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972. *Spasmolytics Derived from Xanthen.*

By A. A. Goldberg and A. H. Wragg.

9-Xanthenyl-acetic and -glycollic and 9-xanthenylideneacetic acid have been synthesised and converted into their 2-dialkylaminoalkyl esters. These, together with their ethobromides, have been examined for antispasmodic activity by the Magnus method.

Because of the high antispasmodic activity of the methobromides of 2-dialkylaminoethyl esters [1] of xanthen-9-carboxylic acid (I), attention was directed to analogous esters in which the distance between the carbonyl group and the $C_{(9)}$-atom was greater. The current theory of antispasmodic action is that the acetylcholine-sensitive receptor surfaces of parasympathetically innervated organs can only be effectively blockaded by a compound which has two foci for attachment to the surface. One of these foci is a terminal tertiary or quaternary nitrogen atom and the other, which must be between 5 and 10 Å distant from the nitrogen head,[2] may be one of a number of, as yet, ill-defined groupings to which is attached one or more groups large enough to constitute a protective shield over the receptors and prevent access to them of the natural spasmogenic neurohormone. From the structure of the most widely used antispasmodics it appears that the unsaturation electrons

[1] Burtner and Cusic, *J. Amer. Chem. Soc.*, 1943, **65**, 1582.
[2] Lands and Luduena, *J. Pharm. Exp. Therap.*, 1956, **117**, 331.

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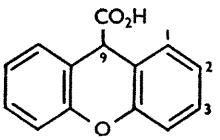
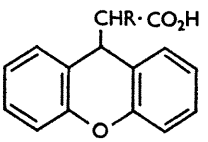
of a polarised carbonyl or ethylene group, or a lone pair on a hydroxyl oxygen or a second nitrogen atom constitutes the second focus for attachment to the reception surface. The value of the xanthenyl group as the shielding structure may be related, not only to its size, but to its ability to tolerate a positive charge because of high resonance stability of the resulting cation; this allows a further supply of electrons to be available at the group attached to the 9-position which may assist the compound to become fastened to the receptors.



(I)



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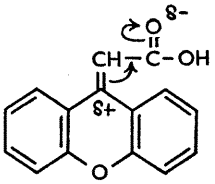

(III)

Accordingly the dialkylaminoethyl esters of 9-xanthenyl-acetic (II; R = H) and -glycollic acids (II; R = OH) have been synthesised and converted into their ethobromides. The distance between the $C_{(9)}$-atom and the carbonyl-carbon atom in these compounds is 1·54 Å greater than in esters of xanthen-9-carboxylic acid. 9-Xanthenylideneacetic acid (III) has also been synthesised and converted into its dialkylaminoethyl ester and the ester ethobromide. In these the $C_{(9)}$–C(O) distance is 1·34 Å greater than in esters of xanthen-9-carboxylic acid and the carbonyl-oxygen atom is very strongly polarised by the mesomeric drift shown; in addition, the molecule has a degree of rigidity because of the double bond. Since this work was completed (B.P. Appl. 9502—4/1956), McConnel *et al.* have reported esters of 9-xanthenylacetic acid but not their activities.

Condensation of 9-hydroxyxanthen with malonic acid in cold acetic acid gave 9-xanthenylmalonic acid which, when heated with pyridine, yielded 9-xanthenylacetic acid (overall yield 86%). This procedure is preferable to that of Fosse [4] since the considerable disproportionation of 9-hydroxyxanthen to xanthone and xanthen is avoided. 3-Chloro-9-hydroxyxanthen by the same method yielded 3-chloro-9-xanthenylacetic acid.

With tartronic acid 9-hydroxyxanthen gave 9-xanthenyltartronic acid but the most favourable yield was 21%, this being reduced by the addition of protonising agents or the use of different solvents. Decarboxylation gave a theoretical yield of 9-xanthenylglycollic acid. To improve the yield and avoid the relatively inaccessible tartronic acid, attempts were made to brominate 9-xanthenylacetic acid in the α-position and obtain xanthenylglycollic acid from the product by hydrolysis. Unfortunately bromination is effected more readily in the nucleus than in the side chain. Bromomalonic acid, however, condensed with 9-hydroxyxanthen to give a red oil from which α-bromo-α-9-xanthenylmalonic acid could not be isolated; on thermal decarboxylation the oil gave α-bromo-α-9-xanthenylacetic acid.

