STUDIES ON THE CHEMICAL BASIS FOR CHOLINOMIMETIC AND CHOLINOLYTIC ACTIVITY

PART I. THE SYNTHESIS AND CONFIGURATION OF QUATERNARY SALTS IN THE 1,3-DIOXOLANE AND OXAZOLINE SERIES

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ABSTRACT

Structure activity relationships in the muscarine and the quaternary 1,3-dioxolane (Fourneau series) series are briefly discussed. The most active member of the latter series (2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide, (IX), F2268) was shown to consist of a mixture of 60% cis and 40% trans isomers. The same was found to apply to all synthetic intermediates in that series. Unequivocal assignments of configuration were made by relating various intermediates leading to (IX) and its analogs to D-*cis*-1,3-dimethyl-1,3-dioxolane itself, obtained by degradation of 1,6-anhydrogalactose. Attempted separation of cis–trans isomers in the 1,3-dioxolane series was not successful. However, a mixture of *cis,trans*-2-trichloromethyl-4-hydroxymethyl-1,3-dioxolane (XVI) could be fractionated by crystallization of the corresponding tosylates. Catalytic hydrogenolysis converted the pure *cis*- and *trans*-trichloromethyl derivatives (XVII) and (XVIII) to pure *cis*- and *trans*-2-methyl-4-hydroxymethyl-1,3-dioxolane tosylates (XIX) and (XX), which eventually afforded for the first time pure *cis*-F2268 and *trans*-F2268 (XXII) and (XXIII).

Optically active members in the 1,3-dioxolane series were prepared. Members of the D(−)-series were conveniently obtained from D-isopropylidene glycerol. Members of the L(+)-series could be obtained in optically impure forms by resolution of *dl*-tertiary bases such as (XXXVI) with D- and L-dibenzoyltartaric acid. The best preparations had an optical purity not exceeding 32%. The resolution of the cis base (X) was unsuccessful.

The synthesis of an oxazoline analog, (XLIV), of F2268 was accomplished. The reaction sequence involves solvolysis of N-acetyl-2,3-dibromo-*n*-propylamine (XLI) to give the 5-bromomethyl-2-methyloxazoline (XLII). This unstable intermediate was reacted with dimethylamine to give the tertiary base (XLIII), which was quaternized with methyl iodide whereupon the quaternary base (XLIV) was formed in good yield. The structure of the latter was established by an independent synthesis of the hydrolysis product (XLV).

Preliminary pharmacological data are reported for the various new quaternary salts. The compounds were assayed for cholinomimetic activity. It is concluded from these studies that quaternary 1,3-dioxolanes display structure-activity relationships analogous to the muscarones. The use of triethylammonium analogs has revealed a large degree of preference of cholinergic receptors for the presence of a cis configuration in 2,4-disubstituted-1,3-dioxolanes. It was also noted that the oxazoline derivative (XLIV) ranks amongst the most active cholinomimetics thus far reported. Relationships between configuration and activity are briefly discussed.

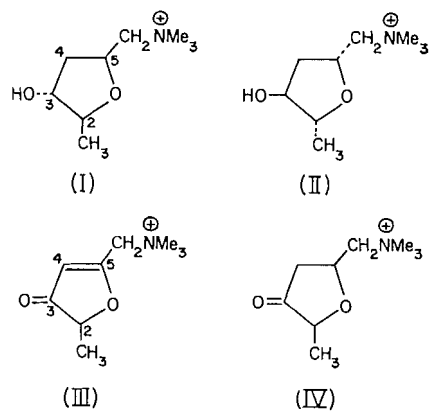
INTRODUCTION

The recent structure elucidation and synthesis of muscarine (1(*a*), 1(*b*)) has created renewed interest in the relationship between the structure and activity of drugs acting on the muscarinic cholinergic receptors. A variety of muscarine analogs have been synthesized and their cholinomimetic activity determined. This subject has been recently reviewed (2), and since then, Waser (3) has examined a number of additional structural analogs. Mention should also be made of the report of Friess, Witkop, and co-workers (4) on the inhibitory properties of a number of muscarine-related compounds towards acetylcholinesterase. It emerges from all these important studies that the optimal structural requirements for muscarinic activity are as follows: (1) The muscarinic receptor displays an almost absolute optical specificity, the non-natural enantiomorph (II)

[1]*Holder of a National Research Council of Canada Postdoctoral fellowship, 1959–1961.*

(Chart 1) being essentially inactive (5, 6). (2) The relative configuration of the substituents on the furan ring of natural muscarine represents also the optimum geometry

CHART 1



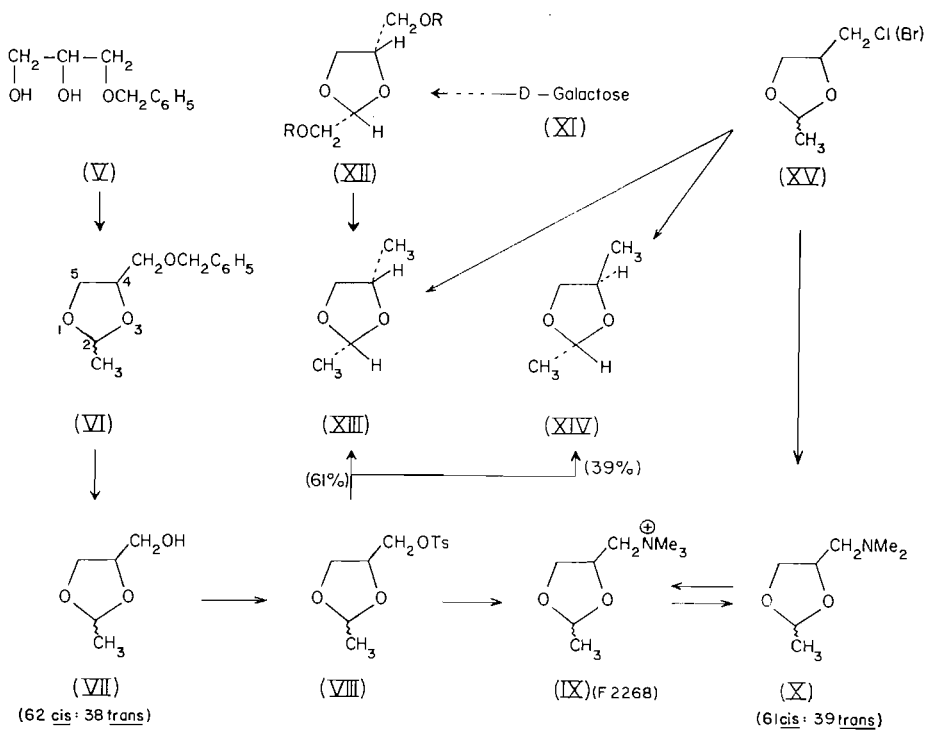
for activity. (3) The asymmetric center at position 5 can be destroyed as in 4,5-dehydromuscarone (III) without drastically changing the activity (7). However, inversion of configuration at the same position but in muscarine is detrimental to activity. The asymmetric center at position 2 is relatively unimportant in the muscarones (IV) (8) but of critical importance in muscarine. (4) The presence of a methyl group at C2 leads to maximum activity; its absence (9, 10), or its substitution for a larger group is detrimental to activity (10). (5) Replacing the furan oxygen by sulphur decreases potency (10). (6) The muscarinic receptor does not display absolute optical specificity towards the muscarones and 4,5-dehydromuscarone, in marked contrast to the specificity towards the muscarine enantiomorph (I) (3, 7, 8).

