281. *Synthetic Neuromuscular Blocking Agents. Part IV.*[1] *Compounds Related to Both Laudexium and Suxamethonium.*

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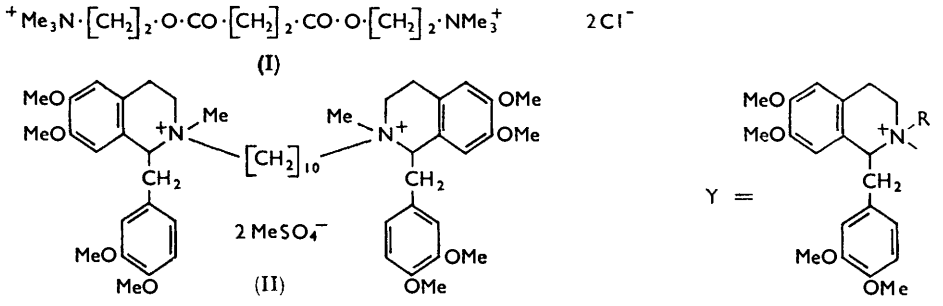
Compounds possessing certain structural features of both laudexium and suxamethonium have been synthesised in an attempt to obtain a short-acting true curarising agent. The action of several of these compounds is antagonised by neostigmine; whilst, however, some are short-acting as expected, others are long-acting. The alkylation of tetrahydropapaverine has been investigated.

The muscle relaxant suxamethonium (I) is very short-acting because of its ready enzymic hydrolysis to the comparatively inactive choline hydrogen succinate; consequently it has proved to be of considerable value in anæsthesia, although the lack of a satisfactory antagonist is a disadvantage. Moreover, since the initial observation by Churchill-Davidson [2] of the post-operative muscle pains and stiffness which occasionally follow its use, growing concern for these factors has been expressed by several groups of workers.[3] Laudexium [4] (II) is antagonised by neostigmine, but has a duration of action greater than



(I)

(II)

(III) $Y\cdot[CH_2]_m\cdot O\cdot CO\cdot[CH_2]_n\cdot CO\cdot O\cdot[CH_2]_m\cdot Y$ $2X^-$

(IV) $Y\cdot[CH_2]_m\cdot CO\cdot O\cdot[CH_2]_n\cdot NR'_3^+$ $2X^-$

(V) $Y\cdot[CH_2]_2\cdot NH\cdot CO\cdot[CH_2]_n\cdot CO\cdot NH\cdot[CH_2]_2\cdot Y$ $2X^-$

that of suxamethonium; [5] however, so far as is known, it does not cause muscle pains or stiffness. It therefore appeared possible that by incorporating certain of the chemical features of both laudexium and suxamethonium into one molecule, some of the products

[1] Part III, E. P. Taylor, *J.*, 1952, 1309.
[2] Churchill-Davidson, *Brit. Med. J.*, 1954, *i*, 74.
[3] *E.g.*, Burtles, *Brit. J. Anæsth.*, 1961, **33**, 147.
[4] E. P. Taylor, *J.*, 1952, 142.
[5] Collier and Macauley, *Brit. J. Pharmacol.*, 1952, **7**, 398.

might combine the valuable properties of each of the analogues. We therefore prepared and investigated three types of compound; these embody one or both of the large terminal end groups of laudexium, connected by a readily breakable linkage such as the ester link of suxamethonium. The types chosen were quaternary derivatives of symmetrical diesters (cf. III), unsymmetrical monoesters (cf. IV), and symmetrical diamides (V).

The preparation of each type involved a supply of *N*-alkylated derivatives of tetrahydropapaverine. The known methods of synthesis of these compounds are usually (*a*) by quaternisation of papaverine and subsequent chemical or catalytic reduction of the resulting quaternary salt [6] or (*b*), in the case of laudanosine, by the treatment of tetrahydropapaverine with formaldehyde, followed by hydrogenation.[7] Since large quantities of tetrahydropapaverine were available from other work it appeared advantageous to investigate the possibility of direct alkylation of tetrahydropapaverine. (After our work had been completed, Dúbravková *et al.*[8] reported the preparation of laudanosine in one step from papaverine by catalytic hydrogenation in absolute methanol.)

Interaction of dimethyl sulphate and tetrahydropapaverine in the presence of aqueous sodium hydroxide gave crude laudanosine (12%), and the hitherto unknown *N*-methyllaudanosinium hydrogen sulphate (59%); however, when diethyl sulphate was used, *N*-ethyltetrahydropapaverine was obtained almost quantitatively. A similar experiment with dipropyl sulphate gave only tetrahydro-*N*-propylpapaverine, but in lower yield (*ca.* 45%). Although this base and its salts gave satisfactory analyses the picrate had a higher m. p. (167—168°) than that recorded by Pyman [9] [122—125° (corr.)]. We found that quaternisation of papaverine with propyl iodide gave a mixture of the hydriodide and propiodide. Reduction of the latter with zinc and hydrochloric acid gave tetrahydro-*N*-propylpapaverine; the m. p.s of this base and its picrate were not depressed on admixture with samples prepared by direct alkylation of tetrahydropapaverine.

