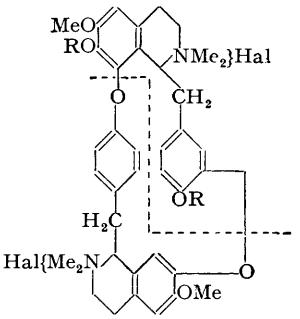
30. *Synthetic Neuromuscular Blocking Agents. Part II.* Bis(quaternary Ammonium Salts) derived from Laudanosine.*

By E. P. Taylor.

In continuation of earlier work, some heterocyclic bis(quaternary ammonium salts) have been prepared which show close chemical similarities to (+)-*OO*-dimethyltubocurarine iodide and possess greater curarising activity in the rabbit than does (+)-tubocurarine chloride.

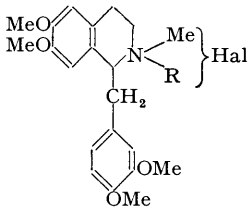
In the search for new curarising agents, the resemblance between the structure of (+)-tubocurarine chloride (I) and those of certain other alkaloids has been taken into consideration by various workers. Thus, Craig and Tarbell (*J. Amer. Chem. Soc.*, 1948, **70**, 2783) prepared and investigated the pharmacological properties of, *inter alia*, *N*-methyllaudanosinium iodide (II) and *N*-benzyl-laudanosinium bromide (III), both of which closely resemble one half of the molecule of (+)-*OO*-dimethyltubocurarine iodide (IV).



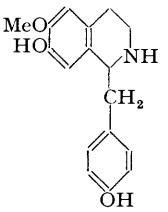
(I; R = H, Hal = Cl)

(IV; R = Me, Hal = I)

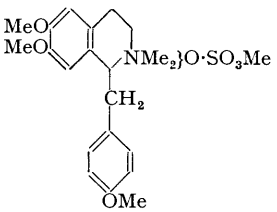
As might be expected, both these salts possess some, although very slight, curare-like activity in mice. More recently, Finkelstein (*ibid.*, 1951, **73**, 550) synthesised the alkaloid coclaurine (V), and its fully methylated quaternary salt (VI), but both were devoid of curare-like activity in dogs at the dosage level used.



(II; R = Me, Hal = I)
(III; R = CH_2Ph, Hal = Br)



(V)



(VI)

In Part I of this series (*J.*, 1951, 1150) it was shown that certain heterocyclic decamethylenebis(quaternary ammonium salts) possess strong neuromuscular blocking activity of true curare type. Consequently, it was decided to prepare some bisquaternary salts of laudanosine. In addition to polymethylene derivatives (VII—XI), compounds (XII and XIII) containing the $[CH_2]_4{\cdot}O{\cdot}[CH_2]_4$ and the $[CH_2]_5{\cdot}O{\cdot}[CH_2]_5$ chain were prepared. Although the products were recrystallised to analytical purity, to remove any monoquaternary salt that might be formed, no attempt was made to ensure complete separation of the diastereoisomers.

Dr. H. O. J. Collier found these bisquaternary laudanosinium salts to be powerful neuromuscular blocking agents, in animals, of true curare type, being antagonised by neostigmine and causing the typical flaccid paralysis in the chick. The paralysing

* Part I, *J.*, 1951, 1150.

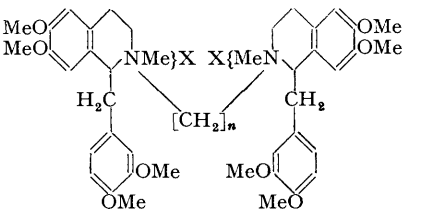
activities of these substances in rabbits and mice are indicated in the table, the last two substances being inserted for comparison. A brief note on these compounds has already appeared (Taylor and Collier, *Nature*, 1951, **167**, 692) and the full pharmacological results will be reported elsewhere (Collier and Macauley, in the press).

Paralysing activity of bislaudanosinium salts.

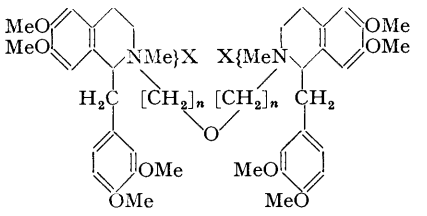
(μg. per kg. of body weight.)