Some attempts at the interpretation of these unusual and puzzling structure-activity relationships have been made (11) and this problem will be dealt with in a future publication. There is little doubt that much knowledge about the nature of muscarinic receptors will be gained when the stereochemical interrelationships become understood. Some interesting generalizations concerning the optimum structural requirements for cholinomimetic activity have been put forward by Ing (11). The kinetics of drug interaction with cholinergic receptors has been examined in considerable detail, especially by Ariëns and van Rossum (12), who extended the original approach of Clark (13). The principles governing the ability of a drug receptor complex to produce an effect were defined in kinetic terms by Ariëns, Stephenson (14), and more recently by Paton (15). It is now recognized that the properties of drugs can best be quantitated in terms of their intrinsic activity, affinity for receptors, and rate of combination with the latter. In spite of these important contributions to the field of receptor theory, the biochemical nature of cholinergic receptors remains unsolved. We have initiated a program aimed at the elucidation of the stereochemical requirements for muscarinic activity with the hope that these studies might throw light on the nature of the receptors.

It has long been known that certain 1,3-dioxolanes exhibit a high degree of parasympathomimetic activity, a discovery due to Fourneau and his collaborators (16). The most active member of this series is 2-methyl-4-trimethylammoniummethyl-1,3-dioxolane

(IX) (Chart 2), which was reported to match muscarine in potency. All of the structural analogs of (IX) appear to be less active. The structural relationship of (IX) with muscarine

CHART 2



and its analogs is obvious and it was of interest to examine the relation between stereochemistry and activity in the Fourneau series. The effect of structural variations about the 2-position and the cationic head of (IX) has been studied by van Rossum and Ariëns (17), who confirmed the operation of the concept of affinity and intrinsic activity in this series. However, the stereochemistry of (IX) in relation to activity has not been investigated. Because activity in the muscarine series is highly dependent on configuration, relative and absolute, similar dependency would be expected in the Fourneau compound (IX). It is a rather curious phenomenon that the configuration of (IX) has never been established, and of the two possible stereoisomers, only one appears to have ever been obtained or prepared. It is not known as yet whether the high activity of (IX) is associated with a trans or cis configuration about the 2- and 4-positions, a situation which, however, has been clarified in the muscarine series. The optical forms of any quaternary-1,3-dioxolanes have also never been reported or tested. The possible inhibitory effect of these drugs on acetylcholinesterase has also not been investigated.

In this first paper of a series, the synthesis and the configuration of (IX) and a number of analogs will be described. Subsequent publications will deal with their effect on acetylcholinesterase and with generalizations regarding the probable nature of the muscarinic cholinergic receptors.

Relative Configuration of (IX)

The method most generally employed for the synthesis of 2-methyl-4-trimethylammoniummethyl-1,3-dioxolane iodide (IX) (F2268) involves the reaction of epichlorohydrin with acetaldehyde in the presence of stannic chloride whereupon the intermediate 2-methyl-4-chloromethyl-1,3-dioxolane (XV) is produced and thence reacted with dimethylamine to give (X), which is finally quaternized using methyl iodide (16). The quaternary salt (IX) so obtained has been repeatedly reported to melt sharply at 140–141° and we have confirmed this. van Rossum (17) has also showed it to be apparently homogeneous as judged from results of paper chromatography. A total of 38 homologous structures in this series were prepared by this author and all were reported to melt sharply and to give rise to single spots when chromatographed on paper.

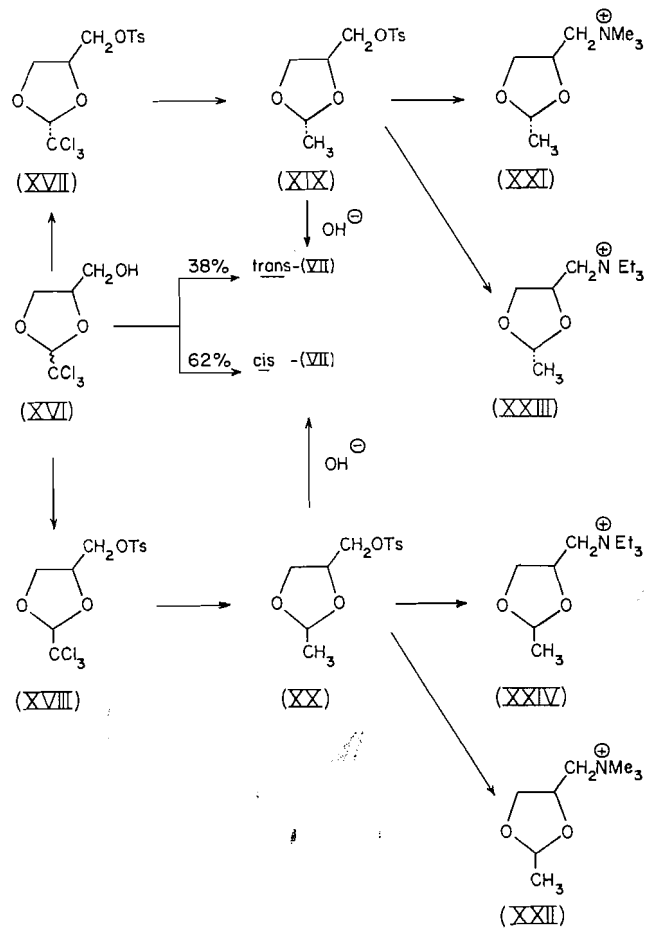
Since the relative configuration of (IX) must be the same as that of the starting dioxolane (XV), we sought to establish the configuration of the latter by relating it to a 2,4-dimethyl-1,3-dioxolane of proven configuration. The reaction of propylene glycol with acetaldehyde has been reported to give a mixture of *cis*- and *trans*-2,4-dimethyl-1,3-dioxolane, (XIII) and (XIV), which has been claimed to be separable by fractional distillation (18). In our hands this separation proved to be far from complete (see Experimental); the fraction of lower boiling point has been assigned the cis configuration. Because of our need for a much more rigorous proof of configuration we sought to synthesize the cis isomer by unambiguous methods. Cleavage of 1,6-anhydrogalactose to D-*cis*-1,3-dioxolane-2,4-dicarboxaldehyde has been reported in the literature (19). Reduction of the latter with sodium borohydride gave the cis diol (XII) (Chart 2), which gave a crystalline di-*p*-nitrobenzoate and a crystalline ditosylate. Attempts to prepare a monotosylate were fruitless, a bicyclic ether being presumably the only product. Hydrogenolysis of the ditosylate with lithium aluminum hydride afforded D-*cis*-2,4-dimethyl-1,3-dioxolane (XIII), which gave rise to a single sharp peak in the vapor phase chromatography (v.p.c.) instrument.

