87. *Spasmolytics derived from Xanthen. Part II.*[1]

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Some 9-(2-dialkylaminoethyl)-and 9-(2-dialkylaminoethylidene)-xanthens, and their alkyl bromides, have been synthesised and examined for spasmolytic activity.

In Part I[1] of this series some dialkylaminoalkyl esters of xanthenyl-formic, -acetic, and -glycollic acid and xanthenylideneacetic acid were reported. These contained the pharmacologically effective C·CO·O·C·C·N group resembling the natural prototype hyoscine. The high spasmolytic activity[2] of 1-(3,3-diphenylpropyl)- (Efosin) and 1-(1-methyl-3,3-diphenylpropyl)-piperidine showed the grouping $C{\cdot}C{\cdot}C{\cdot}NR_2$ to be effective pharmacologically since these compounds possess respectively 10% and 50% of the antimuscarine activity of atropine. 3-Dialkylamino-1,1-diphenylprop-1-enes[3] and but-1-enes[4] have high antimuscarine and antihistamine activities and, in addition, effect conduction anæsthesia and analgesia;[3] these activities are maintained when the umbrella phenyl groups were replaced by thienyl,[5] pyridyl,[6] or cyclohexyl.[7]

Accordingly we synthesised some 9-(2-dialkylaminoethyl)- and 9-(2-dialkylaminoethylidene)-xanthens and examined them for spasmolytic activity. 9-(2-1′-Piperidinylethyl)xanthen has been prepared by Rosicky[8] from sodioxanthen, a method previously used by Cusic[9] for obtaining substituted aminoalkylxanthens; the methobromide of this base was shown by Eichenberger and Emmrich[10] to be a powerful parasympatholytic agent having low mydriatic activity and little inhibitory effect on salivation.

Reaction of 9-xanthenylacetyl chloride with secondary amines gave the corresponding amides which were reduced smoothly by lithium aluminium hydride to the required compounds in good yield. *NN*-Dialkylxanthen-9-carboxyamides similarly gave 9-(dialkylaminomethyl)xanthens.

9-Xanthenylideneacetic acid failed to yield the chloride on treatment with thionyl chloride in refluxing benzene or ether; apparently addition to the double bond takes place. The acid, however, was converted by the Horenstein–Pählicke[11] procedure into the methyl ester which in refluxing piperidine gave the required amide. The latter was reduced by lithium aluminium hydride without the double bond being affected.

Spasmolytic Activities (with B. K. Edwards).—The spasmolytic activities of the tertiary amines and quaternary salts against acetylcholine bromide and histamine spasm of isolated guinea-pig ileum were determined by the Magnus method and are recorded in the Table. The spasmogen dilution (pD) given at the head of each column produced *ca.* 40% reduction of the normal length of the ileum segment in all cases. The activities of the spasmolytic agents are recorded as the dilution potential (pD) which effects 50% release of the spasm; the figures given are the means from 6 strips. Dilutions are given on the pD scale; pDx means 1 part of spasmolyte in 10^x parts of solution.

The following deductions can be made from the tabulated results: 9-(2-1′-Piperidinylethyl)xanthen methobromide has 25% of the antimuscarine activity of atropine and 30%

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[1] Part I, Goldberg and Wragg, *J.*, 1957, 4823.

[2] Report No. PB 981 Office of the Publication Board, Dept. of Comm., Washington, D.C.; quoted by Bergel and Parkes in " Progress in Organic Chemistry," J. W. Cook (Ed.), No. 1, p. 180, Butterworths, 1952.

[3] Adamson, *J.*, 1949, S144.

[4] Adamson and Green, *Nature*, 1950, **165**, 122.

[5] Adamson, *J.*, 1950, 885; B.P. 657,301.

[6] Adamson and Billinghurst, *J.*, 1950, 1039.

[7] Adamson, Barrett, and Wilkinson, *J.*, 1951, 52.

[8] Rosicky, Swiss P. 316,550, 322,804.

[9] Cusic, U.S.P., 2,676,971, 2,368,006.

[10] Eichenberger and Emmrich, *Schweiz. med. Wochenschr.*, 1956, **86**, 1102.

[11] Horenstein and Pählicke, *Ber.*, 1938, **71**, 1644.

of the antihistamine activity of chloropromazine. 9-(2-1′-Pyrrolidinylethyl)xanthen has little antimuscarine activity but has twice the antihistamine activity of chloropromazine; quaternisation increases activity against acetylcholine and decreases activity against histamine spasm. Introduction of the double bond into the propane chain effects a profound change in activity; 9-(2-1′-piperidinylethylidene)xanthen methobromide has little antimuscarinic activity but nearly 3 times the antihistamine activity of chloropromazine. Shortening the carbon chain greatly reduces the antimuscarine but increases the antihistamine activity.

