RESEARCH PAPERS

ALKANOLAMIDES STERICALLY RELATED TO ERGOMETRINE

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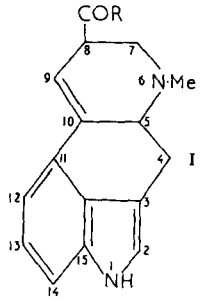
The ethanolamides of 3-dimethylaminopropionic acid, 1-methyl-1,2,5,6-tetrahydronicotinic acid (arecaidine) and 1-methylhexahydronicotinic acid, and propanolamides of 3-dimethylaminopropionic acid and arecaidine have been synthesised. None of these compounds had demonstrable oxytocic activity on the isolated oestrous rat uterus in concentrations up to 1 mg./ml. Arecaidine propanolamide inhibited acetylcholine-induced contractions in concentrations of 0·075 to 0·3 mg./ml. The 2-styryl derivatives of 3-dimethylaminopropionic and 4-dimethylaminobutyric acids were found to be unstable.

No entirely synthetic compound related to the ergot alkaloids has found general clinical acceptance as an oxytocic, nor has any structural feature or combination of features been shown to be consistently associated with oxytocic activity. A major difficulty, however, lies in the assessment of oxytocic activity, since results may vary widely depending on the choice of technique, of experimental animal or on the endocrine balance of the same animal on different occasions (Rosen, Blumenthal, Townsend, Tislow and Seifter, 1956). In addition, the relative potencies of oxytocics on the human uterus have been shown to bear little relation to those observed in experimental animals (De Jongh, 1956; Garrett and Embrey, 1958); indeed clinically useful oxytocics may well have been overlooked because of their low potency in animal experiments.

Almost all structural features which have been shown to be associated with the oxytocic activity of the ergot alkaloids are associated with ring D of the lysergic acid molecule (I, R=OH) (unsaturation in the C(9)–C(10)



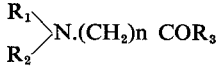
I

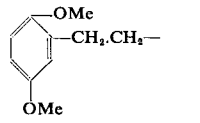
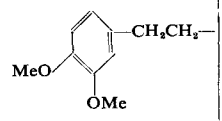
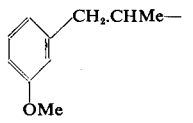
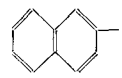
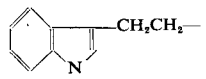
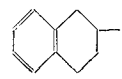
position, Rothlin and Cerletti, 1950, the configuration at C(5), and the nature and configuration of the substituent at C(8), Stoll and Hofmann, 1943). It is not surprising, therefore, that most synthetic oxytocics modelled on lysergic acid have included structures related to this ring or to its open-chain analogues.

Derivatives of ω-amino-acids (Table I) may be considered as open-chain analogues of ring D of lysergic acid. Direct comparison of their oxytocic activities is impossible because of the different methods of assessment used, but it appears that similarity in chemical structure to the ergot

TABLE I

DERIVATIVES OF ALIPHATIC ω-AMINO-ACIDS SHOWING OXYTOCIC ACTIVITY



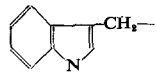
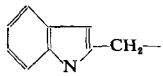
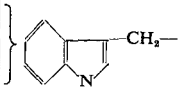
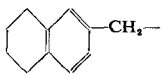
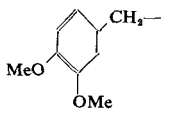
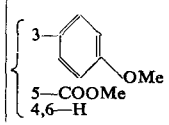
Cpd. No.	n	R_1	R_2	R_3	References	Oxytocic action on animals
II	2	Me		$NH{\cdot}CH_2CH_2OH$	Baltzly, Dvorkovitz and Phillips (1949)	Slight
				OEt		
III	2	Me		OEt		Greater than II
IV	3 to 6	Me			Baltzly and Phillips (1949)	Similar to III
V	2	Me		OEt	Plieninger (1953)	Greater in (−) isomer
VI	2	Me		OEt or NEt_2	Gearien and Liska (1954)	
VII	2	Me		OMe or NEt_2	Norris and Blicke (1952)	Slight
VIII	2	Me		$-NHCH(Me)CH_2OH$	Marini-Bettolo, Chiavarelli; and Bovet-Nitti (1951, 1952)	Comparable with Ergometrine
IX	2	Me	,,	NEt_2	Marini-Bettolo, Chiavarelli and Bovet (1950)	Similar to VIII
X	1	Me	,,	,,	Bovet-Nitti (1952)	Similar to VIII
XI	1	Et	Et	NEt_2	Bovet-Nitti (1952); Marini-Bettolo and Cavalla (1954)	

alkaloids does not tend to be associated with high activity, and Rosen and co-workers (1956) have reported the marked potency of simple glycine derivatives (XI) which bear only a remote resemblance to lysergic acid derivatives. Steric relationships between these compounds and lysergic acid were not generally considered by the authors, although the optical isomers of compound (V) were isolated and found to differ in their oxytocic action (Plieninger, 1953).

Amongst piperidine derivatives which have been prepared as potential oxytocics (Table II) the lack of apparent relation between structural similarity to lysergic acid and oxytocic acitivity is even more marked; *N*-(3-indolylmethyl)piperidine derivatives (XIV) are more active than 2-(3-indolylmethyl)piperidines (XII), and similar compounds with a carboxyl substituent corresponding to the essential C(8) carboxyl in lysergic acid are of negligible activity compared with the same compounds lacking such a carboxyl substituent (De Jongh and van Proosdij-Hartzema,

TABLE II

PIPERIDINE DERIVATIVES SHOWING OXYTOCIC ACTIVITY

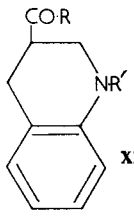
Cpd. No.	Substituent on N	Substituent at C_2	Other substituents	References	Oxytocic activity on animals
XII	Me		H	Akkerman and Veldstra (1954)	Active but less so than XIV and XV
XIII		Me	H	Hoffman and Schellenberg (1954)	
XIV		Me	4,6—Me 3,5—H	Akkerman, De Jongh and Veldstra (1951)	More active than XII, XIII and XV, but unstable
XV		Me	6—Me 3,4,5—H		More active than XII and XIII, less than XIV
XVI		H	H	Schindler and Voegtli (1949)	
XVII		H	H	Votava and Podvalava (1956)	High activity
XVIII	H	Me		Plieninger (1953)	Low activity

1952). On the other hand, compounds (XVI) and (XVII) with little resemblance to lysergic acid are quite powerful oxytocics.