Treatment of the last-mentioned acid with hot concentrated aqueous sodium hydroxide eliminated hydrogen bromide quantitatively, with production of 9-xanthenylideneacetic acid. With water buffered at pH 8, the bromo-acid gave 9-xanthenylglycollic acid and 9-methylenexanthen in 75% and 25% yield respectively; these were easily separable because of the volatility of the latter in steam. This method constitutes a very convenient route to 9-xanthenylglycollic acid. Substantially the same results were obtained at pH 4·5 and 3·0, but at pH 1·3 only 9-methylenexanthen was formed. 9-Xanthenylglycollic acid is stable at all pH values in water at 100°; 9-xanthenylideneacetic acid is stable at high pH but decomposes at low pH without giving 9-methylenexanthen. The production

[3] McConnell, Petrow, and Sturgeon, *J.*, 1956, 812.
[4] Fosse, *Compt. rend.*, 1906, **143**, 749; *Ann. Chim.* (*France*), 1916, **6**, 31; *Bull. Soc. chim. France*, 1908, **35**, 1007.

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of the methylenexanthen therefore appears to be by direct formation from the bromo-acid by simultaneous elimination of hydrogen bromide and carbon dioxide.

Fosse [4] represents the reaction of 9-hydroxyxanthen with a reactive methylene group as a type of Perkin reaction but it appears much more likely to be an alkylation of a carbanion by the xanthenyl cation. As the series benzyl alcohol, diphenylmethanol, triphenylmethanol, 9-hydroxyxanthen is ascended there is increasing tendency for ionisation (with fission of hydroxyl ion) because of increasing resonance stabilisation [5] of the residual cation. Alkylation of the methylene group in malonic esters and acids is normally a base-catalysed reaction; it appears that in a weakly acid (acetic) or weakly basic (pyridine) solvent ionisation of both 9-hydroxyxanthen and the methylene compound is sufficiently pronounced to allow reaction to proceed.

9-Xanthenylideneacetic acid is an exceptionally weak acid, (pK_a 7·4). This is understandable since the carbonyl $-M$ mechanism indicated in (III) will be strongly augmented by the xanthenyl nucleus which can easily tolerate a positive charge.[5]

Conversion of the acids into their dialkylaminoalkyl esters proceeded easily by the Horenstein–Pählicke [6] procedure; quaternisation was carried out in ether or benzene solution.

Spasmolytic Activities [with M. S. Shapero]

The spasmolytic activities of the esters and quaternary salts against acetylcholine bromide, histamine, nicotine, and serotonin spasm of isolated guinea-pig ileum were determined by the Magnus method and are recorded in the Table. The spasmogen dilution

Spasmolytic activities of esters YOX *and amides* YX *of the acids* HOX (I—III).