Compound	Chain	Approx. M.E.D. (rabbit)	E.D.50 (mouse)	Compound	Chain	Approx. M.E.D. (rabbit)	E.D.50 (mouse)
(VII)	Octamethylene	47	260	(XII)	$[CH_2]_4{\cdot}O{\cdot}[CH_2]_4$	70	—
(VIII)	Nonamethylene	26	160	(XIII)	$[CH_2]_5{\cdot}O{\cdot}[CH_2]_5$	200	—
(IX)	Decamethylene	31	300	(I)	(+)-Tubocurarine chloride	100	70
(X)	Undecamethylene	55	410				
(XI)	Dodecamethylene	90	760	(IV)	(+)-*OO*-Dimethyltubocurarine iodide	10	120

Although, in the tubocurarine molecule, the two quaternary groups are separated by a chain containing an ether linkage, the two compounds (XII and XIII) with an ether linkage are weaker than the corresponding polymethylene derivatives (VIII) and (X). In rabbits, the two most active compounds are the nonamethylene (VIII) and the decamethylene (IX) derivative. Although (VIII) shows considerably greater paralysing



(VII, $n = 8$) (VIII; $n = 9$) (IX; $n = 10$) (X; $n = 11$) (XI; $n = 12$)



(XII; $n = 4$) (XIII; $n = 5$)

activity in mice than does (IX), it appears to liberate more histamine in man. Moreover, it will be observed that (+)-*OO*-dimethyltubocurarine iodide (IV), although weaker in mice than is (+)-tubocurarine chloride (I), is a much more powerful paralysant in rabbits (and also in man). For these and other reasons (Bodman, in the press; Collier and Macauley, *loc. cit.*), the decamethylene derivative, under the name "Laudolissin" or "Compound 20" was selected for further investigation. Its action in human volunteers has been studied by Dr. Richard Bodman of the University of Bristol. Preliminary results indicate that it possesses approximately half to two-thirds of the curarising activity of (+)-tubocurarine chloride in man, that it is antagonised by neostigmine, and that it appears not to produce undesirable side-effects. This compound is being subjected to extensive clinical trials.

The bisquaternary salts were prepared by the two general methods described in Part I (*loc. cit.*), by interaction of the appropriate dihalide with tetrahydropapaverine or laudanosine, followed in the former case by treatment of the resultant bistertiary amine with an alkyl halide or sulphate. The five polymethylene di-iodides required have already been described; however, a new and very simple general method of preparing these compounds in excellent yield is to reflux a solution of the appropriate glycol in hydriodic acid (*d* 1·94); the iodide separates as a heavy oil, which can be easily extracted and purified. 4 : 4′-Di-iododibutyl ether and 5 : 5′-di-iododiamyl ether, which appear to be new, were obtained by treatment of the known dichloro-compounds with sodium iodide in acetone. There are various catalytic methods for the reduction of papaverine (Craig and Tarbell, *loc. cit.*) and of its methiodide (Barltrop and Taylor, *J.*, 1951, 108), but, in the apparatus available, these were unsuitable for the preparation of tetrahydropapaverine or of laudanosine in the quantities required. Tetrahydropapaverine was obtained in 60% yield by reduction of papaverine with zinc and hydrochloric acid (cf. Pyman, *J.*, 1909, 1614,

who obtained a 39% yield by reduction with tin and aqueous-alcoholic hydrochloric acid). A similar reduction of papaverine methiodide yielded laudanosine in 73% yield (67% overall yield based on papaverine) (Pyman and Reynolds, *J.*, 1910, 1323, obtained an overall yield of 78%).

Experimental

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s and b. p.s are uncorrected.)

Preparation of Polymethylene Di-iodides.—A mixture of decamethylene glycol (140 g.) and hydriodic acid (618 g.; *d* 1·94; 100% excess) was mechanically stirred and heated under reflux for 6 hours. After cooling and dilution with water the precipitated heavy oil was extracted with ether, the extract washed successively with water, sodium hydrogen carbonate solution, sodium thiosulphate solution, and water, and dried (Na_2SO_4), the ether recovered, and the residue distilled *in vacuo*. The fraction of b. p. 197—200°/12 mm. (299 g.), which solidified, was recrystallised from alcohol, giving decamethylene di-iodide (281 g., 88·5%), m. p. 28—29°.

In a similar manner, octamethylene (80%), nonamethylene (83%), undecamethylene (81%), and dodecamethylene (78·5%) di-iodides were obtained from the corresponding glycols.

4 : 4′-*Di-iodobutyl Ether.*—4 : 4-Dichlorodibutyl ether (Alexander and Schniepp, *J. Amer. Chem. Soc.*, 1948, **70**, 1840; Alexander and Towles, *Org. Synth.*, 1950, **30**, 27) (15 g.) was added to a solution of sodium iodide (33·9 g., 50% excess) in dry acetone (300 ml.), and the mixture refluxed for 7 days. The precipitated salt was then filtered off and washed with acetone, the solvent recovered from the combined filtrate and washings, and the residue dissolved in ether, washed (water, sodium thiosulphate solution, and water), and dried (Na_2SO_4). After recovery of the solvent, the residue was distilled *in vacuo*, and the fraction of b. p. 100—105°/0·02 mm. redistilled, giving 4 : 4′-*di-iodobutyl ether* (23 g., 80%), b. p. 102—104°/0·05 mm. (with slight decomp.) (Found : C, 26·0; H, 4·4; I, 65·6. $C_8H_{16}OI_2$ requires C, 25·1; H, 4·2; I, 66·5%).