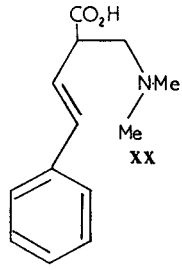
Substitution of a carboxyl group in the 3-position of 1,2,3,4-tetrahydroquinoline (XIX) yields compounds with some structural resemblance to rings C and D of lysergic acid and oxytocic activity has been demonstrated in a compound of this type (XIX; R=NHEt; R′=Me) (Cain, Plampin and Sam, 1955; Koelle and Kamijo, 1954).

Lack of any evident structure-action relation in oxytocics has made the choice of compounds for synthesis and testing necessarily an empirical one. A new approach may however be offered by recent detailed studies of the configuration at C(8) and the conformation of lysergic acid, iso-lysergic acid and their derivatives (Cookson, 1953; Stenlake, 1953;

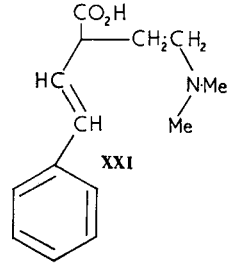
Stoll Petrzilka, Rutschmann, Hofmann and Günthard, 1954; Stenlake, 1955). Since isolysergic acid, with an axial carboxyl substituent at C(8) produces derivatives of negligible oxytocic activity compared with those of lysergic acid in which the carboxyl substituent is equatorial (Stoll and Hofmann, 1943), it appears that the spacial relation between the carboxyl group and neighbouring atoms is of importance in determining the activity of the ergot alkaloids. The synthesis of the model compounds of similar molecular shape described below seemed therefore to be worthy of investigation. Stereochemical considerations are discussed by Chilton and Stenlake (1962).



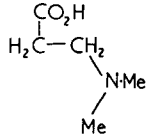
XIX



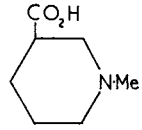
XX



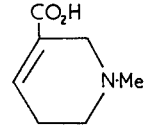
XXI



XXII



XXIII



XXIV

$$NMe_2CH_2CH_2CONH\cdot CH_2CH_2O\cdot CO\cdot CH_2CH_2NMe_2$$

XXV

$$NMe_2CH_2CH_2CO\cdot O\cdot CH_2CH_2NH_2$$

XXVI

$$NMe_2CH_2CH_2CONH\cdot CH_2CH_2OH$$

XXVII

Discussion

Styryl-substituted Aliphatic ω-Amino-acids

Formula XX indicates how 2-styryl-3-dimethylaminopropionic acid may be considered as an open-chain analogue of lysergic acid, the double bond of the styryl substituent corresponding to that in the C(9)–C(10) position of lysergic acid and the phenyl group to Ring A. The only related compounds reported in the literature had benzyl or naphthylmethyl substituents in the 2-position and were inactive as oxytocics (Norris and Blicke, 1952).

Unsuccessful attempts to prepare compound (XX) by a Mannich reaction of styrylacetic acid and its ethyl ester with formaldehyde and dimethylamine indicated that the activity of the 2-methylene group in

styrylacetic acid is not sufficient to permit such a reaction. Potentiation of this activity by the use of styrylmalonic acid in place of styrylacetic acid produced the required reaction with spontaneous decarboxylation. Unfortunately a marked tendency to deamination in aqueous solution, even at room temperature, led to poor recovery of the required product and prevented the preparation of further derivatives. Such deamination of 2-substituted dialkylaminopropionic acids is well known (Mannich and Ganz, 1922) and occurred with the benzyl and naphthylmethyl compounds mentioned previously, but only on prolonged heating above 100°.

The unexpectedly low stability of 2-styryl-3-dimethylaminopropionic acid led to the preparation of the homologous ethyl 2-styryl-4-dimethylaminobutyrate (XXI), since this would be expected to show less tendency to deaminate, while the oxytocic activity of related amino-acid derivatives had been shown to be largely unaffected by increase in the number of methylene groups separating the amino and carboxyl functions (Baltzly and Phillips, 1949). Preparation of this compound by condensation of the sodio derivative of ethyl styrylacetate with dimethylaminoethyl chloride gave a small yield of the required amino-ester, the major product being a dimer of ethyl styrylacetate. The amino-ester was unstable, darkening and resinifying even in a sealed container stored in the dark. Because of the apparent inherent instability of 2-styryl-ω-dialkylamino acids, further routes to these compounds were not explored.

Alkanolamides of Amino-acids

The ethanolamides and propanolamides of 3-dimethylaminopropionic acid (XXII), 1-methylhexahydronicotinic acid (XXIII) and 1-methyl-1,2,5,6-tetrahydronicotinic acid (arecaidine, XXIV) were prepared because of the structural relation between these acids and ring D of lysergic acid and hence between their propanolamides and the corresponding fragment of ergometrine. This relation was considered sufficient to make these compounds of potential value as oxytocics, especially since other amides of simple *N*-substituted 3-aminopropionic acid derivatives had been shown by Rosen and co-workers (1956) to have oxytocic activity. It has also been shown by Chilton and Stenlake (1962) that the propanolamides of (XXII) and (XXIV) and the ethanolamides of (XXII), (XXIII) and (XXIV) have their amino- and carboxyl groups in a steric configuration related to that of ergometrine and different from that of the pharmacologically-inert ergometrinine.

Preparation of these alkanolamides by aminolysis of esters, a standard method for the commercial synthesis of alkanolamides, was successful only for the previously known (Phillips and Baltzly, 1947) ethanolamide of 1-methylhexahydronicotinic acid. The methyl ester of 1-methyl-1,2,5,6-tetrahydronicotinic acid (arecoline) formed an addition compound on heating with ethanolamine, while ethyl 3-dimethylaminopropionate decomposed at the temperature required for reaction.

Synthesis of alkanolamides by reaction of acid chlorides and amino-alcohols does not appear to have been widely investigated, and published

work (Knorr and Rössler, 1903; Brinziger and Koddebusch, 1949) has been largely concerned with reactions of aromatic acid chlorides. We have found that the acid chloride of 3-dimethylaminopropionic acid in chloroform reacts with ethanolamine to produce almost exclusively the unwanted *O*,*N*-bis-(3′-dimethylaminopropionyl)-2-aminoethanol (XXV), with a small yield of 2-aminoethyl 3-dimethylaminopropionate (XXVI). Since *O*-acylation could not be suppressed by variation of the reaction conditions, whereas *N*-acylation was markedly reduced under acidic conditions, the *O*-acyl compound (XXVI) was prepared by reaction of the hydrochlorides and converted to the required 2-(3′-dimethylaminopropionamido)ethanol (XXVII) by alkali-induced acyl migration as described by Phillips and Baltzly (1947) and others. Preparation of (±)-2-aminopropyl 3-dimethylaminopropionate and 2-aminoethyl 1-methylhexahydronicotinate in chloroform by this method resulted in poor yields; reaction of the acid chloride hydrochloride of arecaidine with ethanolamine hydrochloride in chloroform gave no crystalline product.