Laudanosine was also prepared by methylation of tetrahydropapaverine by the Eschweiler–Clarke method; when this was carried out at 65—70°, laudanosine was the major product, although more vigorous reaction conditions (*e.g.*, heating under reflux for 3 hr.) favoured the formation of norcoralydine.

Symmetrical Diesters (III).—These were obtained by (*a*) the quaternisation of *N*-alkyltetrahydropapaverines with suitable ω-bromoalkyl esters of aliphatic dicarboxylic acids or (*b*) condensation of tetrahydropapaverine with the ω-bromoalkyl esters, and quaternisation of the products with alkyl halides or sulphates. The ω-bromoalkyl esters were prepared by an extension of the method of Clinton and Laskowski; [10] some of them have since been described by Tammelin.[11]

Unsymmetrical Monoesters (IV).—Quaternisation of the dialkylaminoalkyl esters of aliphatic ω-bromo-monocarboxylic acids (VI) with an alkyl halide, as expected, was faster than internal self-quaternisation, yielding monoquaternary derivatives of type (VII). Treatment of these with *N*-alkyltetrahydropapaverines gave the required bisquaternary monoesters (IV).

$$\mathrm{Br\cdot[CH_2]_m\cdot CO\cdot O\cdot[CH_2]_n\cdot NR_2} \qquad \mathrm{Br\cdot[CH_2]_m\cdot CO\cdot O\cdot[CH_2]_n\cdot NR_3^+\ \ X^-}$$

(VI) (VII)

Symmetrical Diamides (V).—Dicarboxylic acid chlorides when treated with an excess of ethyleneimine,[12] yielded *NN'*-di-(2-chloroethyl)amides (VIII), which, after conversion

[6] Pictet and Athanasescu, *Ber.*, 1900, **33**, 2346; Pyman and Reynolds, *J.*, 1910, **97**, 1320; Barltrop and D. A. H. Taylor, *J.*, 1951, 108.
[7] Craig and Tarbell, *J. Amer. Chem. Soc.*, 1948, **70**, 2783.
[8] Dúbravková, Ježo, Šefčovič, and Votický, *Chem. Zvesti*, 1958, **12**, 140.
[9] Pyman, *J.*, 1909, **95**, 1738.
[10] Clinton and Laskowski, *J. Amer. Chem. Soc.*, 1948, **70**, 3135; cf. Campbell and E. P. Taylor, *J. Pharm. Pharmacol.*, 1950, **2**, 229.
[11] Tammelin, *Acta Chem. Scand.*, 1956, **10**, 1068.
[12] Cf. Bestian, *Annalen*, 1950, **566**, 210.

into the corresponding 2-iodoethyl derivatives, were quaternised with *N*-alkyltetrahydropapaverines to give the required diamides (V). By using carbonyl chloride in place of a dicarboxylic acid chloride, the corresponding urea derivative (IX) was obtained.

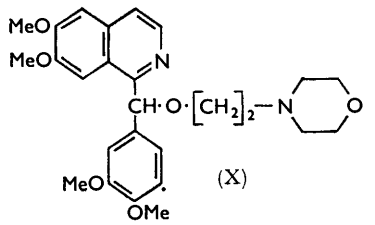
All the resulting bisquaternary ammonium salts (types III—V) were difficult to crystallise, and no attempts to ensure complete separation of diastereoisomers were made.

$$Cl\cdot[CH_2]_2\cdot NH\cdot CO\cdot[CH_2]_n\cdot CO\cdot NH\cdot[CH_2]_2\cdot Cl$$

(VIII)

$$Y\cdot[CH_2]_2\cdot NH\cdot CO\cdot NH\cdot[CH_2]_2\cdot Y \qquad 2X^-$$

(IX) (Y as above)



(X)

Considerable variation in the pharmacological activity of these salts was encountered. While some were short-acting, as expected, others had longer action; most of those examined were antagonised by neostigmine. Only the diester III (R = Me, $m = 3$, $n = 0$) [compound 41] had a briefer action (*ca.* 50%) than suxamethonium. However, it was of relatively low potency in animals, and Dr. H. Churchill-Davidson (personal communication) has shown it to be too weak in human volunteers to be of any value in anæsthesia. The most interesting of the new compounds was the unsymmetrical monoester (IV; R = R′ = Me, $m = 5$, $n = 2$) [compound 43] which consists of half the laudexium molecule joined to a quaternary ester portion resembling that of suxamethonium. In animal experiments, this compound was extremely active [~30 times as potent as (+)-tubocurarine chloride in the cat]. However, it was not antagonised by neostigmine, and its long action (~7 times that of suxamethonium) was a further disadvantage.