Spasmolytic activities of (*B*) *the base and* (*M*) *the methobromide.*

	Acetylcholine bromide pD 7·08		Histamine pD 7·08	
9-Derivative of xanthen	B	M	B	M
$Me_2N{\cdot}CH_2{\cdot}CH_2$	5·30	5·64	7·13	6·77
$Et_2N{\cdot}CH_2{\cdot}CH_2$	6·06	6·04	6·83	6·68
$[CH_2]_4{>}N{\cdot}CH_2{\cdot}CH_2$	6·49	6·96	8·22	7·52
$[CH_2]_5{>}N{\cdot}CH_2{\cdot}CH_2$	6·66	7·48 *	7·08	7·46 *
$\{[CH_2]_4{\cdot}CHMe\}{>}N{\cdot}CH_2{\cdot}CH_2$	6·95	—	6·43	—
$[CH_2]_5{>}N{\cdot}CH_2$	6·11	6·42 †	7·79	7·71 †
$[CH_2]_5{>}N{\cdot}CH_2{\cdot}OH{=}$	5·82	6·44	7·29	8·31
Other compounds				
Atropine	8·85		5·53	
Papaverine	5·04		5·41	
Chloropromazine	5·67		7·89	

* Ethobromides 7·03 and 6·19 respectively. † Methiodide.

EXPERIMENTAL

Molecular weights were determined by titration with anhydrous perchloric acid.

1-(9-*Xanthenylacetyl*)*pyrrolidine*.—A solution of 9-xanthenylacetic acid [1] (24 g., 0·1 mole) in dry benzene (200 c.c.) and thionyl chloride (18 c.c., 0·25 mole) was refluxed for 1½ hr. The solvent was distilled off at reduced pressure; benzene (100 c.c.) was added and then distilled off; addition of a further 100 c.c. of benzene and its removal at reduced pressure left the acid chloride as a pale yellow solid. This was refluxed in benzene (250 c.c.), and anhydrous pyrrolidine (17·8 g., 0·25 mole) added slowly with stirring. After a further 2 hours' refluxing and storage at room temperature overnight the precipitated pyrrolidine hydrochloride was removed and washed with benzene. The filtrate was washed with dilute hydrochloric acid and water, dried, and distilled, yielding 1-(9-*xanthenylacetyl*)*pyrrolidine* (28·3 g., 96%), b. p. 226—230°/1·5 mm. (Found: C, 77·5; H, 6·41; N, 4·7. $C_{19}H_{19}O_2N$ requires C, 77·8; H, 6·5; N, 4·8%).

In the same manner were prepared: 1-(9-*Xanthenylacetyl*)*piperidine*, needles (70%) [from benzene–ligroin (b. p. 60—80°)], m. p. 72° (Found: C, 78·3; H, 6·7; N, 4·5. $C_{20}H_{21}O_2N$ requires C, 78·2; H, 6·8; N, 4·6%.)

2-*Methyl*-1-(9-*xanthenylacetyl*)*piperidine*, b. p. 244—248°/1·5 mm. (97%) (Found: C, 78·1; H, 7·2; N, 4·3. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·2; N, 4·4%).

NN-*Diethyl*-9-*xanthenylacetamide*, b. p. 220—224°/1 mm., needles (90%), m. p. 60—62° (Found: N, 4·7. $C_{19}H_{21}O_2N$ requires N, 4·6%).

NN-*Dimethyl*-9-*xanthenylacetamide* (prepared from the acyl chloride in acetone and aqueous dimethylamine), needles (from ethanol), m. p. 110—112° (72%) (Found: C, 76·4; H, 6·3; N, 5·4. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·3%).

1-9′-*Xanthenylcarbonylpiperidine* (from the acyl chloride and piperidine), needles (84%) (from alcohol), m. p. 152—154° (Found: C, 78·4; H, 6·4; N, 4·7. $C_{19}H_{19}O_2N$ requires C, 77·9; H, 6·4; N, 4·8%).

9-(2-1′-*Pyrrolidinylethyl*)*xanthen*.—1-(9-Xanthenylacetyl)pyrrolidine (14·65 g.) in anhydrous ether (100 c.c.) was added dropwise in 20 min. to a stirred suspension of lithium aluminium hydride (4·75 g.) in ether (250 c.c.) at 10°. The mixture was stirred for a further 5 min., then refluxed for 3 hr., cooled in ice-water, and treated with alcohol (50 c.c.) followed by water (50 c.c.). Next morning the solution was filtered and the residue washed with ether. The ether solution was washed with water (100 c.c.) and extracted with 2N-hydrochloric acid (3 × 50 c.c.). The combined extracts were basified with 10N-potassium hydroxide, and the liberated oil extracted with ether (3 × 100 c.c.). The ethereal solution was washed with a little water, dried (Na_2SO_4), and evaporated. The residual *amine* solidified to needles (12·5 g., 90%), m. p. 80° (Found: *M*, 280. Calc. for $C_{19}H_{21}ON$: *M*, 279). It gave a *hydrogen oxalate*, needles (91%) (from alcohol), m. p. 192—194° (Found: *M*, 367. Calc. for $C_{21}H_{23}O_5N$: *M*, 369); *methobromide* (reaction at room temperature for 6 days) (92%), m. p. 196—198° (Found: C, 64·2; H, 6·4; N, 3·4. $C_{20}H_{24}ONBr$ requires C, 64·2; H, 6·4; N, 3·7%), and *methiodide*, pale buff rhombs, m. p. 174—176° (Found: N, 3·3; I, 29·2. $C_{20}H_{24}ONI$ requires N, 3·3; I, 30·2%).

