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Lythraceous Alkaloids. II.[1] The Structure of O-Methyllythranidine[2]

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Permanganate oxidation of O-methyllythranidine gave the evidence for the presence of 2,2′-disubstituted diphenyl group in the molecule. O,N-Dimethyllythranidine was subjected to repeated Hofmann degradations followed by hydrogenations to give des-N base V, which was oxidized to diketone VI. Subsequently, the presence of a piperidine ring in the alkaloid was proved by a series of reactions. Some reactions and nuclear magnetic resonance spectra investigations of the products led to a conclusion that O-methyllythranidine has structure A.

In the preceding paper,[1] isolation of three new alkaloids, lythranine, lythranidine, and lythramine, from *Lythrum anceps* Makino, characterization of their functional groups, and correlation among these alkaloids were described. In this paper, we wish to report presentation of the plane structure for O-methyllythranidine.

As described in the preceding paper, lythranidine has an aromatic methoxy group, a phenolic hydroxy group, two secondary alcoholic hydroxy groups, an imino group, and six aromatic hydrogens in the molecule. Its molecular formula was shown to be $C_{26}H_{35}O_4N$. Lythranine has the structure in which one alcohol of lythranidine is acetylated, hence it on hydrolysis with alkali gives lythranidine.

Lythranidine (I) on methylation with diazomethane gave amorphous O-methyllythranidine (II) which was characterized on the basis of the spectroscopic evidence, and a crystalline product, mp 166—168°. The benzene adduct of O-methyllythranidine hydrochloride was crystallized and had mp 188—190° (decomp.). The crystal, mp 166—168°, has the molecular formula $C_{28}H_{39}O_4N$, and its nuclear magnetic resonance (NMR) spectrum[4] has a singlet signal at δ 2.51 due to an N-methyl group. The ultraviolet (UV) absorption at 288.5 mμ (ε 7000) did not shift on addition of potassium hydroxide. Thus, it proved to be O,N-dimethyllythranidine (III).

O-Methyllythranidine (II) was subjected to oxidation with permanganate under the alkaline condition to yield acidic products, which were methylated by diazomethane. The mixture of methyl esters was chromatographed on alumina column to give a crystalline substance, mp 172—175°. Its NMR spectrum showed the signals of two methoxy groups (δ 3.81 and 3.87: each 3H, singlet) and a characteristic pattern for 1,2,4-substituted benzene as shown in Fig. 1. No signals other than those shown were recognized. A reasonable explanation for the foregoing NMR spectrum can be given only by an assumption that this compound must

Fig. 1. The NMR Spectrum of IV

1) Part I: E. Fujita, K. Bessho, K. Fuji, and A. Sumi, *Chem. Pharm. Bull.* (Tokyo), **18**, 2216 (1970).
2) For preliminary communication, see *Tetrahedron Letters*, **1967**, 4595.
3) Location: *Uji, Kyoto.*
4) The NMR spectra were taken with Varian A-60 (at 60 Mc) spectrometer for the $CDCl_3$ solutions, unless otherwise stated.

be a symmetrical diphenyl derivative which has two methoxy groups and two carbomethoxy groups. Thus, the apparent numbers of the protons described above should be doubled.

The NMR signal at δ 6.99 can be assigned to a hydrogen *ortho* to a methoxy group based on its chemical shift. Since the same signal is observed as a doublet (J=9 cps), another *ortho* position of this hydrogen is occupied by a hydrogen. Moreover, the both *meta* positions of the former hydrogen are substituted. The latter hydrogen shows a signal of doublet of doublets (J=9 and 2 cps), and the *meta* position of this hydrogen is occupied by a third hydrogen (Another *meta* position is substituted by a methoxy group). A doublet signal (J=2 cps) at δ 7.93 can be assigned to the third hydrogen. Accordingly, the crystalline product was assumed to be dimethyl 2,2′-dimethoxydiphenyl-5,5′-dicarboxylate or dimethyl 4,4′-dimethoxydiphenyl-3,3′-dicarboxylate.[5] The melting point of the product was identical with that of the former compound. A direct comparison of the compound with the authentic sample IV[6] confirmed the assumption to be correct. Thus, the presence of 2,2′-disubstituted diphenyl group in the alkaloid was proved.