Preliminary notes[13] have been published,[13] as have pharmacological results for compound 41 (γ-oxalolaudonium bromide).[14]

Also described here is the preparation of papaverinol 2-morpholinoethyl ether (X) as a potential anti-tussive agent, for which purpose it proved unsatisfactory.

Experimental

(±)-*Laudanosine.*—(i) *The formaldehyde–formic acid (Eschweiler–Clarke) method.* A mixture of tetrahydropapaverine hydriodide (74·4 g.) and 2N-sodium hydroxide (160 ml.) was heated on a steam-bath for 30 min. and cooled. The oily tetrahydropapaverine was extracted with benzene, washed with water, and recovered. It was heated in 90% formic acid (36 g.) with 35% aqueous formaldehyde (48 g.) under reflux for 3 hr. After being cooled, the mixture was made alkaline with 2N-sodium hydroxide, and the gum which was precipitated was washed with water by decantation. The gum crystallised, and it recrystallised from ethanol. The first crop (13·7 g.; m. p. 156—158°) was recrystallised from ethanol, yielding norcoralydine (m. p. and mixed m. p. 157—158°) (Found: C, 70·75; H, 7·1; N, 4·2. Calc. for $C_{12}H_{25}NO_4$: C, 71·0; H, 7·1; N, 3·9%). The main alcoholic filtrate deposited a second crop when kept (2·2 g., m. p. 113—115°, undepressed on admixture with laudanosine), and on dilution with water a third crop (7·0 g.; m. p. 104—105°) which on recrystallisation from ethanol gave laudanosine (5·0 g.; m. p. 112—114°).

When this reaction was carried out at 65—70°, laudanosine was the major product.

(ii) *The dimethyl sulphate method.* Tetrahydropapaverine hydriodide (47·0 g., 0·1 mole) was heated with sodium hydroxide (16·0 g., 0·4 mole) in water (100 ml.) at 90° with stirring, then cooled to 50°. Dimethyl sulphate (15·75 g., 0·125 mole) was then added drop-by-drop with stirring at 50°. The mixture was stirred at 50° for a further 30 min., then allowed to cool. The supernatant liquor was decanted and rejected. The gummy residue was extracted with

[13] Collier, Gladych, Macauley, and Taylor, *Nature*, 1958, **182**, 1424; Atti XI Congresso Società Italiana di Anestesiologia, 1959, p. 162.

[14] Brittain, Collier, and D'Arcy, *Brit. J. Pharmacol.*, 1961, **17**, 116.

benzene, the insoluble portion (A) was dried and retained, and the combined extracts were washed with water and dried ($MgSO_4$). After removal of the solvent, the residue recrystallised from ethanol, giving crude laudanosine (4·3 g., 12%), which after two further crystallisations had m. p. and mixed m. p. 114—115°. The solid (A) (27·5 g., 59%; m. p. 211—213°), after repeated recrystallisation from water, separated as yellowish prisms of *N-methyl-laudanosinium hydrogen sulphate*, m. p. 215—216° (Found: N, 2·9; S, 7·05. $C_{22}H_{31}NO_8S$ requires N, 3·0; S, 6·8%). The m. p. was undepressed on admixture with an authentic sample prepared from laudanosine methiodide and potassium hydrogen sulphate. When this reaction was carried out at room temperature in the presence of benzene (50 ml.), the yield of crude laudanosine increased to 47% but an unidentified crystalline material, m. p. 228·5—229·5° (11·0 g.), insoluble in benzene, was also obtained.

N-*Ethyltetrahydropapaverine*.—Tetrahydropapaverine hydriodide (47·0 g., 0·1 mole) was treated with sodium hydroxide (12 g., 0·3 mole) in water (100 ml.) as described above. Diethyl sulphate (19·25 g., 0·125 mole) was added drop-by-drop to the stirred mixture at 50°, the temperature being controlled by adjusting the rate of addition. After being stirred for a further 30 min. at 50°, during which the oily base solidified, the mixture was cooled, and the solid filtered off, washed with water, and dried. *N*-Ethyltetrahydropapaverine (36·7 g., 99%) crystallised from aqueous ethanol as needles, m. p. 88—89° [lit.,[9] 89° (corr.)] {picrate, m. p. 167—169° [lit.,[9] 167—170° (corr.)]}.