The difference in behaviour between 3-dimethylaminopropionyl chloride hydrochloride and 1-methylhexahydronicotinyl chloride hydrochloride on reaction with ethanolamine hydrochloride was considered to be due to their differing solubilities in the chloroform used as solvent, since the reactivities of the two compounds would otherwise be expected to be of the same order. No suitably inert solvent was found for 1-methylhexahydronicotinyl chloride hydrochloride and reaction was accordingly carried out in the absence of solvent. A mixture of the acid chloride hydrochloride and ethanolamine hydrochloride in fine powder formed a eutectic system melting at about 120° and reacting immediately to form almost exclusively the required 2-aminoethyl 1-methylhexahydronicotinate dihydrochloride, which was readily converted to the corresponding alkanolamide by treatment with aqueous alkali as before.

Analogous reactions of 1-methyl-1,2,5,6-tetrahydronicotinyl chloride hydrochloride with ethanolamine hydrochloride and (±)-2-aminopropanol hydrochloride in the absence of solvent gave good yields of the amino-ester dihydrochlorides. Treatment of the latter with aqueous alkali induced complete $O \rightarrow N$ acyl migration as evidenced by a fall in the potentiometric titre of precisely 50 per cent and a change in the neutralisation curve from that of a diacidic base to that of a monoacidic base. The resultant alkanolamides were however, exceedingly water-soluble, rendering extraction wasteful and tedious, while the isolated compounds were syrupy, very hygroscopic compounds which yielded no crystalline derivatives suitable for characterisation. These alkanolamides were accordingly used in the solution in which they were prepared, excess alkali being neutralised by hydrochloric acid.

1-Methylhexahydronicotinyl chloride hydrochloride and (±)-2-aminopropanol hydrochloride reacted in the absence of solvent with evolution of hydrogen chloride but failed to yield any crystallisable product. Similar failure to obtain a crystalline product on catalytic reduction of (±)-2-aminopropyl 1,2,5,6-tetrahydronicotinate dihydrochloride indicated that the required product may well have been formed

from the acid chloride reaction but is probably inherently non-crystallisable. No other crystallisable derivatives of this amino-ester could be found, and treatment with aqueous alkali gave a gummy hygroscopic product which again failed to form any crystalline derivatives.

The acid chloride hydrochloride of 3-dimethylaminopropionic acid decomposed below the melting point of any mixture of it with ethanolamine or (±)-2-aminopropanol hydrochloride, preventing reaction in the absence of solvent. It was found that the alkanolamides of this acid could be prepared in good yield by reaction of 3-dimethylaminopropionyl chloride with the ethyl esters of glycine and (±)-alanine to form peptide esters, which could be selectively reduced by careful treatment with lithium aluminium hydride to produce the required alkanolamides in satisfactory yield. Similar reductions of ester groups in the presence of amides have been previously described (Felkin, 1950; Berlinguet, 1954). This method offered no advantage for preparation of the ethanolamide but was the best available route to the propanolamide. It would appear to offer a suitable method for the preparation of optically-active alkanolamides, since active amino-acids are available and the mild conditions of reaction should not induce racemisation.

Attempts to prepare the acid azide of arecaidine as an intermediate in the synthesis of alkanolamides as described by Stoll and Hofmann (1943) were not successful.

Pharmacological Action

Pharmacological investigation of the alkanolamides described in this section (for which the authors are indebted to Dr. S. Nanjappa of the Department of Experimental Pharmacology, University of Glasgow) showed that none of these compounds had demonstrable oxytocic activity on the isolated oestrous rat uterus in concentrations up to 1 mg./ml.

The propanolamide of arecaidine inhibited acetylcholine-induced contractions of the oestrous rat uterus in concentrations of 0·075–0·3 mg./ml., an effect also shown by higher concentrations of the propanolamide of dimethylaminopropionic acid (0·3–1·0 mg./ml.) and by the ethanolamides of *N*-methylhexahydronicotinic acid (1 mg./ml.) and 3-dimethylaminopropionic acid (0·7–1 mg./ml.). Whilst these results on the rat do not entirely rule out the possibility of activity in higher animals, it seems unlikely that compounds showing such a low level of activity in animal experiments would prove useful in humans.

No effect on cat blood-pressure was shown by any of the compounds in doses up to 5 mg./kg., nor did they have any inhibitory effect on the action of adrenaline or noradrenaline on cat blood-pressure.

The lack of oxytocic action shown by these alkanolamides reflects the findings of earlier workers who reported that the alkanolamides of derivatives of ω-amino-aliphatic acids, piperidine-carboxylic acids and tetrahydroquinoline were either inert as oxytocics or else showed much less activity than did corresponding esters or simple alkylamides. Amongst purely synthetic compounds, only the propanolamide of *N*-tetrahydronaphthyl-*N*-methyl-3-aminopropionic acid (VIII) is reported to have

marked oxytocic activity ("comparable with ergometrine on the isolated uterus of the guinea pig and rabbit").

It does not seem possible in the light of present evidence to speculate on the nature of the contribution made by the carboxylamido group to the oxytocic activity of the ergot alkaloids and semi-synthetic lysergic acid amides, but it appears that the alkanolamido group is specific in potentiating oxytocic action in only a very small range of compounds.

Experimental

3-Dimethylamino-2-styrylpropionic acid. Styrylmalonic acid (1·03 g., 0·05 mole), prepared by the method of Ivanov and Pschenichnii (1937), was dissolved in 60 per cent aqueous solution of dimethylamine (0·38 ml.) and treated with 40 per cent solution of formaldehyde (0·4 ml.) at 0°. There was an immediate transient effervescence. The mixture was left overnight at 0°, acidified with dilute hydrochloric acid, and the amorphous solid which separated was extracted with ether. Evaporation of the ethereal extract *in vacuo* yielded a solid (0·49 g.) which could not be crystallised, but which gave a crystalline derivative with *p*-bromophenacyl bromide, m.p. 142° (from ethanol), probably *p*-bromophenacyl-2-styrylacrylate. Found: C, 60·5; H, 4·0; Br, 20·8. $C_{19}H_{15}BrO_3$ requires C, 61·4; H, 4·0; Br, 21·3 per cent.

The aqueous fraction remaining after extraction of the acid was treated with a slight excess of sodium bicarbonate and extracted with ether to remove any unchanged dimethylamine, then a slight excess of sodium picrate solution was added. On the addition of a few drops of dilute hydrochloric acid, crystals (23 mg., 0·9 per cent), m.p. 146° (from ethanol) of the *picrate* of *3-dimethylamino-2-styrylpropionic acid* were obtained. Found: C, 51·5; H, 4·5; N, 12·3. $C_{19}H_{20}N_4O_9$ requires C, 50·9; H, 4·5; N, 12·5 per cent.