Similarly, 5 : 5′-dichlorodiamyl ether (Alexander and Schniepp, *loc. cit.*, 1948) was converted into 5 : 5′-*di-iododiamyl ether*, b. p. 136—138°/0·1 mm. (with slight decomp.) (Found : C, 29·6; H, 5·3; I, 62·8. $C_{10}H_{20}OI_2$ requires C, 29·3; H, 4·9; I, 61·95%).

Tetrahydropapaverine Hydriodide.—A solution of papaverine (50 g.) in hydrochloric acid (500 ml.) and water (3750 ml.) was gently refluxed, whilst zinc dust (150 g.) was added in small portions during 2 hours. After a further 24 hours' refluxing, fresh quantities of hydrochloric acid (500 ml.) and zinc dust (150 g.) were added, and refluxing was continued for a total time of 54 hours. The hot solution was then filtered from excess of zinc, the latter was washed with hot water, the combined filtrate and washings were concentrated *in vacuo* to half-volume, then made alkaline with excess of ammonia and cooled. The precipitated bases were extracted with ether (there was a small quantity of insoluble material), the ethereal extract was dried (Na_2SO_4), and the solvent recovered. The oily residue was dissolved in hot dilute hydrochloric acid, and excess of powdered potassium iodide (30 g.) added slowly with stirring. After cooling, the amorphous precipitate was filtered off, washed with cold water, sucked dry, and boiled with alcohol (500 ml.), whereupon it crystallised. After cooling, filtration, and drying, crude tetrahydropapaverine hydriodide (49 g.; m. p. 242—244°) was obtained. This was recrystallised from water, giving pure material (42 g.), m. p. 257—258° [Pyman, *J.*, 1909, 1614, gives m. p. 259—260° (corr.)].

Preparation of Bis(tertiary Amines).—Dihydrochloride of 1 : 10-*bis*-[1-(3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinolino]*decane*. A mixture of decamethylene di-iodide (11·8 g.), tetrahydropapaverine hydriodide (29·7 g., 2·1 mols.), anhydrous potassium carbonate (15 g.), and 95% alcohol (360 ml.) was refluxed for 104 hours. The alcohol was then distilled off, and any residual water removed by azeotropic distillation with benzene. The residue was dissolved as far as possible in hot dry benzene and filtered, and the solvent recovered, finally *in vacuo*. The oily residue was dissolved in the minimum quantity of anhydrous alcohol, and acidified to Congo-red with dry alcoholic hydrogen chloride. After cooling, the resultant dihydrochloride was filtered off, washed with cold alcohol, and dried, giving crude material of m. p. 236—238° (25·6 g., 95%). When this was recrystallised from boiling water (500 ml.), the *product* (20·5 g., 76%) was obtained as a colourless powder, m. p. 242—244° (decomp.) (Found : C, 66·7; H, 7·75; N, 3·2; Cl, 7·95. $C_{50}H_{70}O_8N_2Cl_2$ requires C, 66·9; H, 7·9; N, 3·1; Cl, 7·9%).

The following analogues were prepared in a similar manner :

1 : 8-*Bis*-[1-(3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinolino]*octane dihydrochloride* (from water), m. p. 256—258° (decomp.) (Found : N, 3·0; Cl, 8·5. $C_{48}H_{66}O_8N_2Cl_2$

requires N, 3·2; Cl, 8·2%); 1 : 11-*bis*-[1-(3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinolino]*undecane dihydrochloride* (from alcohol–ether), softens at 207°, m. p. 214—215° (Found : N, 3·05; Cl, 7·7. $C_{51}H_{72}O_8N_2Cl_2$ requires N, 3·1; Cl, 7·8%); 1 : 12-*bis*-[1-(3 : 4-*dimethoxybenzyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinolino]*dodecane dihydrochloride* (from alcohol–ether), m. p. 224—226° (decomp.) (Found : N, 3·0; Cl, 8·0. $C_{52}H_{74}O_8N_2Cl_2$ requires N, 3·0; Cl, 7·7%); and *bis*-{5-[1-(3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-isoquinolino]*amyl*} *ether dihydrochloride* (from alcohol–ether), softens at 198—200°, m. p. 208—210° (Found : N, 3·2; Cl, 7·9. $C_{50}H_{70}O_9N_2Cl_2$ requires N, 3·1; Cl, 7·8%).