The following were obtained in the same way:

9-(2-1′-*Piperidinylethyl*)*xanthen*, b. p. 198—202°/2 mm. (88%) (Found: *M*, 291. Calc. for $C_{20}H_{23}ON$: *M*, 293) [*hydrogen oxalate*, plates (from alcohol), m. p. 200° (decomp.) (Found: C, 69·0; H, 6·5; N, 3·4%; *M*, 379. $C_{22}H_{25}O_5N$ requires C, 69·0; H, 6·5; N, 3·7%; *M*, 383); *methobromide* (80%), needles, m. p. 200—202° (Found: N, 3·4. $C_{21}H_{26}ONBr$ requires N, 3·6%); *methiodide*, pale buff prisms (93%) (from ethanol–ethyl acetate), m. p. 172° (Found: C, 58·5; H, 5·9; N, 3·3; I, 28·8. $C_{21}H_{26}ONI$ requires C, 58·4; H, 6·0; N, 3·2; I, 29·2%)].

9-(2-2′-*Methyl*-1′-*piperidinylethyl*)*xanthen hydrochloride* (from the base and ethereal hydrogen chloride) (82%), m. p. 225—226° (Found: C, 73·5; H, 7·4; N, 3·8; Cl, 10·7. $C_{21}H_{26}ONCl$ requires C, 73·3; H, 7·6; N, 4·1; Cl, 10·3%).

9-(2-*Diethylaminoethyl*)*xanthen hydrogen oxalate*, needles (70%) (from alcohol–acetone), m. p. 129—130° (Found: C, 68·1; H, 6·6%; *M*, 373. $C_{21}H_{25}O_5N$ requires C, 68·0; H, 6·7%; *M*, 371); *methobromide*, hygroscopic needles (94%), m. p. 120—122° (Found: *M*, 377. $C_{20}H_{26}ONBr$ requires *M*, 376), and pale yellow, hygroscopic *methiodide* (96%), m. p. 108—110° (Found: *M*, 426. $C_{20}H_{26}ONI$ requires *M*, 423).

9-(2-*Dimethylaminoethyl*)*xanthen hydrogen oxalate*, needles (95%) (from ethanol), m. p. 198° (decomp.) (Found: C, 66·1; H, 6·3; N, 3·7. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1; N, 4·1%), and *methobromide*, needles (95%), m. p. 226° (Found: *M*, 346. $C_{18}H_{22}ONBr$ requires *M*, 348).

9-1′-*Piperidinylmethylxanthen*, needles (84%), m. p. 78—80° (Found: C, 81·6; H, 7·4; N, 5·0. $C_{19}H_{21}ON$ requires C, 81·7; H, 7·5; N, 5·0%) [*hydrogen maleate* needles (96%), m. p. 168—170° (Found: C, 69·8; H, 6·4; N, 3·6%; *M*, 397. $C_{23}H_{25}O_5N$ requires C, 69·9; H, 6·3; N, 3·6%; *M*, 395); *methiodide* (obtained by refluxing the base and methyl iodide in ether for 5 days), fawn needles (17%), m. p. 196—198° (Found: *M*, 427. $C_{20}H_{24}ONI$ requires *M*, 421)].

9-(2-1′-*Piperidinylethylidene*)*xanthen*.—9-Xanthenylideneacetic acid [1] (11·7 g.), potassium carbonate (7·5 g.), methyl iodide (41 g.), and dry acetone (300 c.c.) were refluxed for 96 hr. The acetone was distilled off, water (300 c.c.) added, and the whole extracted with ether (2 × 100 c.c.). The extract was washed with aqueous sodium carbonate and water and evaporated; *methyl* 9-*xanthenylideneacetate* (12·0 g., 97%) remained as a yellow solid, m. p. 72—74° (Found: C, 76·6; H, 5·0. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%).

The ester (12 g.) and anhydrous piperidine (25 g.) were refluxed together for 14 days. The excess of piperidine was distilled off *in vacuo* and the residual oil dissolved in benzene (100 c.c.), washed with water, 2N-hydrochloric acid, and water, and recovered. Reduction of this crude amide in ether (200 c.c.) with lithium aluminium hydride (7·5 g.) in ether (250 c.c.) yielded the pale yellow solid amine. This was added in hot ethanol (10 c.c.) to oxalic acid dihydrate (2·7 g.) in hot ethanol (10 c.c.). 9-(2-1′-*Piperidinylethylidene*)*xanthen hydrogen oxalate* separated as plates (3·1 g.), m. p. 182° (decomp.) (Found: C, 69·1; H, 5·9; N, 3·8. $C_{22}H_{23}O_5N$ requires C, 69·3; H, 6·0; N, 3·7%).

The free amine was obtained from the oxalate by means of ether and aqueous sodium hydroxide. The *methobromide* separated slowly in pale cream-coloured plates, m. p. 150—152° (Found: *M*, 389. $C_{21}H_{24}ONBr$ requires *M*, 386).

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