4-Dimethylamino-2-styrylbutyric acid. Sodium (0·575 g., 0·025 mole) was dissolved in dry ethanol (20 ml.) and ethyl styrylacetate (4·75 g., 0·025 mole) added with stirring and cooling. After 60 hr. at room temperature, the mixture was treated with a solution of dimethylaminoethyl chloride (obtained from dimethylaminoethyl chloride hydrochloride, 3·58 g., 0·025 mole) in xylene (7 ml.) added dropwise with continuous stirring. On heating under reflux for 2 hr. a white precipitate was obtained. The mixture was cooled, acidified with dilute hydrochloric acid, extracted with ether and the ethereal extract reserved. The aqueous fraction was basified with solution of ammonia and again extracted with ether. The ether extract was dried (Na_2SO_4), evaporated *in vacuo* and the oily residue fractionally distilled *in vacuo* to yield a colourless viscous oil (0·92 g., 14 per cent), b.p. 100–110°/0·4 mm., $n_D^{18°}$, 1·515, probably ethyl 4-dimethylamino-2-styrylbutyrate. Equiv. (potentiometric titration) 258. $C_{16}H_{23}NO_2$ requires equiv. 261. The product resinified and darkened rapidly on storage in a sealed vessel in the dark. The picrate of this base was initially oily, but slowly formed crystals, m.p. 106° (from aqueous ethanol) of the *picrate* of *4-dimethylamino-2-styrylbutyric acid.* Found:

C, 51·4; H, 4·7; N, 12·2. $C_{20}H_{22}N_4O_9$ requires C, 51·95; H, 4·8; N, 12·1 per cent.

The reaction was repeated, heating the sodium ethoxide and ethyl styrylacetate under reflux for 2 hr. initially. The non-basic ether-soluble fraction was again reserved. The yield of base, identical with that from the previous reaction was 0·88 g. (13 per cent).

The non-basic ethereal fractions from the previous reactions were combined and fractionally distilled *in vacuo* to yield ethyl styrylacetate, and a very viscous yellow liquid, b.p. 206–208°/0·8 mm. The latter was hydrolysed by heating under reflux for 30 min. with ethanolic potassium hydroxide. Removal of the alcohol by evaporation *in vacuo*, acidification with hydrochloric acid, and extraction with ether produced an acid, m.p. 153° (from benzene and light petroleum), probably a dimer of styrylacetic acid. Found: C, 74·2; H, 6·6; equiv. (potentiometric titration) 164; m.w. (freezing-point depression of camphor) ca. 294. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2 per cent; equiv. 162; m.w. 324). Styrylacetic acid has m.p. 54°.

Ethyl styrylacetate (4·75 g., 0·025 mole) was added to "molecular" sodium (0·575 g., 0·025 mole) suspended in xylene (30 ml.). No reaction was evident in the cold; on warming, a red resin was formed without evolution of hydrogen.

Reaction of ethyl 3-dimethylaminopropionate and ethanolamine. (*a*) Equal volumes of ethyl 3-dimethylaminopropionate prepared by the method of Adamson (1949) (14·5 g., 0·1 mole) and ethanolamine were heated together in a still fitted with a short fractionating column so that the fraction distilling below 90° was continually removed. The distillate (6·12 g.) gave a positive iodoform reaction (theoretical yield of ethanol, 4·6 g.) and on addition of ethanolic solution of picric acid gave crystals of dimethylamine picrate, m.p. 150° undepressed on mixture with authentic dimethylamine picrate.

The residue in the still fractionally distilled at 1 mm. gave a fore-run of ethanolamine and a few drops of oily liquid distilling at 140–190°. The residue was brown and resinous and could not be distilled. Neither it nor the distillate formed crystalline hydrochlorides, picrates or oxalates.

(*b*) A repeat reaction in which the ester and ethanolamine were heated together at 100° for 4 hr. yielded only unchanged starting material.

2-Aminoethyl 3'-dimethylaminopropionate dihydrochloride. (*a*) A suspension of 3-dimethylaminopropionic acid hydrochloride (6·12 g., 0·04 mole) in thionyl chloride (20 ml.) was heated in a water bath at 65° until effervescence ceased and the mixture became clear. Heating above this temperature caused resinification. Excess thionyl chloride was removed by evaporation *in vacuo* and the white crystalline residue washed with light petroleum and again dried *in vacuo*. The acid chloride hydrochloride so obtained was suspended in dry chloroform (20 ml.) and ethanolamine (2·44 g., 0·04 mole) in dry chloroform (10 ml.) added in one quantity at room temperature with stirring. After standing overnight at room temperature, the chloroform was removed by evaporation *in vacuo* and the syrupy residue dried *in vacuo* over potassium hydroxide.

Ethanol (30 ml.) was added and set aside overnight at 0°. The crystalline residue was filtered off and recrystallised from aqueous ethanol to give 2-aminoethyl 3′-dimethylaminopropionate dihydrochloride (1·1 g., 12 per cent) m.p. 181°. Found: C, 35·9; H, 7·7; Cl, 30·6; N, 12·0. $C_7H_{18}Cl_2N_2O_2$ requires C, 36·0; H, 7·7; Cl, 30·5; N, 12·0 per cent.

The ethanolic mother-liquors left after removal of the amino-ester dihydrochloride were concentrated *in vacuo* and treated with dry ether to yield a deliquescent hydrochloride m.p. 154° (4·1 g. 50 per cent) which on the addition of sodium picrate solution formed the dipicrate of O,N-*bis*-(3-*dimethylaminopropionyl*)*ethanolamine*. Found C, 41·05; H, 4·5; N, 17·3. $C_{24}H_{31}N_9O_{17}$ requires C, 40·2; H, 4·3; N, 17·6 per cent.

(*b*) A suspension of 3-dimethylaminopropionyl chloride hydrochloride (0·05 mole) in dry chloroform (30 ml.) was treated with ethanolamine hydrochloride (4·85 g., 0·05 mole) which had been finely powdered by levigation under dry light-petroleum. No immediate reaction was evident, but, on heating under reflux, hydrogen chloride was evolved and the amount of insoluble matter increased. After 2 hr., evolution of hydrogen chloride ceased, the mixture was allowed to cool and the chloroform removed by evaporation *in vacuo*. The residue was dissolved in a minimum quantity of boiling ethanol, filtered and allowed to cool, yielding 2-aminoethyl 3′-dimethylaminopropionate dihydrochloride (7·5 g.) m.p. 181°, identical with that obtained previously. Evaporation of the mother liquors yielded a further 1·0 g. of product (total yield 8·5 g.; 73 per cent).