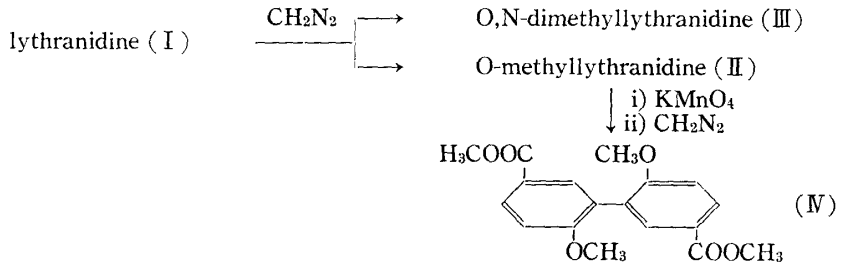


Chart 1

O,N-Dimethyllythranidine(III) methiodide was subjected to Hofmann degradation followed by catalytic hydrogenation to yield a product, whose methiodide was again subjected to Hofmann degradation followed by catalytic hydrogenation to afford a crude neutral product. The latter was purified by chromatography on a neutral alumina column to give des-N base V, $C_{27}H_{38}O_4$, mp 133.5—135°, which on oxidation with chromic anhydride–pyridine complex gave a product, mp 116—118°. The structure VI was assigned to this product, on the

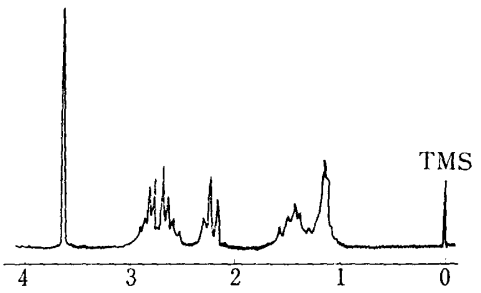


Fig. 2. The Spectrum of VI (100 Mc)

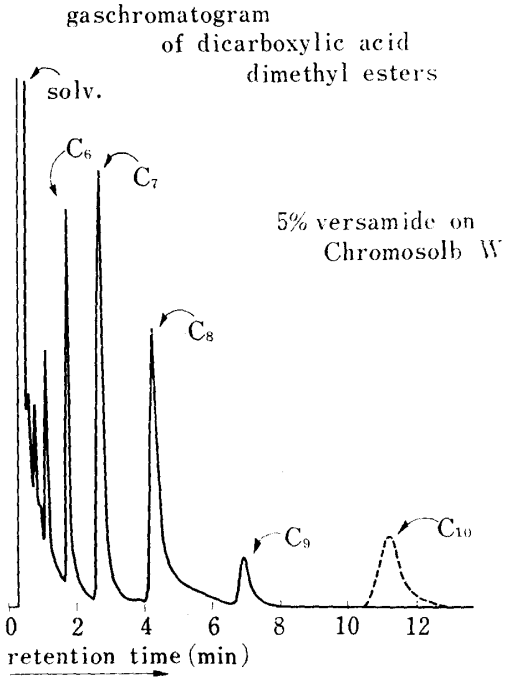


Fig. 3. Gas Chromatogram of Dimethyl Dicarboxylates obtained from VI

5) The melting point of this compound has not been reported.
6) K.V.J. Rao and L.R. Row, *J. Org. Chem.*, **25**, 981 (1960); K.P. Mathai and S. Sethna, *J. Indian Chem. Soc.*, **40**, 347 (1963).

