173. *Some Basic Esters of 9-Xanthenylacetic Acid.*

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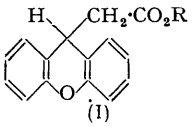
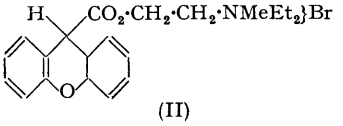
Some basic esters and the corresponding quaternary salts of 9-xanthenylacetic acid (I; R = H) have been prepared for study as spasmolytic agents. In addition, the 2- and 4-methyl, and the 4-methoxy-derivative of methantheline bromide (II) have been prepared.

9-Xanthenylacetic acid was obtained by Fosse [1] by condensation of xanthhydrol with malonic acid in pyridine. The condensation proceeds equally smoothly with alkylmalonic acids, α-9-xanthenylpropionic, α-9-xanthenylbutyric, and β-phenyl-α-9-xanthenylpropionic



(I)



(II)

acid being prepared in this way. The acids were esterified either by reaction with the dialkylaminoethyl halide in propan-2-ol [2] or by conversion into the acid chlorides, followed by reaction with excess of the basic alcohol in benzene. Quaternisation with methyl bromide was carried out in acetone at −10°, and with the other alkyl bromides in a sealed tube at 100°.

2- and 4-Methyl- and 2-methoxy-xanthone were reduced with sodium and ethanol, and the resulting xanthens carboxylated by treating the lithium derivatives with carbon dioxide. The position of carboxylation was proved in each case by oxidation to the original xanthone with chromium trioxide in acetic acid. The xanthen-9-carboxylic acids so obtained were esterified and quaternised in the usual way, to give the 2- and 4-methyl- and 2-methoxy-derivative of the salt (II).

Experimental

The esters described below were prepared by the acid chloride route unless otherwise stated.

α-9-*Xanthenylpropionic Acid.*—A solution of xanthhydrol (4 g.) and methylmalonic acid (2 g.) in pyridine (10 ml.) was heated at 60° for 2 hr., at 80° for 30 min., and finally boiled for 1 hr. The pyridine was evaporated under reduced pressure and the residue dissolved in ether. The acid was extracted with sodium carbonate solution, precipitated with dilute hydrochloric acid, and recrystallised from light petroleum (b. p. 60—80°). α-9-*Xanthenylpropionic acid* formed plates, m. p. 122° (Found : C, 75·3; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

α-9-*Xanthenylbutyric acid* separated in cubes, m. p. 114—116° (Found : C, 76·0; H, 6·2. $C_{17}H_{16}O_3$ required C, 76·1; H, 6·0%), from light petroleum (b. p. 80—100°).

β-*Phenyl*-α-9-*xanthenylpropionic acid* formed plates, m. p. 165° (Found : C, 79·6; H, 5·2. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·5%), from light petroleum (b. p. 60—80°).

2-*Diethylaminoethyl* α-9-*Xanthenylbutyrate Hydrochloride.*—α-9-Xanthenylbutyric acid (5 g.), 2-diethylaminoethyl chloride (3·5 g.), and dry propan-2-ol (50 ml.) were boiled for 4 hr. The

[1] Fosse, *Bull. Soc. chim. France*, 1906, **35**, 1005.
[2] Horenstein and Pahlicke, *Ber.*, 1938, **71**, 1654.

solvent was removed under reduced pressure and the residue treated with sodium carbonate solution and ether. The ethereal layer was washed, dried and evaporated and the product precipitated with ethanolic hydrogen chloride. The *ester hydrochloride* (5 g.) formed plates, m. p. 166° (Found: C, 68·9; H, 7·7; N, 3·8; Cl, 8·7. $C_{23}H_{29}O_3N$,HCl requires C, 68·4; H, 7·4; N, 3·5; Cl, 8·8%), after crystallisation from ethanol–ether. The *methobromide* crystallised from propan-2-ol–ether in needles, m. p. 158° (Found: C, 61·7; H, 6·8; N, 3·3. $C_{24}H_{32}O_3NBr,\frac{1}{2}H_2O$ requires C, 61·3; H, 6·8; N, 3·0%).