Y	Acetylcholine bromide p*D* 7·08 *	Histamine p*D* 7·08 *	Nicotine p*D* 5·34 *	Serotonin p*D* 5·78 *
Acid (I)				
·O·C_2H_4·NEt_2	7·95 (0·04)	6·23 (0·07)	6·80 (0·03)	7·2 (0·18)
·O·C_2H_4·$NEt_3^+Br^-$	8·80 (0·12)	5·40 (0·10)	7·08 (0·05)	8·2 (0·07)
·O·C_2H_4·$NEt_2Me^+Br^-$	8·52 (0·03)	5·34 (0·04)	7·98 (0·04)	8·36 (0·04)
·O·C_2H_4·NPr_2	8·09 (0·02)	5·74 (0·03)	6·32 (0·65)	7·5 (0·21)
·O·C_2H_4·$NPr_2Me^+Br^-$	9·11 (0·07)	5·54 (0·05)	6·38 (0·04)	8·92 (0·08)
Acid (II; R = H)				
·O·C_2H_4·NEt_2	6·00 (0·02)	5·79 (0·10)	6·24 (0·06)	6·27 (0·12)
·O·C_2H_4·$NEt_3^+Br^-$	7·24 (0·24)	4·51 (0·04)	6·90 (0·15)	7·07 (0·06)
·NH·C_3H_6·NEt_2	4·62 (0·05)	4·97 (0·03)	5·27 (0·08)	5·3 (0·05)
·NH·C_3H_6·$NEt_3^+Br^-$	5·40 (0·05)	3·82 (0·02)	5·51 (0·09)	4·65 (0·12)
·NH·C_2H_4·NEt_2	4·61 (0·07)	5·39 (0·05)	5·74 (0·12)	5·6 (0·09)
·NH·C_2H_4·$NEt_3^+Br^-$	5·04 (0·05)	3·95 (0·04)	5·76 (0·10)	5·1 (0·09)
Acid (II; R = OH)				
·O·C_2H_4·NEt_2	5·60 (0·01)	5·0 (0·06)	5·95 (0·11)	5·17 (0·04)
·O·C_2H_4·$NEt_3^+Br^-$	5·79 (0·03)	4·41 (0·04)	5·69 (0·06)	5·67 (0·05)
Acid (III)				
·O·C_2H_4·NEt_2	5·13 (0·05)	5·17 (0·04)	5·85 (0·09)	5·74 (0·07)
·O·C_2H_4·$NEt_3^+Br^-$	5·70 (0·09)	4·62 (0·07)	6·30 (0·12)	6·00 (0·18)
3-Chloro-derivative of acid (II; R = H)				
·O·C_2H_4·NEt_2	5·67 (0·01)	5·47 (0·06)	6·35 (0·12)	5·68 (0·06)
·O·C_2H_4·$NEt_3^+Br^-$	6·89 (0·02)	5·03 (0·05)	6·26 (0·11)	6·00 (0·08)
Atropine	8·85 (0·19)	5·53 (0·08)	7·77 (0·16)	7·17 (0·24)
Papaverine	5·04 (0·03)	5·41 (0·05)	5·40 (0·20)	5·10 (0·17)
Chloropropromazine	5·67 (0·07)	7·89 (0·09)	5·70 (0·10)	6·25 (0·06)

* p*D* of spasmogen in bath.

(p*D*) given at the head of each column produced *ca.* 40% reduction of the normal length of the ileum strip in all cases. The activities of the spasmolytic agents are recorded as the dilution potential (p*D*) which effects 50% release of the spasm; the figures are the means

[5] Shriner in "Roger Adams Symposium," Sept. 1954 (Chapman Hall), p. 103.
[6] Horenstein and Pählicke, *Ber.*, 1938, **71**, 1644.

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from 6 strips with the standard deviations in parentheses. Dilutions are given on the p*D* scale; p*D* *x* means 1 part of spasmolytic in 10^x parts of solution.

The following observations can be made from the tabulated results: (i) In all the compounds quaternisation of the terminal nitrogen atom strongly increases activity against acetylcholine, nicotine, and serotonin but substantially reduces activity against histamine spasm. (ii) Increasing the $C_{(9)}$–C(O) distance effects a pronounced decrease in activity against acetylcholine, histamine, and serotonin, and a definite, although smaller, decrease against nicotine spasm. (iii) Surprisingly, introducing an α-hydroxyl group into the xanthenylacetic ester considerably reduces activity against acetylcholine and serotonin and, to a smaller extent, against histamine and serotonin. (iv) The 9 : α-double bond reduces activities below those of the saturated compounds. (v) The amides are much less active than the corresponding esters.

Experimental

9-Hydroxyxanthen.—The following method is less hazardous and more suitable for large quantities than that recorded in *Org. Synth.*[7] A suspension of finely ground xanthone (50 g.) in 95% alcohol (550 c.c.) was refluxed on the water-bath over 3½% sodium amalgam (600 g.) for 1 hr.; the xanthone dissolved in *ca.* 20 min. The supernatant solution was decanted, filtered, and poured into stirred ice-water (4 l.). The 9-hydroxyxanthen was immediately precipitated. Carbon dioxide was passed in until the liquor was neutral, the colourless precipitate collected, washed with cold water, and dried at 10 mm. over potassium hydroxide for 2 days, then over phosphoric oxide for 2 days, and stored in a tight bottle away from light. The yield was 44 g., and the m. p. 124—126°. Samples thus kept for 2 years were substantially unchanged (contrast Ward [8]) as shown by acetone-solubility and preparation of derivatives. 9-Hydroxyxanthen is very soluble in cold acetone (1 g./10 c.c.); xanthone is almost insoluble.