basis of the following facts. (i) The infrared (IR) spectrum had an absorption at 1705 cm^{-1} due to carbonyl group (s), but no absorption due to hydroxyl group (s). (ii) In the NMR spectrum a four protons' signal centered at δ 2.83 was observed. The signal appeared as typical A_2B_2 type in the 100 Mc NMR spectrum (Fig. 2). These protons were assigned to those of benzyl methylene and adjacent active methylene (ph-C$\underline{H}_2$–C$\underline{H}_2$–CO–). (iii) As the triplet NMR signal (J=7 cps) of two protons at δ 2.32 was changed to a singlet on irradiation at δ 1.42, it was assigned to another active methylene protons (ph-CH_2–CH_2–CO–C$\underline{H}_2$–CH_2–). (iv) A complex signal which corresponded to five protons was recognized at δ 1.0—1.8 in the NMR spectrum. (v) It was proved by a molecular ion peak at m/e 422 ($C_{27}H_{34}O_4$) in the mass spectrum that the foregoing apparent numbers of the protons in the NMR spectra corresponded to a half, because of a completely symmetrical structure.

In order to confirm the assignment of the structure VI, a suspension of the compound in 10% sodium carbonate was oxidized with permanganate to give acidic products, which were methylated with diazomethane and subjected to analysis by gaschromatography. The chromatogram gave four peaks which corresponded to dimethyl esters of aliphatic straight chain dicarboxylic acids from C_6 (adipic acid) to C_9 (azelaic acid), but no peak assignable to the dimethyl ester of C_{10} dicarboxylic acid (sebacic acid), as shown in Fig. 3. The fact showed the presence of seven methylenes between two carbonyl groups in the molecule. Thus, des-N base can be represented as V, and O-methyllythranidine as VII, as shown in Chart 2.

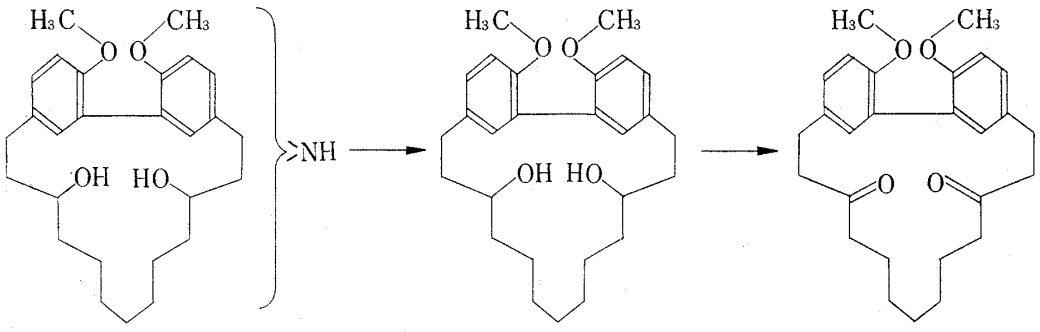
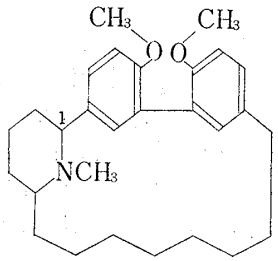


Chart 2

The remaining question is the size of the ring containing the imino group. Lythranine on dehydrogenation at 260° on paladium black gave an oily product, which was subjected to oxidation with permanganate to afford a mixture of carboxylic acids. It was esterified with diazomethane and then, separated into neutral and basic fractions. From the latter fraction, a hexane-soluble substance was crystallized. The pure crystals had mp 121—123°, and its mass spectrum gave the parent peak at m/e 195. Its comparison with an authentic sample of dimethyl dipicolinate (VIII) established their identity (mixed mp, IR and mass spectra, and gaschromatography). Thus, it was elucidated that the alkaloid contains a piperidine ring. Hence, the four possible structures, A, B, C, and D, can be assigned to O-methyllythranidine.