2-*Diethylaminoethyl* β-*Phenyl*-α-9-*xanthenylpropionate Hydrochloride.*—The corresponding acid (5 g.) was heated under reflux in benzene with purified thionyl chloride (5 g.). After 45 min. the solvent was removed under reduced pressure and the residue re-evaporated twice with dry toluene. The acid chloride was dissolved in benzene (50 ml.) and 2-diethylaminoethanol (5 ml.) added, after which the mixture was refluxed for 4 hr. The hydrochloride was decomposed with sodium carbonate solution and the benzene washed thoroughly with water to remove diethylaminoethanol. The *product* (5·3 g.) was precipitated with ethanolic hydrogen chloride and recrystallised from methanol–ethyl acetate, to give needles, m. p. 169° (Found: C, 70·1; H, 7·1; N, 3·3. $C_{27}H_{31}O_3N$,HCl,$\frac{1}{2}H_2O$ requires C, 70·1; H, 7·2; N, 3·0%). The *methobromide* formed needles, m. p. 177—180° (Found: C, 64·4; H, 7·0; N, 3·1. $C_{28}H_{34}O_3NBr,\frac{1}{2}H_2O$ requires C, 64·5; H, 7·0; N, 2·7%), after crystallisation from propan-2-ol–ether.

2-*Methylxanthen.*—2-Methylxanthone (3 g.), dissolved in boiling ethanol (60 ml.), was treated with sodium (7 g.) added as rapidly as possible. Then the ethanol was removed in steam and the residue recrystallised from aqueous alcohol and then from light petroleum (b. p. 40—60°). 2-*Methylxanthen* (2·1 g.) separated in plates, m. p. 98° (Found: C, 86·0; H, 6·3. $C_{14}H_{12}O$ requires C, 85·7; H, 6·1%).

4-*Methylxanthen* crystallised from alcohol in prismatic rods, m. p. 40° (Found: C, 85·4; H, 6·2%). 2-*Methoxyxanthen* formed needles, m. p. 70° (Found: C, 78·7; H, 5·7. $C_{14}H_{12}O_2$ requires C, 79·3; H, 5·7%), on crystallisation from light petroleum (b. p. 40—60°).

2-*Methylxanthen*-9-*carboxylic Acid.*—A solution of butyl-lithium, prepared from lithium (5 g.), *n*-butyl bromide (60 g.), and dry ether (600 ml.) under nitrogen, was treated with 2-methylxanthene (25 g.), in portions. After the vigorous evolution of butane had ceased, the solution was refluxed for 3 hr., allowed to cool and then poured on dry, powdered carbon dioxide. Next day water and ether were added, and the aqueous layer was acidified. 2-*Methylxanthen*-9-*carboxylic acid* (20·5 g.) formed needles, m. p. 198—199° (Found: C, 75·2; H, 5·3. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%), from benzene–light petroleum.

Esters of 9-xanthenylacetic acid.

R *	M. p. or b. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
·CH_2·CH_2·NMe_2,HCl	158°	$C_{19}H_{21}O_3N$,HCl	65·3	6·3	3·8	65·6	6·43	4·0
·CH_2·CH_2·NMe_3}Br	225	$C_{20}H_{24}O_3NBr$ [a]	59·2	6·1	3·3	59·1	5·9	3·3
·CH_2·CH_2·NMe_2Et}Br	135	$C_{21}H_{26}O_3NBr,\frac{1}{2}H_2O$	59·0	6·3	3·5	58·7	6·3	3·3
·CH_2·CH_2·NMe_2Pr^n}Br	125	$C_{22}H_{28}O_3NBr$	60·6	6·5	3·0	60·8	6·5	3·2
·CH_2·CH_2·NMe_2Pr^i}Br	145	$C_{22}H_{28}O_3NBr,H_2O$	58·4	5·9	3·1	58·4	6·4	3·1
·CH_2·CH_2·NEt_2,HCl	140	$C_{21}H_{25}O_3N$,HCl	66·9	6·9	3·3	67·4	6·7	3·7
·CH_2·CH_2·$NMeEt_2$}Br	158	$C_{22}H_{28}O_3NBr$	60·4	6·9	3·1	60·8	6·5	3·2
·CH_2·CH_2·NEt_3}Br	125	$C_{23}H_{30}O_3NBr$ [b]	—	—	3·2	—	—	3·1
·CH_2·CH_2·NEt_2Pr^n}Br	130	$C_{24}H_{32}O_3NBr,\frac{1}{2}H_2O$	61·1	6·7	3·1	61·2	7·0	3·0
·CH_2·CH_2·NEt_2Pr^i}Br	165	$C_{24}H_{32}O_3NBr,\frac{1}{2}H_2O$	61·1	6·8	3·0	61·2	7·0	3·0
·CH_2·CH_2·NPr^n_2	160°/0·05 mm.	$C_{23}H_{29}O_3N$	75·2	8·0	3·7	75·2	7·9	3·8
·CH_2·CH_2·$NMePr^n_2$}Br	138—139	$C_{24}H_{32}O_3NBr$	62·0	7·6	3·0	62·3	6·9	3·0
·CH_2·CH_2·$NEtPr^n_2$}Br	158	$C_{25}H_{34}O_3NBr$ [c]	—	—	2·9	—	—	2·9
·CH_2·$CH_2NPr^n_3$}Br	113—115	$C_{26}H_{36}O_3NBr$	63·7	7·3	3·6	63·7	7·3	2·9
·CH_2·CH_2·NPr^i_2,HCl	130	$C_{23}H_{29}O_3N$,HCl,$\frac{1}{2}H_2O$	66·4	7·0	4·6	66·9	7·5	3·4
·CH_2·CH_2·NC_5H_{10},HCl	168	$C_{22}H_{25}O_3N$,HCl	67·8	6·8	6·4	68·1	6·7	3·6
·CH_2·CH_2·$NMeC_5H_{10}$}Br	98	$C_{23}H_{28}O_3NBr,2H_2O$	57·6	6·6	3·2	57·3	6·6	2·9
·CH_2·CH_2·NC_4H_8O,HCl	158	$C_{21}H_{23}O_4N$,HCl	64·9	6·0	3·7	64·7	6·1	3·6
·CH_2·CH_2·$NMeC_4H_8O$}Br.....	195	$C_{22}H_{26}O_4NBr$	58·8	5·9	3·2	59·1	5·8	3·1
·CH_2·$CHMe$·NEt_2	180°/0·1 mm.	$C_{22}H_{27}O_3N$	75·2	8·0	3·7	74·8	7·6	4·0
·CH_2·$CHMe$·$NMeEt_2$}Br	148	$C_{23}H_{30}O_3NBr$	61·4	6·9	2·9	61·6	6·7	3·2
·CH_2·CH_2·CH_2·NEt_2	180°/0·3 mm.	$C_{22}H_{27}O_3N$	74·6	7·6	3·7	74·8	7·6	4·0
·CH_2·CH_2·CH_2·$NMeEt_2$}Br ...	98—101	$C_{23}H_{30}O_3NBr$	59·3	6·8	3·0	59·5	6·9	3·0
·CH_2·$CHMe$·NC_5H_{10},HCl ...	197	$C_{23}H_{27}O_3N$,HCl	68·3	7·0	3·5	68·7	6·7	3·5
·CH_2·$CHMe$·$NMeC_5H_{10}$}Br ...	93—94	$C_{24}H_{30}O_3NBr,H_2O$	59·7	7·5	2·9	59·4	6·7	2·9