The dioxolane (VI) resulting from the condensation of glycerol 1-monobenzyl ether and acetaldehyde was hydrogenolyzed and the resulting 2-methyl-4-hydroxymethyl-1,3-dioxolane (VII) converted to a crystalline tosylate, (VIII), which eventually afforded F2268 (IX) after reaction with dimethylamine followed by quaternization with methyl iodide. The identity of this material was ascertained by direct comparison (infrared and n.m.r.) with a sample obtained by the general literature method outlined earlier. Hydrogenolysis of the intermediate tosylate (VIII) with lithium aluminum hydride or catalytic hydrogenolysis of the 4-chloromethyl intermediate (XV) afforded 2,4-dimethyl-1,3-dioxolane, which was shown by v.p.c. to consist of a mixture of cis–trans isomers in a ratio of 60:40 (authentic D-*cis*-2,4-dimethyl-1,3-dioxolane (XIII) being used as a standard). In order to establish that crystallization of the quaternary base (IX) did not change the isomer ratio, it was submitted to N-dealkylation by treatment with lithium aluminum hydride (20) and the tertiary base (X) analyzed by v.p.c. The cis–trans isomer ratio proved to be 61:39, thus conclusively establishing that F2268 consists of a mixture of cis and trans isomers in a ratio closely approximating 60:40. This conclusion was confirmed by n.m.r. spectroscopy, which showed clearly the presence of two split methyl groups in a ratio of 60:40 (see Experimental). Moreover, identical v.p.c. patterns were obtained with the product resulting from the reaction of propylene glycol and acetaldehyde. Therefore the synthesis of (IX) proceeds non-stereospecifically and all the intermediates consist of a mixture of 60% of cis and 40% of trans isomers. We have subsequently found this to apply to virtually all solid derivatives in this series. It is clear that *cis*- and *trans*-2,4-disubstituted-1,3-dioxolanes crystallize as molecular compounds and display very

great similarities in their physical properties. Since the time F2268 (IX) was first synthesized *all the pharmacological properties reported for it are, therefore, those of a 60:40 mixture of the cis and trans isomers.* The same would appear to apply to all other homologs, as judged from additional observations recorded below. In view of the structural analogy of (IX) with muscarine, none of the previous pharmacological data can be relied upon for purposes of correlation between stereochemistry and activity.

Numerous attempts to achieve separation of the isomers of (IX) or its precursors on a practical scale by a combination of various techniques were fruitless. However, both the cis and the trans isomers of (IX) could eventually be obtained in pure form by an indirect synthetic route which is described below (Chart 3).

CHART 3



It was found that the reaction product of glycerol and chloral (XVI) (Chart 3) gave a crystalline tosylate melting over a wide range, thus indicating that molecular compound formation was apparently suppressed in this type of 1,3-dioxolane. This proved to be the case, since fractional crystallization of the tosylate led to the isolation of two sharp-melting isomers, isomer A (XVII), m.p. 133–134°, and isomer B (XVIII), m.p. 95–96°. The trichloromethyl group of each isomer was converted to methyl by catalytic hydrogenolysis. The resulting tosylate (XIX) from A had m.p. 66–68° and when submitted to

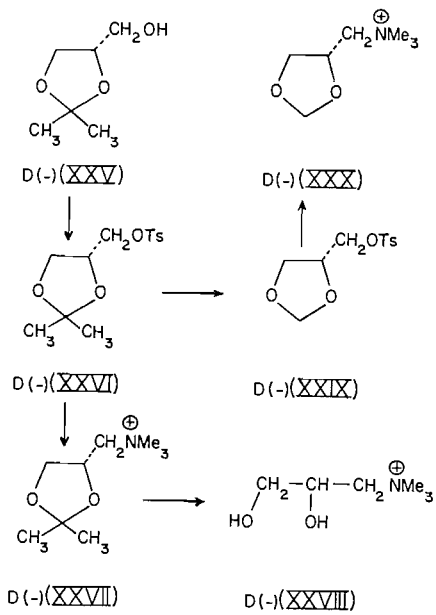
aqueous alkaline hydrolysis gave pure *trans*-2-methyl-4-hydroxymethyl-1,3-dioxolane (VII), as determined by v.p.c. Similarly, the tosylate (XX) from B had m.p. 64–66° and gave, after alkaline hydrolysis, pure *cis*-2-methyl-4-hydroxymethyl-1,3-dioxolane (VII), as established by v.p.c. Reaction of the pure trans tosylate (XIX) with dimethylamine followed by quaternization with methyl iodide afforded *trans*-2-methyl-4-trimethylammoniummethyl-1,3-dioxolane (XXI) (*trans*-F2268), m.p. 131–132°. The homogeneity of the product was confirmed by n.m.r. spectroscopy (single methyl doublet). Similar treatment of the pure cis tosylate (XX) gave *cis*-2-methyl-4-trimethylammoniummethyl-1,3-dioxolane (XXII) (*cis*-F2268), m.p. 143–144°. The n.m.r. spectrum of this compound also proved it to be homogeneous. *This is the first time that the powerful cholinomimetic F2268 becomes available in its pure stereoisomeric forms.*

In view of the fact that the experimental basis for the concept of affinity and intrinsic activity as elaborated by Ariëns and van Rossum lies principally on the inversion of agonistic activity when a trimethylammonium cationic head is changed for a triethylammonium one, it was of interest to prepare the pure *cis*- and *trans*-triethylammonium analogs (XXIV) and (XXIII) of *cis*- and *trans*-F2268. It should be emphasized that Ariëns and van Rossum used what we now recognize to be a 60:40 mixture of cis–trans isomers, thus preventing any definite conclusion regarding the effect of stereochemistry on the cholinolytic activity of triethylammonium analogs.

Synthesis in the Optically Active Series

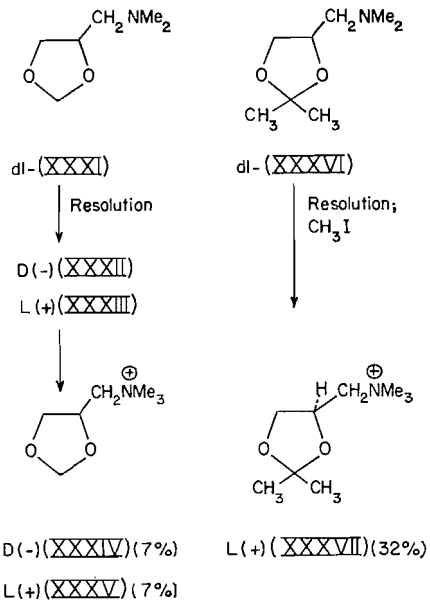
Because of the dramatic difference in cholinomimetic activity between optical isomers in the muscarine series, it was of interest to make available a number of optical isomers in the 1,3-dioxolane series. Quaternary salts of the D-series could be prepared in optically pure forms from optically pure D-isopropylidene glycerol (XXV) (Chart 4). The latter could be converted by way of the D-tosylate (XXVI) to D(−)-2,2-dimethyl-4-trimethylammoniummethyl-1,3-dioxolane iodide (XXVII). The preparation of the 2,2-bisnor

CHART 4



analog (XXX) in optically pure form was best accomplished by mild acid hydrolysis of D-isopropylidene glycerol tosylate (XXVI) followed by condensation with formaldehyde whereupon the tosylate (XXIX) was obtained. Conversion of the latter to D(−)-4-trimethylammoniummethyl-1,3-dioxolane iodide (XXX) was accomplished in the conventional manner described above. In order to gain access to the L-series, the resolution of the corresponding racemic tertiary bases was investigated (Chart 5). Racemic

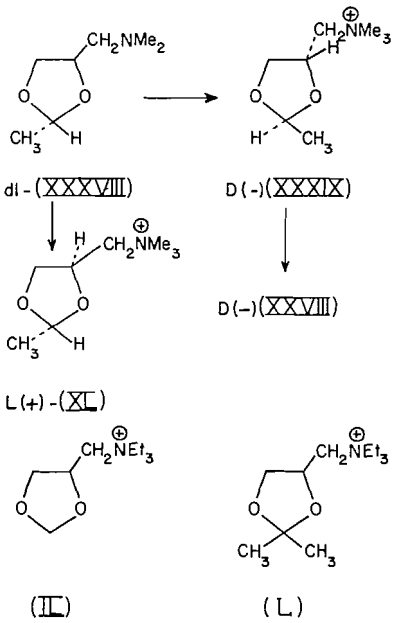
CHART 5



4-dimethylaminomethyl-1,3-dioxolane (XXXI) gave crystalline D- and L-dibenzoyltartrates (XXXII) and (XXXIII), which were recrystallized to constant rotation. The bases were regenerated and converted to the methiodides (XXXIV) and (XXXV). The levorotatory salt is therefore of the D-series. The rotations showed them to be only 7% optically pure. This difficulty in achieving resolution must again reflect the tendency for diastereoisomers of the 2,4-disubstituted-1,3-dioxolane series to crystallize as molecular compounds. Because L-dibenzoyltartaric acid gives rise to (+)-dioxolanes of the L-series, the 2,2-dimethyl tertiary base (XXXVI) (Chart 5) was converted to a crystalline L-dibenzoyltartrate which was recrystallized to constant rotation. Regeneration of the base followed by quaternization with methyl iodide gave L(+)-2,2-dimethyl-4-trimethylammoniummethyl-1,3-dioxolane iodide (XXXVII), which was 33% optically pure.