2-(3′-*Dimethylaminopropionamido*)*ethanol*. 2-Aminoethyl 3′-dimethylaminopropionate dihydrochloride (7·5 g., 0·033 mole) in a minimum volume of water was treated under cooling with a slight excess of potassium hydroxide in a minimum of water and extracted with chloroform (3 × 30 ml.). The combined chloroform extracts were dried ($MgSO_4$) and the chloroform removed by evaporation *in vacuo* to leave an oil (3·0 g., 57 per cent) $n_D^{18°}$, 1·477 probably slightly impure 2-(3′-dimethylaminopropionamido)ethanol. Found equiv. (potentiometric) 164, 165, $C_7H_{16}N_2O_2$ requires equiv. 160.

Short-path distillation of the oil at 0·8 mm. yielded a colourless oily distillate b.p. 155–160°. Some loss of vacuum occurred during heating and the small residue of volatile base recovered from the solid carbon dioxide-acetone cooled vapour trap, gave a picrate m.p. 150° undepressed on mixture with authentic dimethylamine picrate.

A portion of the distillate fraction (b.p. 155–160°, $n_D^{18°}$, 1·489, equiv. 193) was mixed with excess dimethylamine and left at room temperature for 48 hr. Excess dimethylamine was removed at 100° *in vacuo* to yield a residue of equiv. 166. Equimolecular proportions of the base (equiv. 166) and oxalic acid were separately dissolved in minimum amounts of ethanol and mixed. Ethanol was removed by distillation *in vacuo* and the resultant syrup treated with boiling acetone to give, on cooling, crystals m.p. 85° (from acetone) of 2-(3′-*dimethylaminopropionamido*)-*ethanol acid oxalate*. Found: C, 43·1; H, 7·4; N, 11·0. $C_9H_{18}N_2O_6$ requires C, 43·2; H, 7·2; N, 11·2 per cent.

The succinate, prepared as described for the oxalate, using 2 moles of base to each mole of succinic acid consisted of hygroscopic crystals, m.p. 108° (from acetone). Found: C, 49·5; H, 8·8; N, 12·9. $C_{18}H_{38}N_4O_8$ requires C, 49·3; H, 8·7; N, 12·8 per cent.

Attempts to prepare crystalline picrates, picrolonates, hydrochlorides and naphthylisocyanates of the base were unsuccessful.

Ethyl 2-(3′-*dimethylaminopropionamido*)*acetate.* A suspension of 3-dimethylaminopropionyl chloride hydrochloride (0·05 mole) in dry chloroform (30 ml.) was treated with a solution of ethyl aminoacetate (5·15 g., 0·05 mole) in chloroform (20 ml.) added in one quantity. The mixture was heated under reflux until no further hydrogen chloride was evolved (about 2 hr.) and the chloroform removed by evaporation *in vacuo* to leave a gummy solid (9·8 g., 82 per cent) which crystallised on kneading under dry ether. Recrystallisation from ethanol/ether gave highly deliquescent crystals m.p. 124° probably slightly impure ethyl 2-(3′-dimethylaminopropionamido)acetate hydrochloride. Found: Cl, 16·11. $C_9H_{19}ClN_2O_3$ requires Cl, 14·9 per cent. Repeated recrystallisation did not improve the analysis.

The hydrochloride was suspended in dry ether (30 ml.) and dry ammonia passed through it for 10 min. with continual stirring. The product was filtered, the solid re-suspended in ether and the process repeated. After a third repetition the ethereal fractions were combined and the ether removed by evaporation *in vacuo.* The oily residue was left overnight in a desiccator at 0·5 mm. pressure in the presence of potassium hydroxide and paraffin wax to yield *ethyl* 2-(3′-*dimethylaminopropionamido*)*acetate,* $n_D^{18°}$, 1·4621. Found: C, 53·6; H, 8·6; N, 13·6. $C_9H_{18}N_2O_3$ requires C, 53·5; H, 8·9; N, 13·9 per cent.

2-(3′-*Aminopropionamido*)*ethanol by reduction of ethyl* 2-(3′-*amino-propionamido*)*acetate.* Ethyl 2-(3′-dimethylaminopropionamido)acetate (3 g., 0·0015 mole) was dissolved in dry ether (30 ml.) and treated with lithium aluminium hydride (0·68 g., 0·002 mole) added in small portions with continuous stirring and ice-cooling. The mixture was allowed to attain room-temperature with continuing constant stirring, the excess of lithium aluminium hydride was decomposed by the addition of moist ether followed by ice, and the product was filtered. The solid residue, on extraction with chloroform and evaporation of the extract *in vacuo,* yielded an oily base (1·1 g., 46 per cent) which formed an oxalate identical with the acid oxalate of 2-(3′-dimethylaminopropionamido)ethanol obtained previously.

(±)-2-*Aminopropyl* 3′-*dimethylaminopropionate dihydrochloride.* Finely powdered (±)-2-aminopropanol hydrochloride (0·76 g., 0·02 mole) prepared by the method of Vogl and Pöhm was added in one quantity to a suspension of 3-dimethylaminopropionyl chloride hydrochloride (0·005 mole) in dry chloroform and heated under reflux until no more hydrogen chloride was evolved (about 45 min.). The chloroform was removed by evaporation *in vacuo* and the solid residue recrystallised from aqueous ethanol to yield (±)-2-*aminopropyl* 3′-*dimethylaminopropionate dihydrochloride* (0·47 g.) m.p. 189°. Found: C, 38·6; H, 7·8; N, 11·4.

$C_8H_{20}Cl_2N_2O_2$ requires C, 38·9; H, 8·1; N, 11·3 per cent. Concentration of mother liquors yielded a further 0·11 g. of product (total yield 0·58 g. 46 per cent). The residual fraction in the mother liquors (0·49 g.) could not be crystallised and did not give a crystallisable picrate on treatment with sodium picrate solution.

Numerous repetitions of the reaction gave yields varying from 5 to 46 per cent. Increase in scale generally diminished the percentage yield.

(±)-2-(3′-*Dimethylaminopropionamido)propanol.* The method was identical with that described for 2-(3′-dimethylaminopropionamido)ethanol. An oily base was obtained which formed on treatment with oxalic acid the *acid oxalate* of (±)-2-(3′-*dimethylaminopropionamido*)-*propanol*, m.p. 114° (from acetone/ethanol). Found: C, 45·8; H, 7·9; N, 10·5. $C_{10}H_{20}N_2O_6$ requires C, 45·5; H, 7·6; N, 10·6 per cent. The succinate was crystalline but excessively deliquescent.