* ·NC_5H_{10} = piperidino; ·NC_4H_8O = morpholino.
[a] Found: Br, 19·9. Reqd.: Br, 19·7%. [b] Found: Br, 18·0. Reqd.: Br, 17·9%. [c] Found: Br, 17·1. Reqd.: Br, 16·8%.

4-*Methylxanthen*-9-*carboxylic acid* formed needles, m. p. 202—203° (Found: C, 74·8; H, 5·1%), from benzene. 2-*Methoxyxanthen*-9-*carboxylic acid* crystallised from benzene and alcohol in needles, m. p. 203—204° (Found: C, 70·7; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

2-*Diethylaminoethyl* 2-*methylxanthen*-9-*carboxylate* (prepared by Horenstein and Pahlicke's method [2]) distilled as a pale yellow oil, b. p. 160°/0·2 mm. (Found: C, 74·1; H, 7·6; N, 4·0. $C_{21}H_{25}O_3N$ requires C, 74·3; H, 7·4; N, 4·1%). The *methobromide* formed hygroscopic plates, m. p. 137—138° (Found: N, 3·3; Br, 18·5. $C_{22}H_{28}O_3NBr$ requires N, 3·2; Br, 18·4%), from propan-2-ol–ether. The *ethobromide* formed hygroscopic cubes, m. p. 153—154° (Found: N, 2·9; Br, 17·2. $C_{23}H_{30}O_3NBr{\cdot}H_2O$ requires N, 3·0; Br, 17·2%), on similar crystallisation.

2-*Diethylaminoethyl* 4-*methylxanthen*-9-*carboxylate* (prepared by Horenstein and Pahlicke's method [2]) had b. p. 152°/0·1 mm. (Found: C, 73·7; H, 7·5; N, 4·2. $C_{21}H_{25}O_3N$ requires C, 74·3; H, 7·4; N, 4·1%). The *methobromide* formed cubes, m. p. 182—183° (Found: N, 3·2; Br, 18·0. $C_{22}H_{28}O_3NBr$ requires N, 3·2; Br, 18·4%), from propan-2-ol–ether.

Diethyl-2-(2′-*methoxy*-9′-*xanthoyl*)*ethylmethylammonium bromide* formed prisms, m. p. 172—173° (Found: 3·2; Br, 18·4. $C_{22}H_{28}O_4NBr$ requires N, 3·1; Br, 17·7%), on similar crystallisation.

Other *esters* are recorded in the Table.

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