Application of these procedures to racemic *cis*- and *trans*- (X) was only partially successful. With *cis*-(X) it was not possible to obtain crystalline dibenzoyltartrate salts. However, *trans*-(XXXVIII) (Chart 6) gave a crystalline D-dibenzoyltartrate which was recrystallized to constant rotation. Regeneration of the base and quaternization in the usual way gave D(−)-*trans*-F2268 (XXXIX). The optical purity of the latter was established as follows: It was hydrolyzed with dilute hydrochloric acid and the rotation of the resulting quaternary diol (XXVIII) determined. Comparison of this rotation with that of an optically pure sample (Chart 4) derived from optically pure D(−)-(XXVII) by acid hydrolysis under identical conditions showed the D(−)-*trans*-(XXXIX) to be 32%

CHART 6



optically pure. Using again *trans*-(XXXVIII) but L-dibenzoyl tartaric acid as the resolving agent, L(+)-*trans*-F2268 (XL) was ultimately obtained with an optical purity of 32% (Chart 6).

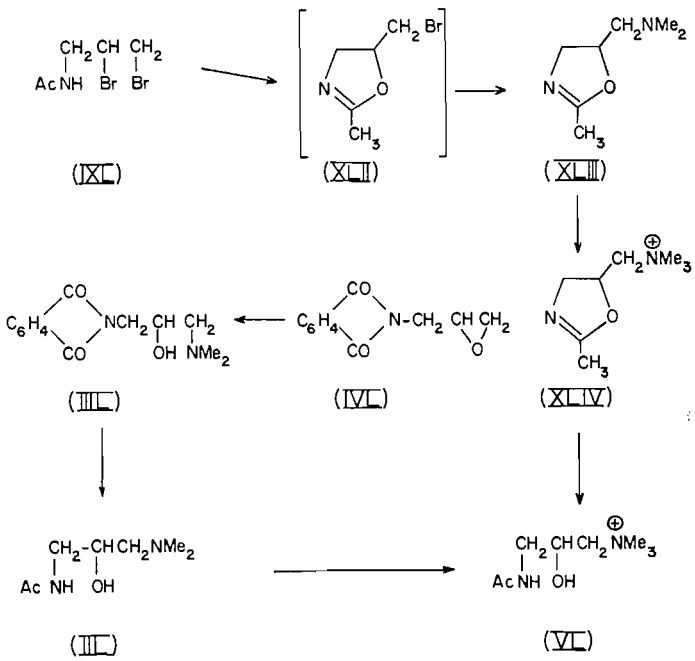
With these isomers of variable optical purity it should be possible to establish whether activity will depend on absolute configuration, as is the case in the muscarine series. If the analogy between muscarine and the 2,4-disubstituted-1,3-dioxolane is real, it would be expected that the isomers of the L(+)-series should similarly be more active cholinomimetics. It will also be of interest to determine the anti-acetylcholinesterase inhibitory property of the various isomeric forms of the above quaternary dioxolanes. This aspect of our work will be reported separately.

Synthesis of 5-Trimethylammoniummethyl-2-methyl-oxazoline Bromide (XLIV)

Perhaps one of the most striking aspects of structure-activity relationships in the muscarine series is the observation that racemic 4,5-dehydromuscarone (III) surpasses L(+)-muscarine in potency (Chart 1). Because D(−)-muscarine displays a very low order of activity, it is surprising that the absence of an asymmetric center at position 5 of 4,5-dehydromuscarone should lead to such a highly active cholinomimetic. Moreover, and in sharp contrast to the muscarine series, the relative configuration of the methyl group in the muscarone series is relatively unimportant, racemic allomuscarone (*trans*-(IV)) being only slightly less active than racemic muscarone (*cis*-(IV)). This result also suggests that destruction of the asymmetric center at position 2 through the introduction of a double bond between carbons 2 and 3 (if this were feasible) might not alter activity in the muscarone series. While this problem is being investigated, it appeared of more immediate interest to transpose this reasoning to the 1,3-dioxolane series and it is obvious that in order to produce a trigonal carbon at position 2 of 1,3-dioxolanes, it is essential that the oxygen atom at position 1 be substituted by a trivalent heteroatom such as

nitrogen. It should be noted that no oxazoline analog in the Fourneau series of cholinomimetics has as yet been reported. Several of the most obvious methods for the synthesis of the desired analog (XLIV) (Chart 7) of (IX) proved unsuccessful. A convenient and

CHART 7



expedient method of synthesis was ultimately discovered which requires the readily available starting material N-allyl acetamide. This was converted to the dibromide (XLI) (Chart 7) as described elsewhere and then solvolyzed in acetonitrile in the presence of silver carbonate. The participation of neighboring amido groups in such solvolyses has previously been demonstrated (21) and allows the prediction that the dibromide (XLI) must be converted largely to 5-bromomethyl-2-methyl-oxazoline (XLII). Attempts to isolate this intermediate were unsuccessful, rapid polymerization of the compound taking place upon removal of the solvent. However, if excess anhydrous dimethylamine was added to the reaction mixture as soon as maximum precipitation of silver bromide had occurred, a good yield of 2-methyl-5-dimethylaminomethyloxazoline (XLIII) was obtained. Quaternization of the latter with methyl iodide finally gave the crystalline salt (XLIV) in high yield. It was desirable to establish the structure of the latter by unambiguous means, since the course of the solvolysis can only be inferred. The quaternary base (XLIV) was hydrolyzed with hot water to give a quantitative yield of 1-acetamido-3-trimethylammonium-2-propanol iodide (XLV). An authentic specimen of the latter was secured by reacting 1-phthalimido-2,3-epoxypropane (XLVI) with dimethylamine, whereupon (XLVII) was produced. Hydrolysis of the latter followed by acetylation and quaternization with methyl iodide afforded (XLV), which proved to be identical with the sample obtained by hydrolysis of the oxazoline (XLIV). It is clear that this method of synthesis of (XLIV) could be extended to the preparation of a variety of trialkylammonium analogs.

PRELIMINARY PHARMACOLOGICAL RESULTS*

The various quaternary dioxolanes and the oxazoline derivative (XLIV) were assayed for muscarinic activity using the guinea pig ileum as the test organ. The minimum concentration of drug necessary to elicit a response is recorded in Table I. Of immediate

TABLE I

Compound number	Concentration, mg/ml, guinea pig ileum ($c \times 10^{-7}$)	Compound number	Concentration, mg/ml, guinea pig ileum ($c \times 10^{-7}$)
Acetyl choline	2.5	L(+)-(XXXIX)†	12.5
(XXI)	12.5	L(+)-(XL)†	0.125
(XXII)	2.5	(XXIII)	500,000.
(XXX)	5,000.	(XXIV)	500.
D(−)-(XXVII)	250,000.	(XLIV)	2.5
L(+)-(XXXV)*	2,500.	(IL)	500,000.
L(+)-(XXXVII)†	2,500.	(L)	5,000,000.