O,N-Dimethyllthranidine (III) on a reaction with phosphoryl chloride in pyridine gave an amorphous product, which was subjected to catalytic hydrogenation. The product was

chromatographed on neutral alumina column to give a crystalline substance IX, mp 168.5—170°, as a major product, and an amorphous substance X, as a minor product. The IR spectrum of IX showed no hydroxy absorption. The Beilstein reaction and mass spectrum showed the presence of chlorine in IX. The molecular formula $C_{28}H_{38}O_2NCl$ was reasonably assigned to IX, on the basis of analysis and mass spectrum. The monochloro-derivative IX was treated with sodium in isopropyl alcohol[7] to give bisdeoxy-O,N-dimethyllythranidine (XI), mp 127—129°. The minor product X was deduced to be dichloro-derivative in which the original two hydroxy groups were substituted, on the basis of no IR absorption of hydroxy groups and a positive Beilstein test. The reductive dehalogenation of X with sodium in *n*-propyl alcohol[7] yielded XI, which confirmed X to be a dichloro-derivative.

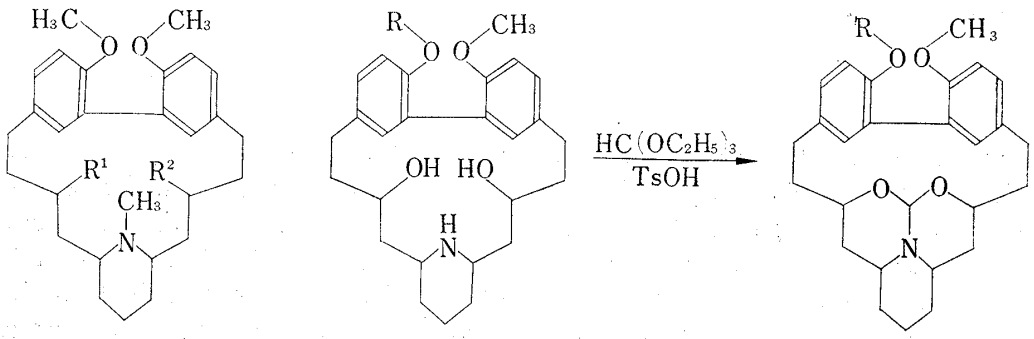


XII

Since the NMR spectra of lythranine, lythranidine and their derivatives gave no signal due to a methine proton between nitrogen and benzene ring, the formula C is least possible. If bisdeoxy-O,N-dimethyllythranidine were represented as XII based on C for O-methyllythranidine, C-1 proton's signal should be observed at a considerably low magnetic field in the NMR spectrum. Actually, however, no signal except a singlet signal of six protons due to two aromatic methoxy groups was observed between δ 3 and 6. Hence, the formula C is excluded.

O-Methyllythranidine was heated with ethyl orthoformate under reflux in the presence of *p*-toluenesulfonic acid to yield a crystalline product, mp 227.5—229.5°. The molecular formula $C_{28}H_{35}O_4N$ was reasonably assigned to the compound on the basis of analysis and mass spectrum. The IR absorption of 3300 cm^{-1} in O-methyllythranidine disappeared in this product. A singlet signal of one proton appeared at δ 5.26 in the NMR spectrum of the product. From these data, the formation of an amidoacetal on two hydroxy groups and an imino group was concluded. A similar reaction occurred with lythranidine. Thus, the acetic acid salt of lythranidine was allowed to react with orthoformate under reflux in the presence of *p*-toluenesulfonic acid to give lythranidine amidoacetal, mp 262—264°, whose molecular formula corresponded to $C_{27}H_{33}O_4N$. Its NMR spectrum also had a singlet signal at δ 5.29.

The easy formation of amidoacetal as such in both cases can be most reasonably explained by the formula A. The detailed investigation on space models, however, recognizes that



IX : $R^1=Cl, R^2=H$
X : $R^1=R^2=Cl$
XI : $R^1=R^2=H$

I : R=H (lythranidine)
II=VII=A : $R=CH_3$

XIII : R=H
XIV : $R=CH_3$

Chart 3

7) H.F.B. Hirschmann and M.A. Daus, *J. Biol. Chem.*, **178**, 751 (1949).

the formulas B and D can form amidoacetals only in the specific configurations. It is, therefore, difficult to exclude B and D without the following discussions, but the foregoing reaction can be represented on the basis of A as Chart 3.