Tetrahydro-N-*propylpapaverine*.—(i) Aqueous tetrahydropapaverine, resulting from the basification of the hydriodide (14·1 g., 0·03 mole) as above, was treated with dipropyl sulphate [15] (6·8 g., 0·0375 mole), drop-by-drop, at 50° with stirring. The mixture was then stirred at 50° for a further 50 min., cooled in ice, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. Absolute ethanol (50 ml.) was added to the oily residue, and the solvent was then distilled off. The oily residue crystallised from aqueous ethanol (5·3 g., 45·7%), and after two recrystallisations from aqueous acetone, *tetrahydro*-N-*propylpapaverine* was obtained as needles, m. p. 69—70° (Found: C, 71·3; H, 7·95; N, 3·9. $C_{23}H_{31}NO_4$ requires C, 71·7; H, 8·1; N, 3·6%). The picrate, yellow prisms from ethanol, had m. p. 167—168° [lit.,[9] 122—125° (corr.)] (Found: C, 56·7; H, 5·6; N, 8·7. Calc. for $C_{29}H_{34}N_4O_{11}$: C, 56·7; H, 5·6; N, 9·1%); the *hydriodide*, yellow prisms from ethanol–ether, had m. p. 162—163° (Found: C, 53·2; H, 6·1; N, 2·8; I, 25·0. $C_{23}H_{32}INO_4$ requires C, 53·8; H, 6·3; N, 2·7; I, 24·8%); the *hydrobromide*, cream-coloured rosettes from ethanol–ether, had m. p. 206—207° (Found: N, 3·0; Br, 17·0. $C_{23}H_{32}BrNO_4$ requires N, 3·0; Br, 17·2%).

(ii) Tetrahydropapaverine hydriodide (9·4 g., 0·02 mole), propyl iodide (3·4 g., 0·02 mole), anhydrous potassium carbonate (2·8 g., 0·02 mole), and 95% ethanol (100 ml.) were heated under reflux for 106 hr. The mixture was then cooled, filtered, and concentrated to about half-volume, and the precipitated potassium iodide filtered off. The filtrate was then diluted with water and subjected to prolonged scratching; tetrahydro-*N*-propylpapaverine (7·7 g.; m. p. 59—63°) separated. This recrystallised from aqueous acetone as needles, m. p. 68—69° (picrate, m. p. 167°).

(iii) Papaverine (20 g.) was quaternised under reflux with propyl iodide (20 g.) and benzene (140 ml.) for 110 hr.; *papaverine propiodide* was obtained as yellow needles (23 g.), m. p. 185—186° from ethanol (Found: N, 2·75; I, 25·6. $C_{23}H_{28}INO_4$ requires N, 2·75; I, 25·0%). When ethanol was used as the solvent for quaternisation of papaverine (25 g.), a mixture of papaverine hydriodide (9·5 g.) and papaverine propiodide (10·3 g.) was obtained.

Reduction of the crude propiodide (23 g.) with hydrochloric acid (250 ml. of concentrated acid in 500 ml. of water) and an excess of zinc dust [16] yielded tetrahydro-*N*-propylpapaverine (10·6 g.), m. p. 68—69° (picrate, m. p. 167—168°).

Tetrahydro-N-2-*hydroxyethylpapaverine*.—Tetrahydropapaverine hydriodide (47·1 g., 0·1 mole), ethylene bromohydrin (12·5 g., 0·1 mole), anhydrous potassium carbonate (13·8 g., 0·1 mole), and 95% ethanol (570 ml.) were heated together under reflux for 106 hr. The solvent was then distilled off *in vacuo*, the residue dried by distillation with benzene, and the benzene then removed. The gummy residue crystallised from aqueous ethanol (28·3 g.; m. p. 63—64°) and after further recrystallisation from aqueous ethanol *tetrahydro*-N-2-*hydroxyethylpapaverine* was obtained as cream-coloured needles, m. p. 71—73° (Found: C, 66·1; H, 7·6; N, 3·6.

[15] Suter and Gerhart, *Org. Synth.*, Coll. Volume II, p. 111; cf. Vogel and Cowan, *J.*, 1943, 16.
[16] Cf. E. P. Taylor, *J.*, 1951, 1150.

$C_{22}H_{29}NO_5,\frac{1}{2}H_2O$ requires C, 66·7; H, 7·6; N, 3·5%) [*hydrochloride*, colourless prisms, m. p. 173—174°, from ethanol (Found: Cl, 8·35; N, 3·3. $C_{22}H_{30}ClNO_5$ requires Cl, 8·4; N, 3·3%); *methiodide*, yellow, decomp. 65—75°, from ethanol–ether (Found: C, 52·2; H, 6·3; I, 23·6; N, 2·7. $C_{23}H_{32}INO_5$ requires C, 52·2; H, 6·1; I, 24·0; N, 2·65%)].