*Optical purity of this isomer is 7%.
†Optical purity is 32%.

interest is the fact that quaternary compounds of the L(+)-series are uniformly much more active than their D(−) counterparts. Hence, the same absolute configurational requirement as in the muscarine series is operative. It is also interesting that *cis*-F2268 (XXII) surpasses *trans*-F2268 (XXI) in potency by a factor of 5. This also parallels the effect of epimerization about the C_2-methyl group of muscarine, racemic allomuscarine being very much less active. However, the magnitude of the differences in potency between *cis*-(XXII) and *trans*-(XXI) on the one hand and (±)-muscarine and (±)-allomuscarine on the other is such as to indicate that the asymmetric center at C_2 of (XXI) and (XXII) is not nearly as important as it is in the muscarine series. In this respect, the ratio of the potencies of *cis*- and *trans*-F2268 suggests that they resemble the muscarones much more than the muscarines. It should be mentioned that Barlow had speculated that *cis*- and *trans*-F2268 would not differ greatly in potency because of a loose structural analogy with the muscarones (IV) (22). It is striking, however, that the L(+)-*trans*-F2268 (XL), which is only 32% optically active, should surpass acetylcholine in potency by a factor of 20. Consideration of the fact that a 32% enrichment in the L(+) isomer increases the potency by a factor of 100 over the pure racemic mixture (XXI) and that the cis racemate (XXII) is five times more active than the latter, suggests that the pure L(+) cis isomer of (XXI) should possess extraordinary potency surpassing all known cholinomimetic drugs. The synthesis of this L(+) cis isomer is under way.

Confirmation that the configuration of the asymmetric center at C_2 of F2268 may not be a critical factor (although it has an influence) for activity is supplied by the high cholinomimetic activity of the quaternary oxazoline (XLIV) in which C_2 is now trigonal. We are fully aware, however, that in this latter case, the presence of a basic nitrogen in the ring introduces an additional factor which may alter the mechanism of interaction with the receptors. We are presently attempting to establish whether the oxazoline (XLIV) interacts with the receptors in the protonated form or as the free base.

Of great interest finally is the marked difference in the relative potencies of the triethylammonium analogs (XXIV) and (XXIII) of *cis*- and *trans*-(F2268). In contradiction with the conclusions regarding the significance of the asymmetric center at C_2 of F2268

Results of our work and that of Dr. M. Pindell and his staff, Bristol Laboratories, Syracuse, N.Y.

(IX), it appears that *in the triethylammonium series (XXIII) and (XXIV) the configuration of the C_2 methyl group is of critical importance.* An interpretation of these results will be given in a forthcoming publication.

EXPERIMENTAL*

cis,trans-2-Methyl-4-hydroxymethyl-1,3-dioxolane (VII)

This was prepared according to the method of Brimacombe, Foster, and Haines (23). The pure alcohol was analyzed by v.p.c. and shown to consist of a mixture of cis–trans isomers in a ratio of 64:36. (see Table II, entry 1). The *tosylate (VIII)* was prepared by treatment with *p*-toluenesulphonyl chloride and

TABLE II

Isomer composition of 2,4-disubstituted-1,3-dioxolanes

Entry	Compound No.	2-Subst.	4-Subst.	% *cis*-	% *trans*-	Column packing*
1	(VII)	Me	CH_2OH	64.0	36.0	A
2	(XIII)+(XIV)†	Me	Me	61.0	39.0	B
3	(X)	Me	CH_2NMe_2	60.5	39.5	A
4	(XV)	Me	CH_2Cl	62.0	38.0	B
5	(XV)	Me	CH_2Br	64.0	36.0	B
6	(XIII)+(XIV)‡	Me	Me	63.0	37.0	B
7	(XIII)+(XIV)§	Me	Me	62.0	38.0	B
8	(XIII)	Me	Me	100.0	—	B
9	(VII)‖	Me	CH_2OH	62.0	38.0	A
10	(XIII)+(XIV)¶	Me	Me	73.0	27.0	B
11	(XIII)+(XIV)**	Me	Me	46.0	54.0	B

*Obtained from Perkin–Elmer and used as such. The v.p.c. apparatus was a Perkin–Elmer instrument. Percentage compositions were determined by taking the ratio of peak areas in the usual way.
†Obtained from (VII) by way of (VIII).
‡Obtained from (XV), entry 4.
§Obtained from (XV), entry 5.
‖Obtained from *cis,trans*-(XVI) by hydrogenolysis.
¶Lower-boiling fraction.
**Higher-boiling fraction.

pyridine at 0°, whereupon an oily tosylate was obtained which crystallized from hexane as colorless needles, m.p. 49–53°. Yield: 74%. Calc. for $C_{12}H_{16}SO_5$: C, 52.9; H, 5.9. Found: C, 52.9; H, 5.9%.

cis,trans-2,4-Dimethyl-1,3-dioxolane (XIII) and (XIV)

A solution of the tosylate of *cis,trans*-2-methyl-4-hydroxymethyl-1,3-dioxolane (VIII) (13.5 g, 0.05 mole) in diglyme was added dropwise to a stirred solution of lithium aluminum hydride (1.9 g, 0.05 mole) in diglyme at 100°. The mixture was kept at this temperature for 2 hours, cooled, and treated with 10% sodium hydroxide and distilled (bath temperature 150°). The distillate was dried (Na_2SO_4) and redistilled to give *cis,trans*-2,4-dimethyl-1,3-dioxolane (4.4 g, 86%), b.p. 90–95°. The results of the vapor phase chromatographic analysis are given in Table II (entry 2).

Attempted Separation of cis and trans Isomers of 2,4-Dimethyl-1,3-dioxolane (XIII) and (XIV)

Two hundred grams of the cis–trans mixture was prepared according to the method of Lucas and Guthrie (18). Repeated fractional distillation and vapor phase chromatographic examination of the fractions revealed an increase in the cis content of the lower-boiling fraction and an increase in the trans content of the higher-boiling fraction, but as the results in Table II (entries 10 and 11 respectively) show, the separation was far from complete.

cis,trans-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (IX)

cis,trans-2-Methyl-4-toluenesulphonyloxymethyl-1,3-dioxolane (VIII) (13.5 g, 0.05 mole) was dissolved in 100 ml of a 30% solution of anhydrous dimethylamine in benzene and kept at 100° for 12 hours; the mixture was cooled, filtered, and the excess dimethylamine removed by heating on the steam bath. Addition of an excess of methyl iodide gave a near quantitative yield of the quaternary iodide; crystallization from isopropanol gave colorless needles (82%), m.p. 141° (unchanged on further crystallization). The n.m.r. spectrum (in pyridine) showed two methyl doublets with an intensity ratio of 3:2.