A sample (4·0 g.) was dissolved in glacial acetic acid (10 c.c.) and added to a solution of toluene-*p*-sulphinic acid (3·2 g.) in hot acetic acid (10 c.c.); a crystalline precipitate rapidly separated. In the morning the mixture was poured into water (100 c.c.), and the precipitate collected and crystallised from acetic acid; *9-toluene*-p-*sulphonylxanthen* (5·2 g., 77%) was obtained in pink needles, m. p. 206—208° (Found: C, 71·1; H, 4·8; S, 9·3. $C_{20}H_{16}O_3S$ requires C, 71·5; H, 4·8; S, 9·5%).

9-Xanthenylacetic Acid.—A solution of malonic acid (20 g.) in glacial acetic acid (200 c.c.) was added to one of 9-hydroxyxanthen (40 g.) in acetic acid (100 c.c.). The mixture was kept at room temperature overnight, then poured into stirred ice-water (1200 c.c.), the precipitate collected and extracted with hot aqueous sodium carbonate, and the 9-xanthenylmalonic acid (52 g., 87%; m. p. 120—130°) precipitated by acidification, collected, washed with water, and dried at 40°. A sample crystallised from aqueous methanol in very pale green needles, m. p. 150—152° after dehydration at 100° (Found: C, 68·0; H, 4·4. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·2%).

The crude 9-xanthenylmalonic acid (50 g.) was refluxed with pyridine (125 c.c.) for ½ hr. and the solution was cooled and poured into stirred 5N-hydrochloric acid (625 c.c.). The precipitate was collected, washed, and stirred with dilute aqueous ammonia, and the insoluble material removed; acidification gave 9-xanthenylacetic acid (43 g., m. p. 150—152°). A sample crystallised from aqueous alcohol in colourless needles, m. p. 154—156° [Found: *M* (by titration), 243; C, 74·7; H, 5·0%. Calc. for $C_{15}H_{12}O_3$: *M*, 240; C, 75·0; H, 5·0%)]. The acid has pK_a 6·6 (xanthen-9-carboxylic acid has pK_a 5·9).

The *chloride*, prepared by refluxing the acid (12 g.) with thionyl chloride (10 c.c.) in benzene (100 c.c.) for 2 hr. and then distilling off the solvent, was obtained in greenish needles (from benzene), m. p. 98° (Found: Cl, 13·7. $C_{15}H_{14}O_2Cl$ requires Cl, 13·7%). This yielded the following colourless derivatives as needles: *amide* (from benzene), m. p. 194° (Found: C, 75·6; H, 5·3; N, 5·7. $C_{15}H_{13}O_2N$ requires C, 75·4; H, 5·4; N, 5·8%); *anilide* (from alcohol), m. p. 220° (Found: C, 79·7; H, 5·2; N, 4·5. $C_{21}H_{17}O_2N$ requires C, 80·0; H, 5·4; N, 4·5%); p-*chloroanilide* (from benzene), m. p. 225° (Found: N, 4·0; Cl, 10·0. $C_{21}H_{16}O_2NCl$ requires N, 4·0; Cl, 10·2%).

[7] *Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 554.
[8] Ward quoted in Ref. 7, p. 555.

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9-Xanthenylacetic acid is recovered in nearly theoretical yield after 1 hour's boiling with excess of 5N-hydrochloric acid or 5N-sodium hydroxide. It is rapidly decomposed by sulphuric acid at 100°.

Bromination of 9-Xanthenylacetic Acid.—(*a*) The acid (5 g.) was heated in acetic acid (45 c.c.) with bromine (3·83 g.) at 80° for 1 hr. The solution was poured into water and extracted with ether (2 × 50 c.c.), and the combined ethereal solutions were extracted with N-sodium hydroxide (2 × 30 c.c.). The alkaline extract gradually deposited a sodium salt (1·2 g.) which gave an acid, m. p. 192°, which must be a (nuclear)*dibromo-9-xanthenylacetic acid* since there was no release of bromide ion in boiling alkali [Found: *M* (by titration), 408; Br, 40·3%. $C_{15}H_{10}O_3Br_2$ requires *M*, 398; Br, 40·2%].