(±)-*Ethyl* 2-(3′-*dimethylaminopropionamido)propionate.* 3-Dimethylaminopropionyl chloride hydrochloride (0·05 mole) was treated with (±)-ethyl 2-aminopropionate to yield an extremely deliquescent hydrochloride, m.p. 96° (from ethanol/ether). Found: Cl, 14·3. $C_{10}H_{21}ClN_2O_3$ requires Cl, 14·1 per cent. Treatment of a suspension of this hydrochloride in dry ether with excess dry ammonia as described previously gave (±)-*ethyl* 2-(3′-*dimethylaminopropionamido)propionate* as a colourless oil, $n_D^{18°}$, 1·4558 (8·78 g., 81 per cent). Found: C, 55·7; H, 9·3; N, 12·9. $C_{10}H_{20}N_2O_3$ requires C, 55·6; H, 9·3; N, 13·0 per cent.

(±)-2-(3′-*dimethylaminopropionamido)propanol by lithium aluminium hydride reduction of ethyl* (±)-2-(3′-*dimethylaminopropionamido)propionate.* The total product from the previous reaction was reduced as described for the corresponding acetate. Excess lithium aluminium hydride was decomposed by the cautious addition of ice and the product filtered. The solid residue was extracted twice with 50 ml. portions of boiling ethanol, which were combined and evaporated *in vacuo* to a syrupy residue. This was extracted with 25 ml. of boiling ethanol, and the extract was treated with ether to form an opalescent solution. After filtration, this was again evaporated *in vacuo* to yield 4·95 g. (70 per cent) of a viscous oil. Oxalic acid (4 g.) was added as an ethanolic solution and the resulting precipitate, consisting mostly of inorganic salts of oxalic acid, was removed by filtration. The filtrate on evaporation to dryness and extraction with boiling acetone gave crystals, m.p. 114° identical with those of the acid oxalate of (±)-2-(3′-dimethylaminopropionamido)propanol obtained previously.

2-(1′-*Methylhexahydronicotinamido)ethanol acid oxalate.* The method of Phillips and Baltzly (1947) was modified as follows: a solution of 1-methylhexahydronicotinic acid hydrochloride, prepared by the method of Preobrazhenskii and Fisher (1941), (3 g., 0·0166 mole) in dry ethanol (30 ml.) was saturated with hydrogen chloride then heated under reflux for 1 hr. The mixture was evaporated *in vacuo* to a syrup which was treated with a slight excess of 20 per cent aqueous sodium hydroxide and at once extracted with chloroform. The chloroform extract was dried (Na_2CO_3) and the chloroform removed by evaporation *in vacuo* to yield

ethyl 1-methylhexahydronicotinate (2·2 g.). The base was mixed with excess ethanolamine (2 ml.) and heated to 180° in a distillation flask fitted with a short fractionating column. Ethanol, b.p. 78° was evolved for about 20 min., after which no distillate boiling below 160° could be obtained and heating was stopped. Excess ethanolamine was removed by evaporation *in vacuo*, the viscous oil (2·1 g.) dissolved in a little ethanol, mixed with a slight excess of ethanolic oxalic acid, then evaporated to a syrup *in vacuo*. On extraction with boiling acetone and cooling, 2-(1′-*methylhexahydronicotinamido)ethanol acid oxalate* (1·8 g., 46 per cent), m.p. 124° (from acetone) was obtained. Found: C, 48·8; H, 7·4; N, 10·0. $C_{11}H_{20}N_2O_6$ requires C, 47·8; H, 7·25; N, 10·15 per cent.

Treatment of the product of this reaction with a large excess of ethanolic hydrogen chloride gave crystals of 2-aminoethyl 1′-methylhexahydronicotinate dihydrochloride, m.p. 216° (from ethanol). Phillips and Baltzly (1947) gave m.p. 214°.

2-*Aminoethyl* 1′-*methylhexahydronicotinate dihydrochloride.* (*a*) A suspension of 1-methylhexahydronicotinic acid hydrochloride (4·49 g., 0·025 mole) in thionyl chloride (25 ml.) was heated under reflux for 15–20 min. until evolution of hydrogen chloride ceased and the mixture became homogeneous. Excess thionyl chloride was removed by evaporation *in vacuo* and the crystalline residue washed with dry light petroleum until the washings were colourless. Light petroleum was removed by decantation followed by drying *in vacuo* and the product suspended in dry chloroform (60 ml.). Finely powdered ethanolamine hydrochloride (2·85 g., 0·03 mole) was added, and the mixture heated under reflux until hydrogen chloride ceased to be evolved (5–6 hr.). The chloroform was evaporated *in vacuo* and the residue dissolved in a minimum volume of boiling ethanol. On cooling, 2-aminoethyl 1′-methylhexahydronicotinate dihydrochloride (315 mg., 5 per cent), m.p. 216° (from ethanol) was obtained.

Evaporation of the alcoholic mother liquors gave 4·1 g. of an uncrystallisable residue which was almost completely soluble in chloroform. The small portion of chloroform-insoluble material was identical with the aminoester dihydrochloride m.p. 216° obtained initially. The chloroform-soluble portion could still not be crystallised, but yielded on treatment with sodium picrate, *O,N-bis-*(1′-*methylhexahydronicotinyl*)-2-*aminoethanol dipicrate* m.p. 227° (decomp.) (from aqueous ethanol). Found: C, 43·4; H, 4·4; N, 16·5. $C_{28}H_{35}N_9O_{17}$ requires C, 43·7; H, 4·6; N, 16·4 per cent.

(*b*) The previous preparation was repeated, replacing the dry chloroform by dry tetrahydrofuran. The yield of amino-ester dihydrochloride was as before.

(*c*) The acid chloride hydrochloride was prepared as before from 1-methylhexahydronicotinic acid hydrochloride (0·18 g., 0·001 mole). The washed and dried product was then mixed intimately with dry and finely powdered ethanolamine hydrochloride (0·12 g., 0·0012 mole) and heated slowly on an oil bath. The mixture melted at a bath temperature of about 120° and evolved hydrogen chloride, whereupon heating was continued at 120–140° until no more gas was evolved (about 20 min.). It was then allowed to cool and dissolved in a minimum quantity of boiling

ethanol, which on cooling yielded 177 mg. (68 per cent) of crystals m.p. 216° (from ethanol) identical with the 2-aminoethyl 1′-methylhexahydronicotinate dihydrochloride obtained previously.