**All melting points were determined microscopically on a Kofler hot stage and are uncorrected. The boiling points are also uncorrected. Infrared spectra were determined using a Perkin–Elmer Infracord instrument. The n.m.r. spectra were recorded with a Varian instrument operating at 60 Mc. Microanalyses by Miss E. Busk, Chemistry Department, University of Ottawa.*

cis,trans-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane (X)

The finely powdered preceding methiodide (IX) (7.2 g, 0.025 mole) was suspended in diglyme (20 ml) with lithium aluminum hydride (0.025 mole) and the reaction mixture heated to 150° for 6 hours and then decomposed with 10% sodium hydroxide (10 ml), filtered, saturated with salt, and extracted several times with ether to give *cis,trans*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane (2.6 g, 71.2%). The results of the vapor phase chromatographic analysis are given in Table II (entry 3).

cis,trans-2-Methyl-4-chloro- (or bromo-) methyl-1,3-dioxolane (XV)

These were prepared from glycerol α-monochlorhydrin or monobromhydrin and acetaldehyde by reaction in boiling benzene, the water being continuously removed with a Dean–Stark trap. The results of the vapor phase chromatography experiments are given in Table II (entries 4 and 5). The configurations were established by hydrogenolysis to the corresponding 2,4-dimethyl-1,3-dioxolanes as follows: *cis,trans*-2-methyl-4-halomethyl-1,3-dioxolane (0.1 mole) in absolute ethanol in which was suspended sodium bicarbonate (0.5 mole) and 10% Pd/C (0.5 g) was reduced at 3 atm pressure of hydrogen for 3 hours. The reaction mixture was filtered and a sample of the filtrate analyzed by vapor phase chromatography to give the results shown in Table II (entries 6 and 7). These results (Table II) confirm the configurations suggested by vapor phase chromatographic analysis of the halomethyl derivatives themselves (see above).

D-*cis-2,4-(Dihydroxymethyl)-1,3-dioxolane (XII)*

Crude 1,3-dioxolane-*cis*-2,4-dicarboxaldehyde (19) (0.1 mole) was dissolved in absolute methanol and cooled in ice. A solution of sodium borohydride (6.0 g, 0.15 mole) in water was added dropwise with stirring at 10–15°. Stirring at room temperature was continued for a further 3 hours, 25 ml of 10% sodium hydroxide was added, and carbon dioxide bubbled in until the solution was saturated. The solution was evaporated to dryness and the residue extracted with ethyl alcohol to give D-*cis*-2,4-bis(hydroxymethyl)-1,3-dioxolane (XII) as a viscous oil (12.1 g, 90.3%). Calc. for $C_5H_{10}O_4$: C, 44.8; H, 7.5. Found: C, 44.3; H, 7.1%. Without further purification, this D-*cis*-2,4-(dihydroxymethyl)-1,3-dioxolane (6.7 g, 0.05 mole) was dissolved in dry pyridine and the solution added dropwise to a stirred and cooled solution of *p*-nitrobenzoyl chloride (20.5 g, 0.11 mole) in dry pyridine; after 12 hours the reaction mixture was poured over ice, filtered, washed with ice-cold water, dried, and recrystallized from benzene to give the *cis*-bis(2,4-dinitrobenzoate) as very pale yellow needles (15.0 g, 71.2%), m.p. 94°. $[\alpha]_D^{22} = -18.5°$ (c = 1.2, acetone). Calc. for $C_{19}H_{16}N_2O_{10}$: C, 52.8; H, 3.7. Found: C, 52.6; H, 3.3%.

The *bis(dinitrobenzoate)* (10.8 g, 0.025 mole) was dissolved in aqueous ethanol (100 ml) containing sodium hydroxide (6 g) and heated under reflux for 5 hours. The solution was cooled, saturated with carbon dioxide, evaporated to dryness, and extracted with absolute ethanol to give D-*cis*-2,4-(dihydroxymethyl)-1,3-dioxolane (XII) (2.5 g, 74.6%) as a viscous oil. Calc. for $C_5H_{10}O_4$: C, 44.8; H, 7.5. Found: C, 44.3; H, 7.2%.

The pure D-*cis-(2,4-dihydroxymethyl)-1,3-dioxolane* (2.0 g, 0.015 mole) so obtained was dissolved in dry pyridine at 0°, and *p*-toluenesulphonyl chloride (6 g, 0.033 mole) was added. After 24 hours at room temperature a large excess of ether was added and the solution was extracted with 10% hydrochloric acid until free from pyridine. The ethereal solution was dried (Na_2SO_4), filtered, and evaporated to give the ditosylate as colorless needles (4.4 g, 66%), m.p. 84–86°. $[\alpha]_D = -25.5$ (c = 2, acetone). Calc. for $C_{19}H_{22}S_2O_8$: C, 51.6; H, 5.0. Found: C, 52.1; H, 5.1%.

D-*cis-2,4-Dimethyl-1,3-dioxolane (XIII)*

This was prepared by lithium aluminum hydride reduction of the preceding ditosylate by the procedure described above in the case of the preparation of *cis,trans*-2,4-dimethyl-1,3-dioxolane (XIII) + (XIV). The yield of crude D-*cis*-2,4-dimethyl-1,3-dioxolane was only 23% and the quantity was not sufficient for purification and empirical analysis. However, vapor phase chromatographic analysis was unambiguous as it showed that the compound could only be pure *cis*-2,4-dimethyl-1,3-dioxolane (XIII) (Table II, entry 8).

cis,trans-2-Trichloromethyl-4-hydroxymethyl-1,3-dioxolane (XVI)

This was prepared according to the method of Hibbert (24). It was found that by increasing the reaction temperature and time to 90° and 24 hours respectively the yield was increased to 65–70%.

The dioxolane so obtained (22.0 g, 0.1 mole) was dissolved in 80% aqueous methanol (100 ml) containing sodium bicarbonate (33.6 g, 0.4 mole) and 10% Pd/C (0.5 g). The mixture was reduced at 5 atm pressure of hydrogen for 5 hours. The solution was filtered and distilled to give *cis,trans*-2-methyl-4-hydroxymethyl-1,3-dioxolane (VII) (7.5 g, 63.5%), b.p. 70–75° at 8 mm. The isomer ratio was 62:38 (Table II, entry 9). Calc. for $C_5H_{10}O_3$: C, 50.9; H, 8.5. Found: C, 51.1; H, 8.6%.

Separation of cis,trans-2-Trichloromethyl-4-hydroxymethyl-1,3-dioxolane (XVI)

The above trichloromethyl dioxolane (892 g, 4.0 moles) was dissolved in dry pyridine (1.5 liters) and the solution cooled to 0° and treated with *p*-toluenesulphonyl chloride (840 g, 4.4 moles) over a period of 12 hours. The reaction mixture was then allowed to stand for 24 hours at room temperature and then poured into 5 liters of ice water. The precipitate was filtered, washed with water, and dried in air to give the *p*-toluenesulphonate (1495 g, 99%), white needles, m.p. 110–120°, which upon repeated recrystallization from methanol yielded the trans tosylate (XVII), m.p. 133–134° (250 g). Calc. for $C_{12}H_{13}SO_5Cl_3$: C, 38.3;

H, 3.5. Found: C, 38.1; H, 3.4%. The mother liquors from the first crystallization yielded, on repeated crystallization from methanol, the cis tosylate (XVIII), m.p. 95–96° (130 g). Found: C, 38.4; H, 3.4%.

cis- and trans-2-Methyl-4-hydroxymethyl-1,3-dioxolanes (cis-VII) and (trans-VII)

The preceding trans tosylate (XVII) (19.0 g, 0.05 mole) was added to 200 ml of aqueous methanol (1:1, v/v) together with sodium bicarbonate (14.8 g, 0.2 mole) and hydrogenated at 3–5 atm pressure with 10% Pd/C catalyst (0.5 g) for 24 hours to give the trans tosylate (XIX), m.p. 66–68°; yield 10.1 g. It was recrystallized from pentane. Calc. for $C_{16}H_{16}SO_5$: C, 52.9; H, 5.9. Found: C, 52.7; H, 5.9%. By the same procedure, the cis tosylate (XVIII) gave the cis tosylate (XX), m.p. 64–66°; yield 9.8 g. It was recrystallized from pentane. Calc. for $C_{12}H_{16}SO_5$: C, 52.9; H, 5.9. Found: C, 52.9; H, 5.6%.