Tetrahydro-N-3-*hydroxypropylpapaverine*.—The base was prepared in a similar manner to the hydroxyethyl derivative, but did not crystallise. It was treated with ethanolic hydrogen chloride, the solution evaporated, and the residue treated with excess of sodium iodide solution. The resulting precipitate was filtered off, washed with a little water, and recrystallised from ethanol, giving cream-coloured rosettes of the *tetrahydro*-N-3-*hydroxypropylpapaverine hydriodide*, m. p. 200—202° (decomp.) (Found: C, 52·1; H, 6·3; I, 23·8; N, 2·3. $C_{23}H_{32}INO_5$ requires C, 52·2; H, 6·1; I, 24·0; N, 2·65%).

Papaverinol 2-Morpholinoethyl Ether (X).—Papaverinol [17] (7·1 g., 0·02 mole), dissolved in warm anhydrous benzene (100 ml.), was added to a suspension of sodium methoxide, prepared from sodium (0·47 g., just >0·02 mole) and anhydrous methanol (10 ml.), in anhydrous benzene (50 ml.). The mixture was distilled during 30 min. until the temperature of the vapour reached 78°, then *N*-2-chloroethylmorpholine (freshly liberated from 3·9 g. of the hydrochloride) in anhydrous benzene (75 ml.) was added. The mixture was then heated under reflux for 96 hr., cooled, washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was extracted with boiling anhydrous ethanol. The mixture was allowed to cool and filtered, and light petroleum (b. p. 40—60°) was added to the filtrate until turbidity just appeared. A slight excess of ethanolic hydrogen chloride was then added, followed by an excess of ether; a gum separated. This was recrystallised, first from ethanol–ether, then from ethanol, giving colourless *papaverinol 2-morpholinoethyl ether dihydrochloride*, m. p. 158—160° (decomp.) (Found: C, 57·15; H, 6·4; Cl, 12·2; N, 4·6; O, 19·2. $C_{26}H_{34}Cl_2N_2O_6,C_2H_5{\cdot}OH$ requires C, 57·2; H, 6·9; Cl, 12·1; N, 4·8; O, 19·1%).

ω-*Bromoalkyl Esters of Dicarboxylic Acids*.—These were prepared by the interaction of the acid and ω-bromoalkanol in ethylene dichloride in the presence of catalytic amounts of sulphuric acid.[10] This method gave the following di-(2-bromoethyl esters): oxalate, plates, m. p. 55—56° (lit.,[11] 54—55°), from ethanol (Found: C, 23·9; H, 2·65; Br, 51·6. Calc. for $C_6H_8Br_2O_4$: C, 23·7; H, 2·65; Br, 52·6%); malonate, b. p. 151—153°/1 mm. (lit.,[11] 152°/1 mm.) (Found: C, 26·75; H, 3·5; Br, 50·2. Calc. for $C_7H_{10}Br_2O_4$: C, 26·4; H, 3·2; Br, 50·3%); succinate, b. p. 140—142°/0·2 mm. (lit.,[11] 161°/1 mm.) (Found: C, 28·95; H, 4·2; Br, 48·0. Calc. for $C_8H_{12}Br_2O_4$: C, 28·9; H, 3·6; Br, 48·2%); glutarate, b. p. 134—136°/0·08 mm. (lit.,[11] 148°/0·3 mm.) (Found: C, 31·6; H, 4·1; Br, 45·9. Calc. for $C_9H_{14}Br_2O_4$: C, 31·2; H, 4·1; Br, 46·2%); adipate, b. p. 142—144°/0·1 mm. (lit.,[11] 156—161°/0·3 mm.) (Found: C, 33·5; H, 4·6; Br, 44·2. Calc. for $C_{10}H_{16}Br_2O_4$: C, 33·3; H, 4·5; Br, 44·4%); *di*-(3-*bromopropyl*) *oxalate* prisms, m. p. 45—45·5°, from ethanol (Found: C, 29·4; H, 3·7; Br, 47·5. $C_8H_{12}Br_2O_4$ requires C, 28·9; H, 3·6; Br, 48·2%); *di*-(3-*bromopropyl*) *malonate* b. p. 167—168°/0·5 mm. (Found: C, 31·2; H, 4·2; Br, 46·2. $C_9H_{14}Br_2O_4$ requires C, 31·2; H, 4·1; Br, 46·2%).