Reaction of methyl 1-*methyl*-1,2,5,6-*tetrahydronicotinate and ethanolamine.* Methyl 1-methyl-1,2,5,6-tetrahydronicotinate hydrobromide (Arecoline Hydrobromide B.P.C., 1·18 g., 0·005 mole) in water (0·8 ml.) was treated with potassium hydroxide (0·4 g.) in water (0·5 ml.) and the mixture extracted with three successive portions of chloroform (20 ml.) which were combined, dried (Na_2CO_3), and evaporated to a syrup *in vacuo*. An equal volume of ethanolamine was added and the mixture heated as described for the previous two reactions to yield a viscous oil (0·774 g.) on evaporation of excess ethanolamine. Treatment with excess ethanolic oxalic acid gave a gummy residue which crystallised from aqueous methanol, m.p. 205–206° (decomp.). Found: C, 49·0; H, 7·6; N, 11·0, 11·3 per cent. This is not in agreement with the required values for 2′-(1-methyl-1,2,5,6-tetrahydronicotinamido)ethanol acid oxalate ($C_{11}H_{18}N_2O_6$ requires C, 48·2; H, 6·6; N, 10·2).

The product may have been *NN*-bis-4-(1-methyl-3-(2′-hydroxyethyl)-carbonamidopiperidyl)ethanolamine dioxalate ($C_{24}H_{43}N_5O_{13}$ requires C, 47·3; H, 7·1; N, 11·5) since a sample of hydrochloride (prepared by treatment of an aqueous solution of the oxalate with an equivalent amount of calcium chloride solution and filtering) showed no absorption maximum between 200 and 250 mμ, compared with arecoline hydrobromide which had E (1 per cent, 1 cm.) = 563 at 205 mμ.

2′-*Aminoethyl* 1-*methyl*-1,2,5,6-*tetrahydronicotinate dihydrochloride.* The acid chloride hydrochloride was prepared from 1-methyl-1,2,5,6-tetrahydronicotinic acid hydrochloride (0·89 g., 0·005 mole) as described for the corresponding hexahydronicotinic acid derivative and mixed intimately with finely powdered ethanolamine hydrochloride (1 g.) by trituration under light petroleum. The solvent was removed by decantation, the solid residue dried *in vacuo* and heated on an oil bath. Frothing and evolution of hydrogen chloride occurred at about 140°, whereupon the temperature was raised slowly to 180° and maintained at that temperature until no further reaction was visible (about 20 min.). After cooling, the product was dissolved in a minimum volume of boiling ethanol which yielded on cooling 0·84 g. (65 per cent) of brownish platelets. Recrystallisation from ethanol (charcoal) gave 2′-*aminoethyl* 1-*methyl*-1,2,5,6-*tetrahydronicotinate dihydrochloride* m.p. 258° (decomp.). Found: C, 41·8; H, 6·9; Cl, 27·1; N, 10·7. $C_9H_{18}Cl_2N_2O_2$ requires C, 42·0; H, 7·0; Cl, 27·6; N, 10·9 per cent.

2′-(1-*Methyl*-1,2,5,6-*tetrahydronicotinamido*)*ethanol.* (*a*) A saturated aqueous solution of 2′-aminoethyl 1-methyl-1,2,5,6-tetrahydronicotinate dihydrochloride (1·28 g., 0·005 mole) was treated with a slight excess of 40 per cent aqueous potassium hydroxide and extracted with three portions of chloroform (30 ml.). The combined chloroform extracts were dried (Na_2SO_4) and evaporated *in vacuo* to a very viscous syrup. Treatment with a slight excess of ethanolic oxalic acid gave a product (1·02 g.) m.p. 92° (from aqueous ethanol). Recrystallisation from methanol and

acetone gave a product m.p. 158° (decomp.) but in poor yield. This material on further recrystallisation from aqueous acetone had m.p. 92°, undepressed on mixture with the original product. Found for oxalate: m.p. 92°; C, 40·6; H, 7·7; N, 8·8. $C_{11}H_{18}N_2O_6 3H_2O$ requires C, 40·2; H, 7·3; N, 8·5 per cent.

An aqueous solution of the oxalate, treated with a slight excess of calcium chloride, filtered and titrated potentiometrically showed a neutralisation curve typical for the dihydrochloride of a diacid base. The oxalate was therefore *2-aminoethyl 1-methyl-*1,2,5,6-*tetrahydronicotinate oxalate.*

(*b*) 2′-Aminoethyl 1-methyl-1,2,5,6-tetrahydronicotinate dihydrochloride (25·7 mg., 0·1 millimole) was dissolved in electrolyte-free water (10 ml.) and an aliquot portion (2 ml., 0·02 millimole) titrated potentiometrically with carbonate-free potassium hydroxide solution. The volume required for complete neutralisation was 1·10 ml. and the titration curve was characteristic of a diacidic base. The remainder of the solution was adjusted to a pH value of 13 by the addition of solution of potassium hydroxide and allowed to stand overnight. It was then brought to pH 3 by the addition of hydrochloric acid, made up to 10 ml. with electrolyte-free water, and a further aliquot portion (2·5 ml., 0·02 millimole) was again titrated under identical conditions. The volume required for complete neutralisation was now 0·512 ml. and the neutralisation curve was typical of that for a monoacidic base as shown by comparison of the pH values at $\frac{1}{2}$, $\frac{2}{3}$ and $\frac{1}{3}$ neutrality. This indicated that O → N acyl-migration had occurred and that the solution contained the required 2′-(1-*methyl-*1,2,5,6-*tetrahydronicotinamido)ethanol.* Attempts to prepare a crystalline oxalate of this base were unsuccessful, as were attempts to prepare crystalline succinates, tartrates and phthalates.

(±)-2′-*Aminopropyl 1-methyl-*1,2,5,6-*tetrahydronicotinate dihydrochloride.* Using the method described for 2′-aminoethyl 1-methyl-1,2,5,6-tetrahydronicotinate, 1-methyl-1,2,5,6-tetrahydronicotinic acid hydrochloride (890 mg., 0·005 mole) and (±)-2-aminopropanol hydrochloride (1 g.) gave a crystalline product (825 mg. 61 per cent) which was recrystallised from ethanol (charcoal) to yield (±)-2′-*aminopropyl* 1-*methyl-*1,2,5,6-*tetrahydronicotinate dihydrochloride,* m.p. 215° (decomp.). Found: C, 43·9; H, 7·4; Cl, 25·4; N, 10·0. $C_9H_{18}Cl_2O_2$ requires C, 44·3; H, 7·4; Cl, 26·2; N, 10·3 per cent.

(±)-2′-(1-*Methyl-*1,2,5,6-*tetrahydronicotinamido)propanol.* (±)-2-Aminopropyl 1-methyl-1,2,5,6-tetrahydronicotinate dihydrochloride was treated with alkali as described for corresponding aminoethyl ester. The product was a hygroscopic, amorphous semi-solid which failed to form a crystallisable oxalate, succinate, picrate, tartrate or phthalate.