The trans tosylate (XIX) (5.4 g, 0.02 mole) was heated under reflux for 4 hours with a 10% excess of sodium hydroxide in 70% aqueous ethanol. The solution was then saturated with carbon dioxide, evaporated to dryness, and the residue extracted with absolute ethyl alcohol to give chromatographically pure (v.p.c.) *trans*-2-methyl-4-hydroxymethyl-1,3-dioxolane (*trans*-VII), b.p. 76–80° at 9 mm (2.1 g, 70.0%). Similarly, the cis tosylate (XX) yielded chromatographically pure (v.p.c.) *cis*-2-methyl-4-hydroxymethyl-1,3-dioxolane (*cis*-VII), b.p. 78–80° at 10 mm (2.0 g, 67.0%).

Lithium aluminum hydride reduction of the trans tosylate (XIX) and the cis tosylate (XX) by the procedure described above in the case of (VIII) gave the corresponding pure *cis*- and *trans*-2,4-dimethyl-1,3-dioxolanes, as evidenced by v.p.c.

cis- and trans-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane Methiodides (XXII) and (XXI)

cis- and *trans*-2-Methyl-4-*p*-toluenesulphonyloxymethyl-1,3-dioxolanes (XX) and (XIX) (5.4 g, 0.02 mole) were converted into the corresponding 4-dimethylaminomethyl derivatives by the method described above for the mixture of cis–trans isomers. Treatment with methyl iodide and crystallization from ethyl acetate – isopropanol gave pure *cis*-(XXII) and pure *trans*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodides (XXI), m.p. 143–144° and 131–132° respectively. Calc. for: $C_8H_{18}N_1O_2I$: (*trans*): C, 33.5; H, 6.3. Found: (*cis*): C, 33.8; H, 6.1; (*trans*): C, 33.6; H, 6.2%. The n.m.r. spectra (in pyridine) of both isomers showed a single methyl doublet.

cis- and trans-2-Methyl-4-diethylaminomethyl-1,3-dioxolane Ethiodides (XXIV) and (XXIII)

These were prepared in a way similar to that used for the corresponding 4-dimethylaminomethyl compounds. Pure *trans*-2-methyl-4-diethylaminomethyl-1,3-dioxolane ethiodide (XXIII) had m.p. 129–131° (from isopropanol – ethyl acetate) but the cis isomer (XXIV) failed to crystallize. Calc. for $C_{11}H_{24}NO_2I$: C, 40.2; H, 7.3. Found: (*trans*): C, 40.4; H, 7.0; (*cis*): C, 40.5; H, 7.1%.

Other Quaternary Salts of 1,3-Dioxolanes

These were the previously known 4-dimethylaminomethyl- and 2,2-dimethyl-4-dimethylaminomethyl-1,3-dioxolane methiodides (*dl*-XXX) and (*dl*-XXVII), and the 4-diethylaminomethyl- and 2,2-dimethyl-4-diethylaminomethyl-1,3-dioxolane ethiodides (IL) and (L). Their physical constants agreed with the literature values (16).

Resolution of 4-Dimethylaminomethyl-1,3-dioxolane (XXXI)

The amine (XXXI) (0.15 mole) was dissolved in dry ether, and a solution of D-dibenzoyltartaric acid (0.15 mole) in dry ether added and the mixture allowed to stand overnight. The ether was decanted and the viscous precipitate recrystallized to constant rotation from ethanol to give 13.0 g of colorless crystals, m.p. 131–132°, $[\alpha]_D^{20} = -90°$ ($c = 2$, methanol). Calc. for $C_{24}H_{25}NO_{10}$: C, 59.1; H, 5.2. Found: C, 59.0; H, 5.7%.

It was not possible to obtain the (+)-salt from the mother liquors. The above procedure was therefore repeated using L-dibenzoyltartaric acid, whereupon the (+)-salt was obtained in the same state of purity as the (−)-salt.

The free bases were regenerated from the (+)- and (−)-salts by treatment in dry ethanol with an equimolar amount of sodium ethoxide. The precipitated disodium dibenzoyltartrates were removed by filtration after dilution with ether. The filtrate was treated with excess methyl iodide and the pure methiodides collected after 24 hours. Both had m.p. 157–158°. The *D(−)-quaternary salt* (XXXIV) had $[\alpha]_D^{20} = -2.2$ ($c = 2$, H_2O). The optical purity was 7% (see below). Calc. for $C_7H_{16}O_2NI$: C, 30.8; H, 5.9. Found: C, 30.9; H, 5.6%. The *L(+)-quaternary salt* (XXXV) had $[\alpha]_D^{20} = 2.2°$ ($c = 2$, H_2O). The optical purity was 7%. Calc. for $C_7H_{16}O_2NI$: C, 30.8; H, 5.9. Found: C, 30.9; H, 5.8%.

Optically Pure D(−)-4-Dimethylamino-1,3-dioxolane Methiodide (XXX)

D-Isopropylidene glycerol (25) was converted to the *tosylate* (XXVI) by the general procedure outlined above. It crystallized from hexane as colorless needles, m.p. 24–27°. Calc. for $C_{13}H_{18}O_5S$: C, 54.5; H, 6.3. Found: C, 54.7; H, 6.2%.

The *tosylate* was hydrolyzed by heating to 50° in excess 2 *N* hydrochloric acid for 4 hours. The solution was taken to dryness *in vacuo* and the residue reacted in benzene with paraformaldehyde in the presence of some *p*-toluenesulphonic acid. The water was continuously removed with a Dean–Stark trap and the product

isolated in the usual manner. It crystallized from benzene–pentane, m.p. 35.7°. This optically pure D(−)-4-tosyloxymethyl-1,3-dioxolane (XXIX) had $[\alpha]_D^{20} = -10.0°$ (c = 2, isopropanol). Calc. for $C_{11}H_{14}O_5S$: C, 50.5; H, 5.5. Found: C, 50.8; H, 5.4%.

This *tosylate* (*XXIX*) was converted to D(−)-4-dimethylaminomethyl-1,3-dioxolane methiodide (XXX) by the general procedure outlined above. The *methiodide* had m.p. 147–148° (isopropanol); $[\alpha]_D^{20} = -32.5°$ (c = 2, H_2O). Calc. for $C_7H_{16}O_2NI$: C, 30.8; H, 5.9. Found: C, 31.3; H, 5.8%.

D(−)-2,2-Dimethyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (XXVII)

The preceding tosylate of D-isopropylidene glycerol (XXVI) was reacted with dimethylamine and the resulting base quaternized with methyl iodide by the procedures described above. The quaternary iodide (XXVII) had m.p. 215–216° (ethanol); $[\alpha]_D^{20} = -12.0°$ (c = 2, H_2O). Calc. for $C_9H_{20}O_2NI$: C, 35.9; H, 6.7. Found: C, 36.1; H, 6.4%.

Of this quaternary salt, 200 mg was heated at 90° in excess 2 *N* hydrochloric acid for 5 hours. The solution was taken to dryness *in vacuo* and the residue (XXVIII) made up to 5 ml with water. The solution had $\alpha_D^{20} = -1.38°$. This solution was used as a standard for the determination of the optical purity of other dioxolanes described below.