Symmetrical Diesters (III).—Two general methods of preparing these compounds were employed. (a) *Quaternisation of* N-*alkyltetrahydropapaverines by di*-(ω-*bromoalkyl*) *esters*. In general, the tertiary base (3 mol.) and the appropriate ester (1 mol.) were heated in anhydrous benzene under reflux for 130—1500 hr., then allowed to cool. The supernatant liquid was decanted and rejected, and the residue washed three times by decantation with hot benzene. After drying *in vacuo*, the residue was dissolved in anhydrous methanol or ethanol and added drop-by-drop to stirred anhydrous ether. The precipitation was usually repeated twice, the required diquaternary esters being obtained as cream-coloured powders. In all cases, the products had no sharp m. p.s, sintering and decomposition occurring over a range. Quaternisation of the *N*-alkyltetrahydropapaverines proceeded most readily with laudanosine, the reaction time varying from 130 to 500 hr. When *N*-ethyltetrahydropapaverine was used, a quaternisation time of 1400—1500 hr. was necessary, and the yields were low; the major product isolated from the reaction between tetrahydro-*N*-propylpapaverine and di-(2-bromoethyl) malonate was tetrahydro-*N*-propylpapaverine hydrobromide, only a trace of the required diquaternary ammonium salt being obtained. Other salts were obtained from the dibromides by conventional double decomposition. The properties of these salts are summarised in the Table.

[17] Gadamer, *Arch. Pharm.*, 1915, **253**, 284.

NN'-Alkanedioyldi[oxymethylene-(*N*-alkyltetrahydropaverinium)] dihalides (III).

					Found (%)			Reqd. (%)	
R	*m*	*n*	X^-	M. p.*	Hal	N	Formula	Hal	N
Me	2	0	Br^-	70—80°	16·0	3·0	$C_{48}H_{62}Br_2N_2O_{12}$	15·7	2·75
Me	2	0	NO_3^-	50—55	—	5·76	$C_{48}H_{62}N_4O_{18}$	—	5·70
Me	2	1	Br^-	85—95	15·3	2·7	$C_{49}H_{64}Br_2N_2O_{12}$	15·5	2·7
Me	2	1	ClO_4^-	80—90	6·55	2·6	$C_{49}H_{64}Cl_2N_2O_{20}$	6·6	2·6
Me	2	2	Br^-	93—103	15·8	2·7	$C_{50}H_{66}Br_2N_2O_{12}$	15·3	2·7
Me	2	3	Br^-	70—80	14·5	2·65	$C_{51}H_{68}Br_2N_2O_{12}$	15·1	2·6
Me	2	4	Br^-	90—100	14·6	2·85	$C_{52}H_{70}Br_2N_2O_{12}$	14·9	2·6
Me	3	0	Br^-	140—148	14·75	2·7	$C_{50}H_{66}Br_2N_2O_{12}$	15·3	2·7
Me	3	1	Br^-	85—95	15·0	2·6	$C_{51}H_{68}Br_2N_2O_{12}$	15·1	2·6
Et	2	1	Br^-	50—60	15·8	2·7	$C_{51}H_{68}Br_2N_2O_{12}$	15·1	2·6
Et	2	4	Br^-	65—75	15·0	2·7	$C_{54}H_{74}Br_2N_2O_{12}$	14·5	2·5
Pr	2	1	Br^-	105—115	15·45	3·0	$C_{53}H_{72}Br_2N_2O_{12}$	14·7	2·6

* With decomp. over a range.

(b) *Reaction of tetrahydropapaverine with a di-(ω-bromoalkyl) ester, and quaternisation of the product.* The oxalate (III; R = Me, *m* = 3, *n* = 0, X^- = Br). Tetrahydropapaverine was liberated from its hydriodide (171·6 g., *ca.* 0·36 mole) as in previous experiments and, after drying, the base was dissolved in anhydrous acetone (1 l.) and added to a solution of di-(3-bromopropyl) oxalate (60·6 g., *ca.* 0·18 mole) in anhydrous acetone (4 l.). Anhydrous potassium carbonate (54·65 g., 0·396 mole) was then added, and the mixture was boiled under reflux for 104 hr., with stirring and protection from moisture. The mixture was then allowed to cool, the inorganic solids were filtered off and rejected, and methyl bromide (140 g.) was passed into the cooled acetone filtrate under anhydrous conditions. The solution was then left at room temperature for 10 days, during which a gum was deposited. Anhydrous ether (4 l.) was then added, the mixture set aside, and the supernatant liquid was then decanted and rejected. The residue was then triturated with anhydrous ether; it solidified; the solid was filtered off, washed rapidly with anhydrous ether, and dried (165·6 g.). The product was then triturated with anhydrous acetone (550 ml.), the solvent decanted, and the residue triturated with anhydrous ether (550 ml.). After filtration, the residue was dried *in vacuo*, first at room temperature, then at 80—90°/0·5 mm. (45 hr.) and finally at 115—120°/1 mm. (45 hr.). *Di-*[3-(*tetrahydro-*N-*methyl-2-papaverinyl*)*propyl*] *oxalate dibromide* (132·5 g.) was obtained as a pale yellow solid, m. p. 140—148° (decomp.) (Found: C, 57·0; H, 6·4; Br, 15·2; Br^-, 14·9; N, 2·9; O, 18·35. $C_{50}H_{66}Br_2N_2O_{12}$ requires C, 57·4; H, 6·4; Br, 15·3; N, 2·7; O, 18·3%).