(*b*) The unbrominated acid (2·4 g.; 0·01 mol.) was refluxed with thionyl chloride (10 c.c.) for 2 hr., then bromine (0·53 c.c.) in thionyl chloride (7·5 c.c.) was added. After 1 hr. the solution was poured on ice (40 g.) and left for 2 days. The green precipitate was collected, shaken overnight with 20% aqueous sodium carbonate (25 c.c.), and the mixture filtered and acidified. A (nuclear)*monobromo-9-xanthenylacetic acid* (0·9 g.), m. p. 160—162°, was precipitated (Found: *M*, 312; Br, 24·7%. $C_{15}H_{10}O_3Br$ requires *M*, 319; Br, 25·1%).

α-Bromo-α-9-xanthenylacetic Acid.—Solutions of bromomalonic acid (40 g.) in warm acetic acid (160 c.c.) and 9-hydroxyxanthen (40 g.) in the same solvent (200 c.c.) were mixed and kept at room temperature for 190 hr. Water (400 c.c.) and saturated aqueous sodium chloride (60 c.c.) were added, and the small precipitate (A) was collected. The filtrate was evaporated to *ca.* 300 c.c. at 10 mm., and the mixture diluted with water (300 c.c.), again evaporated to *ca.* 300 c.c., and made alkaline with sodium carbonate. The precipitate (A) was added, and the mixture filtered, chilled, and shaken with ether for 10 min. during which hydrochloric acid was added until the pH was 2. The ethereal extract was washed with water (150 c.c.), dried (Na_2SO_4), and evaporated. The remaining red oil (crude malonic acid) was refluxed in toluene (400 c.c.) and benzene (100 c.c.) for 3 hr. Next morning the mixture was extracted with saturated potassium hydrogen carbonate solution (3 × 80 c.c.), and the aqueous extract washed with ether, chilled, acidified with hydrochloric acid, and extracted with ether (2 × 80 c.c.). The dried ethereal solution was evaporated, the remaining oil ground with ligroin (b. p. 40—60°) until it crystallised, and the solid drained and washed with a little cold toluene. Crystallisation from ligroin (b. p. 100—120°) gave *α-bromo-α-9-xanthenylacetic acid* (19 g.) in colourless prisms, m. p. 148—150° (Found: *M*, 322; Br, 25·2%. $C_{15}H_{11}O_3Br$ requires *M*, 319; Br, 25·1%). The acid has pK_a 3·9. Treatment of this acid (1·0 g.) in acetic acid (75 c.c.) with chromic acid (5 g.) for 15 min. gave a 55% yield of xanthone.

9-Xanthenyltartronic Acid.—A solution of tartronic acid [9] (36 g.) in warm glacial acetic acid (140 c.c.) was added to one of 9-hydroxyxanthen (60 g.) in the same solvent (200 c.c.). The solution was kept at room temperature for 72 hr., then poured into ice-water (1200 c.c.), the precipitate collected, and the filtrate (B) kept. The precipitate was extracted with a slight excess of 2N-aqueous ammonia, and the extract added to the above filtrate (B). The combined solution (which was still acid) was extracted with ether (2 × 300 c.c.), and the ethereal solution re-extracted with 2N-ammonia (3 × 50 c.c.). The aqueous alkaline solution was acidified with hydrochloric acid, and the precipitate collected; crystallisation from water gave *9-xanthenyltartronic acid* as colourless needles (20 g.), m. p. 174° (decomp.) (Found: C, 63·7; H, 4·0. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%).

9-Xanthenylglycollic Acid.—A solution of the foregoing acid (20 g.) in pyridine (80 c.c.) was refluxed for 30 min., cooled, and poured into 5N-hydrochloric acid (350 c.c.) at 5° and the crystalline *9-xanthenylglycollic acid* (15 g.), m. p. 224—226°, collected (Found: C, 70·1; H, 4·6. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%). The acid has pK_a 4·7.

9-Xanthenylideneacetic Acid.—A solution of α-bromo-α-9-xanthenylacetic acid (20 g.) in 2N-sodium hydroxide (380 c.c.) was refluxed for 2½ hr. In the morning a little water was added to dissolve the small precipitate, the filtered solution adjusted to pH 2 with hydrochloric acid, and the solution extracted with ether (3 × 300 c.c.). The ethereal solution was washed with water (50 c.c.) and dried (Na_2SO_4), and the ether removed, first at atmospheric and then at reduced pressure. Benzene (500 c.c.) was added and some distilled off at reduced pressure to remove traces of water; the residual solution (250 c.c.) was diluted with ligroin (b. p. 40—60°), and the precipitated *9-xanthenylideneacetic acid* (13·1 g.; m. p. 122—126°) collected. Crystallisation from benzene–ligroin gave the pure compound (12·2 g., 82%) as pale yellow needles,

[9] Bak, *Annalen*, 1938, **337**, 286.