A solution of the dihydrochloride (27 mg., 0·1 millimole) in water (10 ml.) was then treated with aqueous alkali as described for the aminoethyl ester. A portion equivalent to 0·02 millimole had an initial titre of 0·809 ml. of potassium hydroxide solution and a titration curve typical of that for a diacidic base. After treatment with alkali and neutralisation the titre was 0·404 ml. and the curve characteristic of a monoacidic base,

indicating that the solution contained (±)-2′-(1-*methyl*-1,2,5,6-*tetrahydronicotinamido*)*propanol.*

Attempted preparation of (±)-2′-*aminopropyl*-1-*methylhexahydronicotinate hydrochloride.* (*a*) The acid chloride hydrochloride, prepared from 1-methylhexahydronicotinic acid hydrochloride (0·18 g., 0·001 mole), was heated with (±)-2-aminopropanol hydrochloride (0·14 g., 0·0012 mole) in the absence of solvent as described previously. Reaction occurred with evolution of hydrogen chloride, but the product was very hygroscopic and could not be crystallised.

(*b*) (±)-2′-Aminopropyl 1-methyl-1,2,5,6-tetrahydronicotinate dihydrochloride (0·27 g., 0·001 mole), was dissolved in water (5 ml.) and hydrogenated at atmospheric pressure in the presence of a platinum oxide catalyst. Reduction was complete in 4 hr. The product, on evaporation to dryness *in vacuo* was again amorphous, hygroscopic and could not be crystallised. The non-crystalline residue was treated with aqueous alkali, extracted with chloroform, the chloroform extract evaporated to dryness *in vacuo* and the residue treated with a slight excess of ethanolic solution of oxalic acid. The resultant oxalate could not be crystallised, nor could any other crystalline derivatives be prepared.

References

Adamson, D. W. (1949). *J. Chem. Soc., Supp. Issue No.* 1, S 144–155.
Akkerman, A. M. and Veldstra, H. (1954). *Rec. Trav. chim. Pays-bas*, **73**, 629–648.
Akkerman, A. M., de Jongh, D. K. and Veldstra, H. (1951). *Ibid.*, **70**, 899–916.
Baltzly, R., Dvorkovitz, V. and Phillips, A. P. (1949). *J. Amer. chem. Soc.*, **71**, 1162–1164.
Baltzly, R. and Phillips, A. P. (1949). *Ibid.*, **71**, 3421–3422.
Berlinguet, L. (1954). *Can. J. Chem.*, **32**, 31–39.
Bovet-Nitti, F. (1952). *R.C. Ist. Sup. Sanit.*, **15**, 989–1007.
Brinzinger, H. and Koddebusch, H. (1949). *Ber. dtsch. chem. Ges.*, **82**, 201–203.
Cain, C. K., Plampin, J. N. and Sam, J. (1955). *J. org. Chem.*, **20**, 466–474.
Chilton, J. and Stenlake, J. B. (1962). *J. Pharm. Pharmacol.*, **14**, 367–370.
Cookson, R. C. (1953). *Chem. and Ind. (Rev.)*, 337–340.
Felkin, H. (1950), *C.R. Acad. Sci. Paris*, **230**, 304–306.
Garrett, W. J. and Embrey, M. P. (1958). *J. Pharm. Pharmacol.*, **10**, 325–327.
Gearien, J. E. and Liska, K. J. (1954). *J. Amer. chem. Soc.*, **76**, 3554–3555.
Hoffmann, K. and Schellenberg, H. (1944). *Helv. chim. Acta*, **27**, 1782–1790.
Ivanov, D. and Pshenichniĭ, G. (1937). *Ann. Univ. Sofia II. Faculté phys.-math. Livre* 2, **33**, 213–217; through *Chem. Abstr.* (1938), **32**, 3358.
de Jongh, D. K. (1956), *Arch. exp. Path. Pharmak.*, **228**, 106–123.
de Jongh, D. K. and van Proosdij-Hartzema, E. G. (1952). *J. Pharmacol.*, **105**, 130–138.
Knorr, L. and Rössler, P. (1903). *Ber. dtsch. chem. Ges.*, **36**, 1278–1283.
Koelle, G. B. and Kamijo, K. (1954). *J. Pharmacol.*, **112**, 444–461.
Mannich, C. and Ganz, E. (1922). *Ber. dtsch. chem. Ges.*, **55**, 3486–3504.
Marini-Bettolo, G. B. and Cavalla, J. F. (1954). *Gazz. chim. ital.*, **84**, 896–907.
Marini-Bettolo, G. B., Chiavarelli, S. and Bovet-Nitti, F. (1951). *Gazz. chim. ital.*, **81**, 587–595.
Marini-Bettolo, G. B., Chiavarelli, S. and Bovet-Nitti, F. (1952). *R.C. Ist. sup. Sanit.*, **15**, 804–807.
Norris, P. E. and Blicke, F. F. (1952). *J. Amer. pharm. Ass.*, **41**, 637–639.
Phillips, A. P. and Baltzly, R. (1947). *J. Amer. chem. Soc.*, **69**, 200–204.
Plieninger, H. (1953). *Ber. dtsch. chem. Ges.*, **86**, 25–31.
Preobrazhenskiĭ, N. A. and Fisher, L. B. (1941). *J. gen. Chem. Moscow*, **11**, 140–142.
Proosdij-Hartzema, E. G. van and de Jongh, D. K. (1954). *Arch. int. Pharmacodyn.*, **98**, 335–339.
Rosen, H., Blumenthal, A., Townsend, P. N., Tislow, R. and Seifter, J. (1956). *J. Pharmacol.*, **117**, 488–493.

Rothlin, E. and Cerletti, A. (1950). *Arch. int. Pharmacodyn.*, **82**, 118–125.
Schindler, O. and Voegtli, W. (1949). *Pharm. Acta Helvet.*, **24**, 207–216.
Stenlake, J. B. (1953). *Chem. and Ind. (Rev.)*, 1089–1090.
Stenlake, J. B. (1955). *J. chem. Soc.*, 1626–1628.
Stoll, A. and Hofmann, A. (1943). *Helv. chim. Acta*, **26**, 944–965.
Stoll, A., Petrzilka, T., Rutschmann, J., Hofmann, A. and Günthard, H. H. (1954). *Helv. chim. Acta*, **37**, 2039–2057.
Vogl, O. and Pöhm, M. (1952). *Mh. Chem.*, **83**, 541–543.
Votava, Z. and Podvalova, I. (1956). *Arch. exp. Path. Pharmak.*, **228**, 150.