The corresponding *di-iodide* (obtained by using methyl iodide in place of methyl bromide) was yellow and had m. p. 95—120° (decomp.) (Found: I, 22·7; N, 2·5. $C_{50}H_{66}I_2N_2O_{12}$ requires I, 22·3; N, 2·5%).

Unsymmetrical Monoesters (IV).—The intermediate ω-bromoalkanoic acids were prepared by the action of hydrobromic and sulphuric acid on the ethyl esters of the corresponding ω-hydroxy-acids.[18]

The salt (IV; R = R' = Me, *m* = 5, *n* = 2, X^- = I^-). 6-Bromohexanoic acid (3 g., ~0·015 mole) and thionyl chloride (17·8 g.) were heated together under reflux for 3 hr., after which the excess of thionyl chloride was distilled off, finally with anhydrous benzene *in vacuo*. The yellow oily residue was then dissolved in anhydrous benzene (9 ml.); to this was gradually added 2-dimethylaminoethanol (1·38 g., ~0·015 mole) in anhydrous benzene, heat being evolved and crystals separating. The mixture was heated under reflux for 1 hr., cooled, and treated with an excess of anhydrous ether. The solid precipitate was filtered off, washed with ether, and dried *in vacuo* (4·3 g.); it was then dissolved in water (15 ml.), and the solution was made alkaline (pH 9) with 2N-sodium hydroxide. The resulting oil was extracted with chloroform, the extracts were washed with water and dried ($MgSO_4$), and the chloroform was then removed *in vacuo*. The residual crude dimethylaminoethyl 6-bromohexanoate was dissolved in ethyl methyl ketone (22 ml.) and treated with a solution of methyl iodide (3·15 g.) in ethyl methyl ketone (22 ml.). The mixture was left at room temperature for 95 hr., filtered to remove a trace of impurity, and treated with an excess of anhydrous ether. The precipitated solid (4·3 g.) was filtered off, washed with dry ether, and recrystallised from anhydrous ethanol–ether. 2-*Dimethylaminoethyl* 6-*bromohexanoate methiodide* was obtained as pale yellow crystals, m. p. 74—76° (Found: C, 33·95; H, 6·15; Hal, 46·45; N, 3·2. $C_{11}H_{23}BrINO_2,\frac{3}{4}C_2H_5{\cdot}OH$ requires

[18] Cf. Barger, Robinson, and Smith, *J.*, 1937, 718.

C, 33·9; H, 6·3; Hal, 46·8; N, 3·2%). This substance (1·78 g.) was dissolved in anhydrous acetone (10 ml.) and added to a solution of sodium iodide (0·61 g., 1 mol.) in anhydrous acetone (10 ml.). The resulting solution was heated under reflux for 1 hr., then cooled, and the inorganic solids were filtered off and rejected. Adding an excess of anhydrous ether to the filtrate precipitated a pale cream-coloured solid (1·56 g.). This was heated under reflux with laudanosine (3·5 g., 3 mol.) and anhydrous acetone (60 ml.) for 150 hr. The mixture was then cooled, and the supernatant liquid decanted from the gummy solid and rejected. The residue was washed by decantation with anhydrous acetone and triturated with anhydrous ether; the resulting cream-coloured solid (1·73 g. after drying *in vacuo*) was dissolved in chloroform and carefully precipitated with anhydrous ether. After two further precipitations, the product was dried (9 hr. at 50°/0·5 mm., 9 hr. at 80°/0·5 mm., and 9 hr. at 100°/0·5 mm.), giving N-(5-2′-*dimethylaminoethyloxycarbonylpentyl*)*tetrahydropapaverine dimethiodide* (1·21 g.) as cream-coloured crystals, m. p. 135—137° (decomp.) (Found: C, 46·7; H, 6·4; I, 31·5; N, 3·5; O, 12·3. $C_{32}H_{50}I_2N_2O_6$ requires C, 47·3; H, 6·2; I, 31·3; N, 3·45; O, 11·85%).

