2Cl_2$	63.17	6.10	3.68	63.13	6.12	3.75
Cl	CH_2CH_2N(morpholine) .HCl	139–140°[e]	81							
OCH_2CH_2N(pyrrolidine)	C_2H_5	195–197°/1 mm	58	$C_{22}H_{25}NO_3$	74.54	7.96	3.95	74.74	7.72	4.34
OCH_2CH_2N(pyrrolidine)	Na	291–292°	81	$C_{20}H_{23}NO_3Na$	68.95	6.65	4.02	69.24	6.51	4.13

[a]Lit. value 184–186° (5). [b]Lit. value 173–173.5° (6). [c]Lit. value 181.5–182.5° (6). [d]Lit. value 183–185° (4). [e]Lit. value 151.5–152° (7).



I



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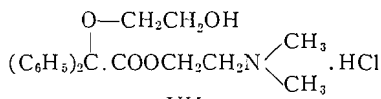
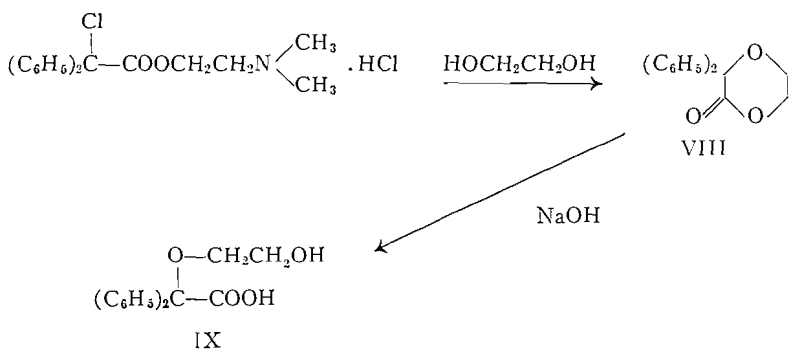


VII



VIII

IX

EXPERIMENTAL

Dialkylaminoethyl Benzilate Hydrochlorides (Table II)

These compounds were prepared from benzilic acid and the required 2-chloroethyldialkylamine according to the general method of Horenstein and Pahlicke (3).

Dialkylaminoethyl Alkoxydiphenylacetate Hydrochlorides (Table I)

Compounds III, IV, and V were prepared from the dialkylaminoethyl benzilate hydrochlorides by way of the corresponding chlorodiphenylacetate hydrochlorides as described by Klosa (4). Details of the preparation of dimethylaminoethyl 2-chloroethoxydiphenylacetate (III) are given below, since Klosa's procedure was modified in this case.

A mixture of 15 g of dimethylaminoethyl chlorodiphenylacetate hydrochloride, 3 g of calcium carbonate, and 76 ml of freshly distilled 2-chloroethanol was refluxed for 24 hours with mechanical stirring. The hot reaction mixture was filtered and then allowed to cool. The solvent was distilled under reduced pressure and the residue extracted with acetone and filtered. After distillation of the acetone the residue was treated with 200 ml of 10% sodium hydroxide and extracted with ether. The dried ether layer (calcium chloride) was then saturated with hydrogen chloride at 3 to 4°. The hydrochloride precipitated as a crystalline product, 8.5 g (51%), m.p. 145–151°.

The material was purified by dissolving it in isoamyl alcohol and slowly pouring the resulting solution into anhydrous ether containing some seed crystals, m.p. 145–148°. The mixture was not stirred but kept overnight at 5°. Filtration yielded crystals melting at 145–148°.

Diethylaminoethyl 2-(1-Pyrrolidyl)ethoxydiphenylacetate (VI)

This compound was prepared from ethyl benzilate according to the method of Morrison, Konigstein, and Cohen (1).

2,2-Diphenyl-3-keto-1,4-dioxane (VIII)

A mixture of 20 g of dimethylaminoethyl chlorodiphenylacetate hydrochloride, 4.5 g of calcium carbonate, and 100 ml of ethylene glycol was heated for 24 hours at 90–100°. After the solution was filtered it was made basic with sodium hydroxide. The resulting solid was filtered and washed with dilute hydrochloric acid. After recrystallization from alcohol–water a yield of 8.5 g (59%), m.p. 95–97°, was obtained. A second recrystallization raised the melting point to 98–99°. Anal. Calc. for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.11; H, 5.62.

Diphenyl(2-hydroxyethoxy)acetic Acid (IX)

2,2-Diphenyl-3-keto-1,4-dioxane (1 g) was refluxed with 10 ml 10% sodium hydroxide for 2 hours. After dilution and acidification of the solution, the product, m.p. 122–123°, after recrystallization from alcohol–water, was obtained. Anal. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.88. Found: C, 70.64; H, 6.06. Neut. eq. Calc.: 272. Found: 272.

1. A. L. Morrison, M. Konigstein, and A. Cohen. J. Chem. Soc. 2887 (1950).
2. J. Klosa. Arch. Pharm. **287**, 321 (1954).
3. H. Horenstein and H. Pahlicke. Ber. **71**, 1644 (1938).
4. J. Klosa. Arch. Pharm. **288**, 42 (1955).
5. J. Klosa. Deut. med. Wochschr. **75**, 870 (1950).
6. R. B. Moffett, J. L. White, B. D. Aspergren, and F. E. Visscher. J. Am. Chem. Soc. **77**, 1565 (1955).
7. L. C. Cheney and W. G. Bywater. J. Am. Chem. Soc. **64**, 970 (1942).

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