Preparation of Bis(quaternary Ammonium Salts).—Note : the analyses of all quaternary compounds described below were carried out on material dried *in vacuo* at 100°.

Method I. *Decamethylenebis*-[1-(3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinolinium *methosulphate*] (IX). The dihydrochloride (20 g.) of 1 : 10-bis-[1-(3 : 4-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinolino]decane was dissolved in boiling water (700 ml.), made alkaline with sodium hydroxide, and saturated with sodium chloride, and the brown oil which separated extracted with hot benzene. The benzene solution was shaken with solid potassium hydroxide, filtered, and concentrated to approx. 100 ml. A solution of methyl sulphate (8·45 g., 50% excess) in dry benzene (25 ml.) was added, and the mixture refluxed for 48 hours. A heavy oil soon separated, which slowly thickened to a gummy solid. The benzene was then decanted off, and the residue washed three times by decantation with hot benzene and then dried *in vacuo*, yielding a light brown friable solid. This was dissolved in hot anhydrous alcohol, ether was added to the warm solution, and the mixture left to crystallise slowly. After two further recrystallisations, the *product* was obtained as a cream-coloured granular powder (10 g.), m. p. 172—174° after darkening at 164—166° (Found : C, 60·1; H, 7·75; N, 2·5; S, 5·9. $C_{54}H_{80}O_{16}N_2S_2$ requires C, 60·2; H, 7·5; N, 2·6; S, 5·95%).

The *undecamethylene* (X) (from alcohol–ether), m. p. 187—189° after darkening at 170° (Found : C, 60·8; H, 7·3; N, 2·7; S, 5·85. $C_{55}H_{82}O_{16}N_2S_2$ requires C, 60·55; H, 7·6; N, 2·6; S, 5·9%), and the *dodecamethylene* analogue (XI) (from alcohol–ether), softens at 202°, m. p. 205—207° (Found : C, 61·0; H, 7·65; N, 2·7; S, 5·9. $C_{56}H_{84}O_{16}N_2S_2$ requires C, 60·9; H, 7·7; N, 2·5; S, 5·8%), were similarly prepared, as was the 6-*oxaundecamethylene* analogue (XIII) (from alcohol–ether), darkens at 142°, m. p. 154—156° (Found : C, 58·8; H, 7·4; N, 2·6; S, 5·9. $C_{54}H_{80}O_{17}N_2S_2$ requires C, 59·3; H, 7·4; N, 2·6; S, 5·9%).

Method II. *Decamethylenebis*-[1-(3 : 4-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-2-*methyl*isoquinolinium *iodide*] (IX). Decamethylene di-iodide (1 g.) and laudanosine (3·63 g., 100% excess) in dry benzene (25 ml.) were refluxed for 108 hours. The solution became faintly cloudy after 4 hours, and slowly deposited a heavy oil, which solidified on cooling. After filtration the residue was crushed, thoroughly washed with benzene, and dried. The pale yellow friable residue was dissolved in methyl alcohol, and poured into excess of ether with stirring. After repetition of this precipitation, it was possible to recrystallise the material from methyl alcohol–ether in the normal manner. The *product* (1·1 g.) was obtained as cream-coloured granules, which softened at 136—138° and melted at 146—148° (Found : C, 55·9; H, 6·65; N, 2·4; I, 22·6. $C_{52}H_{74}O_8N_2I_2$ requires C, 56·3; H, 6·7; N, 2·5; I, 22·9%).

The corresponding *bromide*, prepared from decamethylene dibromide, was obtained as granules (from butyl alcohol–ether), which softened at 93—95° and melted at 105—107° (Found : N, 2·65; Br, 16·0. $C_{52}H_{74}O_8N_2Br_2$ requires N, 2·8; Br, 15·8%).

Iodides were prepared in a similar manner of the *octamethylene* (VII), granules (from butyl alcohol–ether), softens at 127—129°, m. p. 135—137° (Found : N, 2·55; I, 23·3. $C_{50}H_{70}O_8N_2I_2$ requires N, 2·6; I, 23·5%), *nonamethylene* (VIII), granules (from butyl alcohol), softens at 130—132°, m. p. 139—141° (Found : N, 2·7; I, 23·1. $C_{51}H_{72}O_8N_2I_2$ requires N, 2·6; I, 23·2%), and 5-*oxanonamethylene* analogue (XII) granules (from butyl alcohol), softens slightly at 118—120°, m. p. 130—132° (Found : N, 2·3; I, 22·8. $C_{50}H_{70}O_9N_2I_2$ requires N, 2·55; I, 23·2%).

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