The valerate (IV; R = R′ = Me, $m = 4$, $n = 3$, $X^- = I^-$). δ-Bromovaleric acid (2·8 g.) was converted into 3-*dimethylaminopropyl* δ-*bromovalerate methiodide* in a manner similar to that described in the previous experiment. Crystallised from ethanol–ether it was pale cream-coloured and had m. p. 57—58° (2·2 g.) (Found: C, 34·2; H, 6·3; Hal, 46·9; N, 2·7. $C_{11}H_{23}BrINO_2,\frac{1}{4}C_2H_5{\cdot}OH$ requires C, 33·9; H, 6·3; Hal, 46·8; N, 3·2%). Treatment with sodium iodide and laudanosine as described above then yielded cream-coloured N-(4-3′-*dimethylaminopropoxycarbonylbutyl*)*tetrahydropapaverine dimethiodide*, m. p. 124—130° (decomp.) (from methanol–ether) (Found: I, 31·1; N, 3·25. $C_{32}H_{50}I_2N_2O_6$ requires I, 31·3; N, 3·45%).

Symmetrical Diamides (V).—Ethyleneimine [19] with dicarboxylic acid chlorides gave [12] the following NN′-*di*-(2-*chloroethyl*)*diamides*: oxamide, needles, m. p. 204—205° (lit.,[12] 200°), from methanol (Found: C, 33·6; H, 5·2; Cl, 33·0; N, 13·1. Calc. for $C_6H_{10}Cl_2N_2O_2$: C, 33·8; H, 4·7; Cl, 33·3; N, 13·15%); *succinamide*, scales, m. p. 163—164°, from ethanol (Found: C, 40·35; H, 5·7; Cl, 29·05; N, 11·3. $C_8H_{14}Cl_2N_2O_2$ requires C, 39·8; H, 5·9; Cl, 29·5; N, 11·6%); *glutaramide*, plates, m. p. 146—147°, from acetone (Found: C, 42·1; H, 6·3; Cl, 27·7; N, 10·8. $C_9H_{16}Cl_2N_2O_2$ requires C, 42·35; H, 6·3; Cl, 27·8; N, 11·0%); adipamide, m. p. 154—155° (lit.,[12] 151°), used without crystallisation. When ethyleneimine was treated with carbonyl chloride the crude *NN′*-di-(2-chloroethyl)urea had m. p. 124·5—126° (lit.,[12] 127°) and was used without purification.

Treatment of these amides with sodium iodide in anhydrous acetone yielded the following NN′-*di*-(2-*iodoethyl*)*diamides*: *oxamide*, plates, m. p. 221—222° (decomp.), from aqueous dimethylformamide [Found: C, 20·8; H, 2·8; I, 58·55; N, 7·1. $2C_6H_{10}I_2N_2O_2,H{\cdot}CO{\cdot}N(CH_3)_2$ requires C, 20·8; H, 3·15; I, 58·7; N, 8·1%]; *glutaramide*, scales, m. p. 148—149°, from acetone (Found: C, 24·8; H, 3·7; N, 6·3. $C_9H_{16}I_2N_2O_2$ requires C, 24·7; H, 3·7; N, 6·4%); *adipamide*, prismatic needles, m. p. 166—167°, from acetone (Found: C, 26·9; H, 4·0; I, 56·1; N, 6·1. $C_{10}H_{18}I_2N_2O_2$ requires C, 26·55; H, 4·0; I, 56·2; N, 6·2%); NN′-*di*-(2-*iodoethyl*)*urea*, needles, m. p. 156—157°, from ethanol (Found: C, 16·7; H, 2·85; I, 68·8; N, 7·8. $C_5H_{10}I_2N_2O$ requires C, 16·3; H, 2·7; I, 69·0; N, 7·6%).

NN′-*Oxalyl di*-(N-2-*aminoethyltetrahydropapaverine*) *Dimethiodide*, (V; R = Me, $n = 0$, $X^- = I^-$).—A mixture of *NN′*-di-(2-iodoethyl)oxamide (0·66 g.), laudanosine (1·8 g.), and anhydrous benzene (40 ml.) was heated under reflux for 416 hr., then allowed to cool. The supernatant liquid was decanted and rejected, and the gummy residue washed by decantation three times with anhydrous benzene and dried *in vacuo*, then dissolved in methanol and precipitated with anhydrous ether. After repetition of this purification, the *dimethiodide* was obtained as a yellow solid (0·4 g.), m. p. 180—183° (decomp.) (Found: I, 22·1; N, 5·0. $C_{48}H_{64}I_2N_4O_{10}$ requires I, 22·9; N, 5·05%). Similar experiments with the glutaramide and adipamide gave as only solid product laudanosine hydriodide, m. p. and mixed m. p. 195—197°. However, the urea gave NN′-*ureido di*-(N-*ethyltetrahydropapaverine*) *dimethiodide* (IX), a yellow solid, m. p. 150—153° (decomp.) (from ethanol–ether) (Found: I, 22·8; N, 5·15. $C_{47}H_{64}I_2N_2O_9$ requires I, 23·5; N, 5·2%).

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[19] Wystrach and Schaefer, *J. Amer. Chem. Soc.*, 1956, **78**, 1263.