As described in the preceding paper,[1] lythramine is completely identical with the product derived from lythranine and formalin. It has a structure in which a methylene bridge is built between the alcoholic hydroxy group and the imino group of lythranine and a new six-membered or larger ring is formed. On these considerations, the structure of lythramine is represented as XV-A, XV-B, or XV-D based on A, B, or D, respectively (Chart 4).

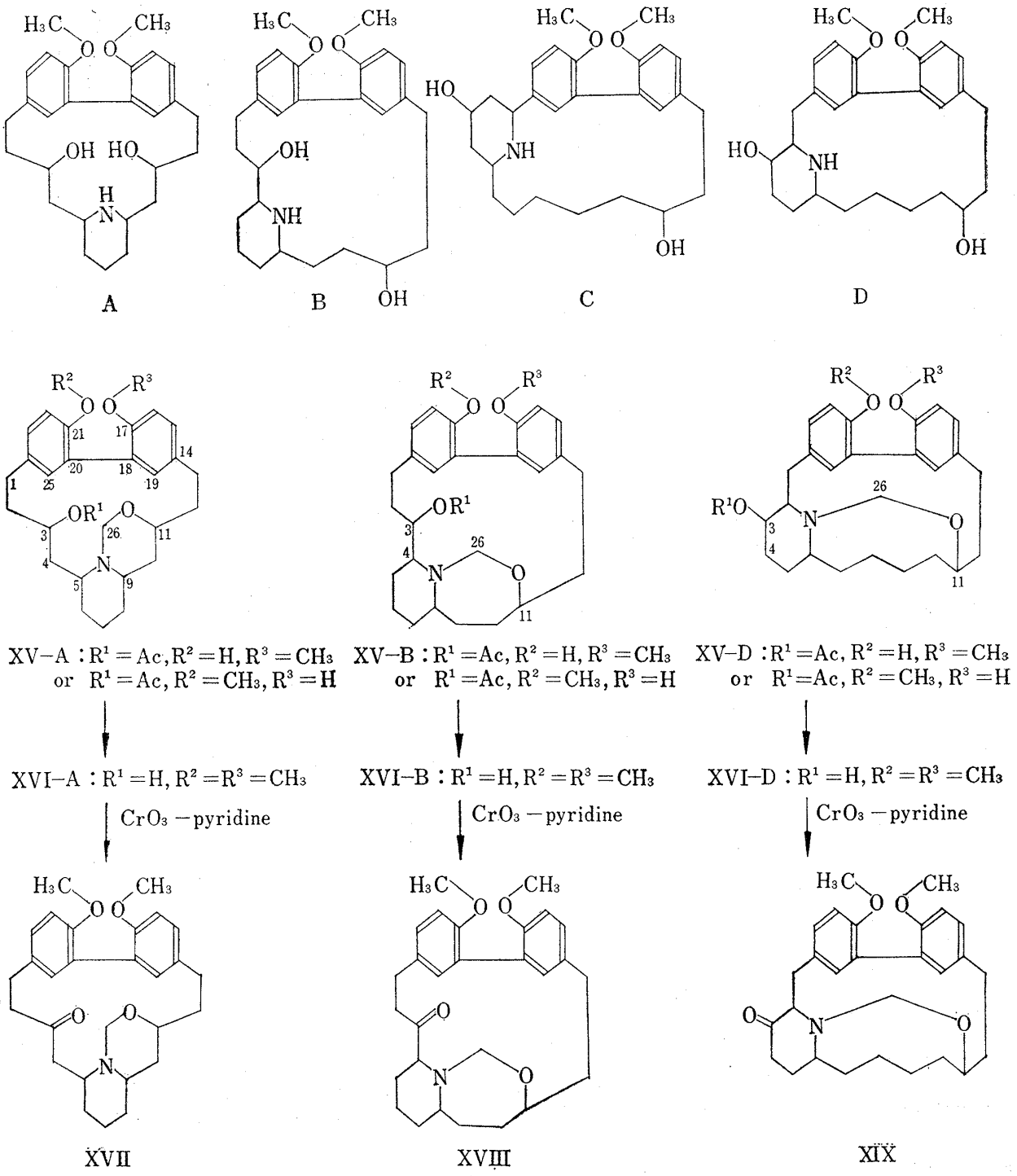


Chart 4

The NMR spectrum of lythramine taken by 100 Mc was investigated (Fig. 4). The multiplet signal of two protons at δ 4.80 is an overlapped pattern of the C-3-H signal and the one[8] of the AB-type signal of C-26 methylene. There are observed a multiplet signal due to C-11-H at δ 3.50, a multiplet signal of two protons due to >CH–N–CH< at δ 3.00, and a multiplet signal of four protons due to two benzyl groups at δ 2.70. In addition, another multiplet signal of two protons appears at δ 2.26. The spin decoupling experiment (Fig. 4) showed it to be coupled to C-3-H, and the latter to be coupled to protons signal at δ 1.42. Hence, the signal at δ 2.26 is assigned to two protons at C-4. The formula XV-B can not explain the foregoing data reasonably.

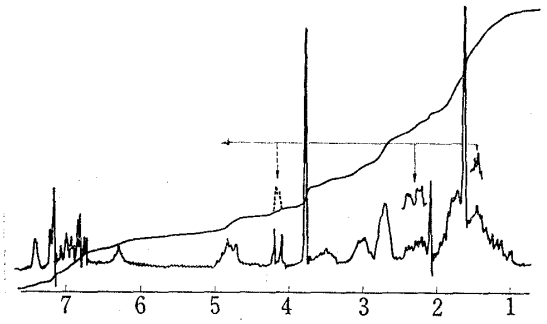


Fig. 4. The NMR Spectrum of Lythramine (100 Mc)

O-Methyldeacetyllythramine (XVI-A or XVI-B or XVI-D) was oxidized with chromic anhydride-pyridine complex to give a ketone, mp 245—247°, whose NMR spectrum gave an AB type signal due to C-26 methylene. The structure of the ketone is represented as XVII, XVIII, or XIX. While XVII has four active hydrogens, XVIII or XIX has only three. Then, the ketone was treated with sodium deuteroxide in deuterium oxide and