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m. p. 142° (Found: C, 75·5; H, 4·2. $C_{15}H_{10}O_3$ requires C, 75·7; H, 4·2%). The acid has pK_a 7·4.

Hydrolysis of α-Bromo-α-9-xanthenylacetic Acid.—(i) *At* pH 7·0. A solution of the acid (10·6 g.), disodium hydrogen phosphate dodecahydrate (35·8 g.), and potassium dihydrogen phosphate (9·1 g.) in water (110 c.c.) and dioxan (85 c.c.) was refluxed for 25 hr. The solvent was removed at reduced pressure and the residue lixiviated with aqueous sodium carbonate. The insoluble methylenexanthen was filtered off, the solution acidified with dilute nitric acid, and the precipitated 9-*xanthenylglycollic acid* (6·5 g.; m. p. 220°) collected. This crystallised from ethyl acetate–toluene in colourless needles (5·7 g., 67%), m. p. and mixed m. p. 225° (Found: *M*, 257; C, 70·1; H, 4·6%. $C_{15}H_{12}O_4$ requires *M*, 256; C, 70·3; H, 4·7%).

The crude 9-*methylenexanthen* was distilled in a current of steam and obtained in lustrous colourless plates (1·5 g., 23%), m. p. 112° (Found: C, 86·4; H, 5·2. $C_{14}H_{10}O$ requires C, 86·6; H, 5·2%). 9-Methylenexanthen is unchanged at the b. p. by 2N-hydrochloric acid or 5N-sodium hydroxide for 24 hr.

(ii) *At* pH 4. A solution of the acid (10·6 g.), sodium formate (18·1 g.), and formic acid (6·4 c.c.) in water (120 c.c.) and dioxan (85 c.c.) was refluxed for 24 hr. In the same manner there were obtained 9-xanthenylglycollic acid (4·9 g., 58%), m. p. and mixed m. p. 225°, and methylenexanthen (1·0 g., 15%), m. p. 112°.

When the sodium formate and formic acid were replaced by sodium acetate (10·3 g.) and acetic acid (1·8 c.c.) (pH 4·7) there were obtained 3·9 g. (49%) of the glycollic acid, m. p. 225°, and 2 g. (33%) of methylenexanthen, m. p. 112°.

(iii) *At* pH 7—2. A solution of the acid (10·6 g.) and potassium carbonate (2·25 g., 1 equiv.) in water (300 c.c.) was refluxed for 30 min. The solution rapidly became cloudy and an oil was precipitated, the pH falling from 7·0 to 2·0. There were obtained 2·9 g. (34%) of glycollic acid and 4·0 g. (63%) of methylenexanthen.

(iv) *At* pH 1·5—1·0. A solution of the acid (10·6 g.) in water (140 c.c.) and dioxan (85 c.c.) was refluxed for 24 hr., giving 0·7 g. (11%) of methylenexanthen, m. p. 112°, and 7·3 g. of an intractable mixture of 9-xanthenylglycollic acid and unchanged starting material.

3-*Chloro*-9-*hydroxyxanthen.*—A suspension of finely divided 3-chloroxanthone (25 g.) in 95% ethanol (300 c.c.) was refluxed for 2 hr. over 3½% sodium amalgam (300 g.), the solid dissolving. The filtered solution was poured with stirring into ice-water (2 l.), the suspension neutralised with carbon dioxide, and the colourless precipitate of 3-*chloro*-9-*hydroxyxanthen* (23·1 g., 92%), m. p. 175—177°, collected, washed with water, and dried *in vacuo* (Found: Cl, 14·8. $C_{13}H_9O_2Cl$ requires Cl, 15·3%). The material cannot be purified by crystallisation. The following derivatives were made by adding a warm saturated solution of the alcohol in acetic acid to a hot solution of benzamide or toluene-*p*-sulphonamide in the same solvent; the derivatives separated overnight almost quantitatively in colourless needles and were recrystallised from alcohol–pyridine: 9-*Benzamido*-3-*chloro*-, m. p. 234—236° (Found: N, 4·3; Cl, 10·7. $C_{20}H_{14}O_2NCl$ requires N, 4·2; Cl, 10·6%), and 3-*chloro*-9-*toluene*-p-*sulphonamido-xanthen*, m. p. 172—174° (Found: N, 3·7; Cl, 9·1; S, 8·2. $C_{20}H_{16}O_3NSCl$ requires N, 3·6; Cl, 9·2; S, 8·3%).