L(+)-2,2-Dimethyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (XXXVII)

The corresponding tertiary base *dl*-2,2-dimethyl-4-dimethylaminomethyl-1,3-dioxolane (XXXVI) was resolved with L-dibenzoyltartaric acid in the same manner as described above in the case of (XXXI). The salt was recrystallized to constant rotation. It had m.p. 133–136°; $[\alpha]_D^{20} = 70°$ (c = 2, methanol). Calc. for $C_{26}H_{31}O_{10}N$: C, 60.35; H, 6.05. Found: C, 60.5; H, 6.2%.

This L-dibenzoyltartrate salt was decomposed as described above in the case of (XXXI) and the regenerated base reacted with methyl iodide whereupon the methiodide (XXXVII) was obtained, m.p. 204–208° (isopropanol). It had $[\alpha]_D^{20} = 4.0°$ (c = 2, H_2O). Since the rotation of the optically pure enantiomorph (XXVII) is −12.0°, the optical purity of this L(+)-isomer (XXXVII) is 33%. Calc. for $C_9H_{20}O_2NI$: C, 35.9; H, 6.7. Found: C, 36.1; H, 6.9%.

D(−)-trans-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (XXXIX)

The tertiary base (XXXVIII) was resolved with D-dibenzoyltartaric acid by the same procedure outlined above in the case of (XXXI). The salt, obtained in 25% yield, was recrystallized to constant rotation, m.p. 131–132°, $[\alpha]_D^{20} = -84°$ (c = 2, methanol). Calc. for $C_{25}H_{27}O_{10}N$: C, 60.0; H, 5.4. Found: C, 60.3; H, 5.5%.

Regeneration of the base followed by quaternization with methyl iodide in the usual manner afforded the D(−)-methiodide (XXXIX), m.p. 100–110° (isopropanol), $[\alpha]_D^{20} = -8.25$ (c = 2, H_2O). Calc. for $C_8H_{18}ONI$: C, 33.5; H, 6.3. Found: C, 33.8; H, 6.1%.

A 200-mg portion of the methiodide was hydrolyzed in 2 *N* hydrochloric acid as described above in the case of (XXVII). The resulting quaternary diol (XXVIII) had $[\alpha]_D^{20} = -0.44°$. Since the pure D(−) quaternary diol had $[\alpha]_D^{20} = -1.38°$ under the same conditions, the optical purity of the D(−)-*trans*-methiodide (XXXIX) obtained by resolution is 32%.

L(+)-trans-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (XL)

The same procedure just described above in the case of (XXXIX) was applied throughout except that L-dibenzoyltartaric acid was used. The L-dibenzoyltartrate salt of (XXXVIII) had m.p. 131–132°, $[\alpha]_D^{20} = 85°$ (c = 2, methanol). Calc. for $C_{25}H_{27}O_{10}N$: C, 60.0; H, 5.4. Found: C, 60.1; H, 5.8%.

The L(+)-methiodide (XL) had m.p. 100–110°, $[\alpha]_D^{20} = 8.3°$ (c = 2, H_2O).

The quaternary diol (XXVIII) obtained by hydrolysis had $[\alpha]_D^{20} = 0.44°$. The optical purity of the L(+)-*trans*-methiodide (XL) obtained by resolution is therefore 32%.

With *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane (*cis*-X) no crystalline salts with D- or L-dibenzoyltartaric acid could be obtained.

2-Methyl-5-dimethylaminomethyl-oxazoline (XLIII) and Its Methiodide (XLIV)

After several trial runs, the following procedure proved to be the most convenient: to a solution of 30 g of N-acetyl-2,3-dibromo-1-propylamine (IXL) (prepared by bromination of N-allyl acetamide according to the literature) (26) in 130 ml of dry acetonitrile was added, with stirring, 16 g of dry and freshly precipitated silver carbonate. When all the silver carbonate appeared to have been converted to silver bromide (about 1/2 to 1 hour), it was quickly filtered and 100 ml of a 20% solution of dry dimethylamine in benzene was added. The mixture was stirred and allowed to stand overnight. Another portion of 16 g of dry silver carbonate was added and the precipitated silver bromide filtered off. The filtrate was evaporated *in vacuo* at 40° and the residue distilled *in vacuo*; at 57–58° at 5 mm, 8.5 g of colorless liquid (XLIII) was obtained. It gave a strong band at 1675 cm^{-1} in the infrared. Calc. for $C_7H_{14}ON_2$: C, 59.15; H, 9.85. Found: C, 59.30; H, 10.0%.

The *methiodide* (XLIV) was obtained in high yield by reacting the base with 20% less than the theoretical amount of methyl iodide in acetone (a purer product is obtained in this manner). The yield of colorless crystals, m.p. 134.5–135°, was quantitative (based on methyl iodide). The product can be recrystallized from methanol–acetone. Calc. for $C_8H_{17}ON_2I$: C, 33.8; H, 5.98. Found: C, 33.7; H, 5.88%.

N-Acetyl-N'-dimethyl-1,3-diamino-2-propanol Methiodide (VL) by Hydrolysis of (XLIV)

A solution of 100 mg of the quaternary iodide (XLIV) was heated to 100° in distilled water for 60 hours. The water was evaporated *in vacuo* and the residue crystallized from methanol–acetone, m.p. 119–120°, unchanged by recrystallization. It proved identical with an authentic sample of (VL) synthesized as described below.

1-Phthalimido-3-dimethylamino-2-propanol (IIIL)

A solution of 1-phthalimido-2,3-epoxypropane (40 g) in 250 ml of 20% dimethylamine in benzene was heated to 100° for 4 hours. Evaporation of the solvent gave (IIIL) as a viscous oil. Calc. for $C_{13}H_{16}O_3N_2$: C, 62.8; H, 6.5; N, 11.29. Found: C, 62.3; H, 6.9; N, 11.01%.

N-Acetyl-N'-dimethyl-1,3-diamino-2-propanol Methiodide (VL)

The preceding phthalimido derivative (IIIL) was hydrolyzed by heating under reflux with concentrated hydrochloric acid for 10 hours. The phthalic acid was filtered from the cooled solution and the filtrate concentrated *in vacuo* to give the dihydrochloride salt as an uncrystallizable oil. A crystalline dipicrate, m.p. 207–209° (isopropanol), was prepared. Calc. for $C_{17}H_{20}O_{15}N_8$: C, 35.4; H, 3.5. Found: C, 35.4; H, 3.5%.

The N,N-dimethyl-1,3-diamino-2-propanol dihydrochloride (0.04 mole) was converted to the N'-acetyl derivative by reaction with an equimolar amount of acetic anhydride in some water containing 4 g of sodium acetate. The reaction mixture stood for 2 hours, was neutralized with sodium hydroxide, and evaporated to dryness. The residue was extracted with alcohol–ether and the extract distilled; at 130° at 0.01 mm the acetyl derivative (IIL) was obtained as a vicous oil which could not be induced to crystallize. Calc. for $C_7H_{16}O_2N_2$: C, 52.5; H, 10.1. Found: C, 52.65; H, 10.1%.

The *methiodide* was obtained in the usual manner and crystallized from methanol–acetone, m.p. 119–120°. No depression of the melting point was observed when it was admixed with a sample secured by hydrolysis of (XLIV) as described above. The infrared spectra of the two compounds (Nujol mull) were superimposable. Calc. for $C_8H_{19}O_2N_2I$: C, 31.8; H, 6.3. Found: C, 31.9; H, 6.0%.

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