deuteriomethanol (CH_3OD) to give a deuterized product,[9] whose mass spectrum gave the molecular ion peak at *m/e* 453, whilst that of the original ketone at *m/e* 449. Thus, it was clarified that the ketone has four active hydrogens. The reasonable assignment of the structure XVII to the ketone, therefore, the structure XV-A to lythramine, is achieved. Hence, the plane structure A is presented for O-methyllythranidine.

Experimental

Methylation of Lythranidine (I) with Diazomethane——To a solution of 248 mg of lythranidine in 15 ml of MeOH was added the ethereal solution of diazomethane and the mixture was allowed to stand overnight. A sample of the product gave a negative reaction with Millon test. Evaporation of the solvent and the chromatography of the residue on 10% deactivated alumina by elution of ether afforded 157 mg of non-crystalline O-methyllythranidine (II). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (broad), 1605, 1500. NMR δ_{ppm}: 3.26 (1H, m, >CHOH), 3.76 (6H, s, $OCH_3 \times 2$), 3.89 (1H, m, >CHOH), 4.69 (3H, br. s, >OH×2, >NH×1), 6.75—7.39 (6H, arom. H).

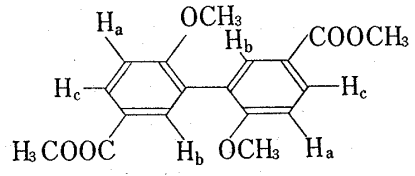
To a benzene solution of O-methyllythranidine (II) was introduced HCl gas to give precipitate which was recrystallized from EtOH twice. O-Methyllythranidine hydrochloride, mp 188—190° (decomp.) was shown to have 1 mole of benzene as the solvent of crystallization by its NMR spectrum. *Anal.* Calcd. for $C_{27}H_{37}O_4N \cdot HCl \cdot C_6H_6 \cdot 1\frac{1}{2}H_2O$: C, 68.20; H, 8.15; N, 2.41. Found: C, 68.07; H, 8.32; N, 2.60. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 3100, 1610, 1520, 1500. NMR δ_{ppm}: 3.72 (6H, s, $-OCH_3 \times 2$), 6.71—7.60 (6H, arom. H), 7.34 (6H, s, benzene).