3-*Chloro*-9-*xanthenylmalonic Acid.*—3-Chloro-9-hydroxyxanthen (16·7 g.) and malonic acid (7·2 g.) were kept in acetic acid (80 c.c.) for 96 hr. at room temperature, the mixture was poured into water (250 c.c.), the precipitated oil (C), which partially solidified, was collected, and the filtrate extracted with ether (2 × 100 c.c.). The ethereal solution was extracted with 4N-ammonia (2 × 150 c.c.), the extracts were combined with the solid (C), and the insoluble non-acidic material was removed. Acidification of the filtrate precipitated 3-*chloro*-9-*xanthenylmalonic acid* as a buff powder (17 g.; m. p. 140—144°); this was collected, washed, and dried *in vacuo*. A sample separated from aqueous methanol as a pale brown-green powder, m. p. 166—168° (decomp.) (Found: equiv., 161; Cl, 11·0%. $C_{16}H_{11}O_5Cl$ requires equiv., 159; Cl, 11·1%).

3-*Chloro*-9-*xanthenylacetic acid.*—A solution of the foregoing crude acid (25 g.) in pyridine (75 c.c.) was refluxed for ½ hr., chilled, and poured into stirred 5N-hydrochloric acid (300 c.c.). The precipitate was separated and stirred with excess of dilute aqueous sodium carbonate, the insoluble material removed, and the filtrate acidified with dilute hydrochloric acid. 3-*Chloro*-9-*xanthenylacetic acid* (18 g., 83%) was obtained as a buff solid; a sample separated from aqueous methanol in colourless rhombs, m. p. 118—120° (Found: *M*, 278; Cl, 13·1%. $C_{15}H_{11}O_3Cl$ requires *M*, 274·5; Cl, 12·9%).

2-*Diethylaminoethyl* 3-*Chloro*-9-*xanthenylacetate.*—3-Chloro-9-xanthenylacetic acid (6 g.), 2-diethylaminoethyl chloride (4·5 g.), and anhydrous potassium carbonate (3·1 g.) were

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refluxed with dry chloroform (100 c.c.) for 24 hr. The chloroform solution was washed with 2N-sodium carbonate (50 c.c.) and then with water (2 × 50 c.c.) and dried (K_2CO_3) and the chloroform distilled off; the ester remained as a pale yellow oil. It was dissolved in the minimum of boiling alcohol and added to a concentrated hot solution of oxalic acid dihydrate (1 mol.) in alcohol; the *ester hydrogen oxalate* separated in colourless plates (5·4 g.) [Found: *M* (by titration with $HClO_4$), 467; N, 3·1; Cl 7·6%. $C_{23}H_{26}O_7NCl$ requires *M*, 463·5; N, 3·0; Cl, 7·7%]. The following were prepared in the same manner, the yields in all cases being *ca.* 80%.

2-*Diethylaminoethyl* 9-*xanthenylideneacetate hydrogen oxalate*, needles (from alcohol), m. p. 172—174° (Found: C, 64·8; H, 6·3; N, 3·3. $C_{23}H_{25}O_7N$ requires C, 64·7; H, 5·9; N, 3·3%).

2-*Diethylaminoethyl* 9-*xanthenylglycollate hydrogen oxalate*, needles (from alcohol) containing 1EtOH of crystallisation (Found: *M*, 491; N, 2·9%. $C_{23}H_{27}O_8N,C_2H_5{\cdot}OH$ requires *M*, 491; N, 2·9%).

2-*Diethylaminoethyl* 9-*xanthenylacetate hydrogen oxalate*, leaves (from alcohol), m. p. 132° (Found: *M*, 429; C, 64·0; H, 6·3; N, 3·4%. $C_{23}H_{27}O_7N$ requires *M*, 429; C, 64·3; H, 6·3; N, 3·3%). The *hydrochloride* of the base separated from benzene in colourless leaves, m. p. 146—148° (Found: N, 4·0; Cl, 9·8. $C_{21}H_{26}O_3NCl$ requires N, 3·7; Cl, 9·5%).

2-*Diethylaminoethyl xanthen*-9-*carboxylate hydrogen oxalate*, needles (from alcohol) (Found: *M*, 412. $C_{22}H_{25}O_7N$ requires *M*, 415).

2-*Diisopropylaminoethyl xanthen*-9-*carboxylate*, an oil which slowly solidified (Found: *M*, 351; N, 4·0%. $C_{22}H_{27}O_3N$ requires *M*, 353; N, 4·0%).

2-*Diethylaminoethyl* 3-*Chloro*-9-*xanthenylacetate Ethobromide*.—2-Diethylaminoethyl 3-chloro-9-xanthenylacetate hydrogen oxalate (10 g.) was shaken with excess of 10% aqueous sodium carbonate and benzene. The benzene extract was dried (K_2CO_3), a part of the benzene distilled off, and to the residual solution (100 c.c.) of the free ester ethyl bromide (20 c.c.) was added. The solution was gently refluxed for 5 days during which the quaternary *salt* (10 g.) precipitated as a microcrystalline hygroscopic powder (Found: *M*, 489; N, 3·0; Br, 16·6; Cl, 7·2%. $C_{23}H_{29}O_3NClBr$ requires *M*, 482·5; N, 2·9; Br, 16·6; Cl, 7·4%).

For preparing the methobromides it was preferable to keep an excess of methyl bromide and the tertiary ester in anhydrous ether at room temperature for 5 days. The methobromides separated in almost quantitative yield: The following were prepared in the same manner:

2-*Diethylaminoethyl* 9-*xanthenylideneacetate ethobromide*, needles, m. p. 168° (Found: *M*, 445. $C_{23}H_{28}O_3NBr$ requires *M*, 446).

2-*Diethylaminoethyl* 9-*xanthenylglycollate ethobromide* (Found: N, 3·8; Br, 17·6. $C_{23}H_{30}O_4NBr$ requires N, 3·0; Br, 17·2%).

2-*Diethylaminoethyl* 9-*xanthenylacetate ethobromide*, m. p. 164° (Found: C, 61·0; H, 6·7; N, 3·2; Br, 17·6. $C_{23}H_{30}O_3NBr$ requires C, 61·6; H, 6·7; N, 3·1; Br, 17·8%).

2-*Diethylaminoethyl xanthen*-9-*carboxylate ethobromide*, needles, m. p. 194° (Found: N, 3·5; Br, 19·0. $C_{22}H_{28}O_3NBr$ requires N, 3·2; Br, 18·4).

N-2-*Diethylaminoethyl*-9-*xanthenylacetamide*.—9-Xanthenylacetic acid (12 g.) was refluxed with benzene (80 c.c.) and thionyl chloride (9 c.c.) for 2 hr., the solvent distilled off, benzene (60 c.c.) added, and this distilled off at reduced pressure. The residual acid chloride was dissolved in benzene (100 c.c.), 2-diethylaminoethylamine (13 g.) added during 10 min., and the mixture refluxed for 1 hr., cooled, and washed with N-sodium hydroxide and then water. The benzene solution was dried, concentrated, and diluted with ligroin (b. p. 60—80°). The *amide* (9 g.) separated in colourless needles, m. p. 122° (Found: C, 74·9; H, 7·9. $C_{21}H_{26}O_2N_2$ requires C, 74·6; H, 7·7%). The *ethobromide* was obtained by the benzene method in needles (Found: N, 6·4; Br, 18·2. $C_{23}H_{31}O_2N_2Br$ requires N, 6·3; Br, 17·9%).

In the same manner was prepared N-3-*diethylaminopropyl*-9-*xanthenylacetamide*, needles, m. p. 106° (Found: *M*, 348; C, 74·6; H, 8·0; N, 7·5%. $C_{22}H_{28}O_2N_2$ requires *M*, 352; C, 75·0; H, 8·0; N, 8·0%); the *ethobromide* had m. p. 130—140° (Found: *M*, 461. $C_{24}H_{33}ON_2Br$ requires *M*, 461).

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