In another experiment, to a solution of 513 mg of lythranidine in 30 ml MeOH was added the ethereal solution of diazomethane and the mixture was left for 2 days. After removal of the solvent, the syrupy residue was chromatographed on neutral alumina. Elution of benzene–$CHCl_3$ (1:1) afforded non-crystalline O,N-dimethyllythranidine which was again chromatographed on neutral alumina. Elution of MeOH–ether (1:19) afforded crystals which were recrystallized from ethyl acetate-isopropyl ether for three times to yield O,N-dimethyllythranidine, mp 167—169°. It was proved to be identical with O,N-dimethyllythranidine obtained from the reduction of O-methyllythramine with $LiAlH_4$ by comparison of IR spectra and TLC (alumina, 10% MeOH-$CHCl_3$) and mixture melting point determination.

Oxidation of O-Methyllythranidine with $KMnO_4$——To a suspension of 1.0 g of O-methyllythranidine in 20 ml of 2.5% aqueous Na_2CO_3 was added small amount of acetone. After 4.0 g of $KMnO_4$ was gradually added to the mixture over the period of 6 hr, the reaction mixture was stirred overnight. Resultant precipitate was filtered and extracted with warm aqueous Na_2CO_3 for four times. Filtrate and extract were combined, extracted with ether, and acidified with HCl followed by extraction successively with ether and

8) The other is observed at δ 4.13 as a doublet of $J=9$ cps.
9) D.H. Williams, J.M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963).

ethyl acetate. Evaporation of ether and ethyl acetate gave each 260 mg of complex mixture which showed a positive reaction with Dragendorff reagent. These mixtures were again subjected to oxidation with $KMnO_4$ in aqueous Na_2CO_3. The same treatment as above gave 283 mg of the acidic fraction which was methylated with diazomethane. The crude ester was chromatographed on neutral alumina with benzene to afford 59 mg of dimethyl 2,2′-dimethoxy-diphenyl-5,5′-dicarboxylate (IV), which was purified by recrystallization from MeOH for three times and distillation under the reduced pressure (1 mmHg) to yield analytical sample, mp 172—175°. *Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.78; H, 5.67. IR ν_{max}^{KBr} cm^{-1}: 1715, 1670 (sh.), 1510, 1495. NMR δ_{ppm}: 3.81 (6H, s, OCH_3), 3.87 (6H, s, OCH_3), 6.97 (2H, d, J=8.5 cps, Ha), 7.91 (2H, d, J=2 cps, Hb), 8.05 (2H, d, d, J=8.5, 2 cps, Hc). The substance was proved to be identical with the authentic sample by IR and NMR spectra and mixture melting point determination.



Hofmann Degradation of O,N-Dimethyllythranidine (III)——To a solution of 1.0 g of O,N-dimethyllythranidine (III) in 20 ml of MeOH was added 10 ml of methyl iodide and the solution was refluxed for 3.5 hr. After evaporation of the solvent the residual oil was dried over silica gel in a desicator *in vacuo* overnight. To the dried material, was added a solution of 1.3 g of potassium metal in 50 ml of anhydrous *t*-butanol, and the solution was heated under reflux for 11 hr. After addition of water and evaporation of *t*-butanol *in vacuo*, the reaction mixture was treated with water and $CHCl_3$. Chloroform layer was washed with water, dried, and evaporated to give 920 mg of oil which was chromatographed on neutral alumina. Elution with 10% $CHCl_3$–ether afforded 649 mg of an amorphous material which showed a single spot on TLC on neutral alumina. The substance on hydrogenation over PtO_2 in MeOH gave 651 mg of oily material which was refluxed in 100 ml of MeOH and 10 ml of methyl iodide to give a methiodide. It was again treated in the same way as described above to yield 433 mg of a neutral oil, which on hydrogenation gave 417 mg of oily product. The latter was chromatographed on neutral alumina. The ethereal eluate gave crystals which on recrystallizations from ether–heptane twice afforded 108 mg of des-N base V, mp 133.5—135°. *Anal.* Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 75.74; H, 9.09. IR ν_{max}^{KBr} cm^{-1}: 3400, 1610, 1505. UV λ_{max}^{MeOH}: 228 mμ (ε 4030). NMR δ_{ppm}: 2.72 (4H, t, J=7 cps, ph-C<u>H</u>$_2$–C<u>H</u>$_2$– ×2), 3.69 (2H, m, >C<u>H</u>OH ×2), 3.76 (6H, s, OCH_3 ×2), 6.82—7.28 (6H, arom. H).

Oxidation of Des-N Base V with Chromic Anhydride. Diketone VI——To 356 mg of des-N base V was added the complex prepared from 350 mg of chromic anhydride and 7 ml of pyridine. After standing overnight it was poured into ice–water and extracted with ether. The ether extract was washed successively with 5% HCl and water, dried over Na_2SO_4 and evaporated to give 311 mg of a crystalline mass which was crystallized from aqueous MeOH to yield 245 mg of needles. The mother liquor on chromatography on neutral alumina afforded another 8 mg of crystals. Combined crystals were recrystallized from aqueous MeOH for three times to give pure diketone VI, mp 116—118°. *Anal.* Calcd. for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.89; H, 8.20. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1605, 1500. NMR δ_{ppm}: 2.32 (4H, t, J=7 cps, –C<u>H</u>$_2$–CO– ×2), 2.83 (8H, m, –CO–C<u>H</u>$_2$C<u>H</u>$_2$-ph ×2), 3.74 (6H, s, OCH_3 ×2), (6.79—7.26 6H, arom. H). Mass Spectrum *m/e*:422 (M^+).

Oxidation of Diketone VI with $KMnO_4$——To a suspension of 85 mg of VI in water was slowly added 700 mg of $KMnO_4$. After stirring overnight $NaHSO_3$ was added to the mixture to give a clear solution, which was made alkaline and extracted with ether. Evaporation of ether gave a syrup whose thin-layer chromatography (TLC) on silica gel showed it to be the starting material VI. Aqueous layer was acidified with HCl and extracted with ethyl acetate to give 22 mg of acidic material. The latter on methylation with diazomethane gave a mixture of methyl esters, which was analyzed by gaschromatography on 5% Versamide at 150°. The chromatogram gave four peaks assigned to the dimethyl esters of adipic acid (r.t. 1.8 min), pimeric acid (r.t. 2.7 min), suberic acid (r.t. 4.3 min), and azelaic acid (r.t. 7.0 min). Another gaschromatogram on 10% SE-30 at 230° showed the identical peak with dimethyl 2,2′-dimethoxydiphenyl-5,5′-dicarboxylate (r.t. 4.7 min).

Dimethyl Dipicolinate (VIII)——Nine hundred and seventy-four mg of lythranine was well mixed with 500 mg of palladium black and dehydrogenated at 260° under reduced pressure of aspirator. After 2 hr the reaction mixture was extracted with $CHCl_3$ to yield 546 mg of syrup, 220 mg of which was suspended in aqueous dioxane and mixed with 2 g of $KMnO_4$. The mixture was stirred overnight at room temperature, then at 40° for 2 hr to complete the reaction. The resultant precipitate was filtered and extracted with warm 0.5% Na_2CO_3 solution. The combined mixture of the filtrate and extract was acidified with HCl and extracted with ethyl acetate to give 66 mg of an acidic mass, which was methylated with diazomethane in MeOH. The mixture of methyl esters was separated into 43 mg of a neutral fraction and 2.5 mg of a basic fraction. The latter was treated with hot hexane to yield crystals of mp 121—123° after cooling. The identity of the crystals with authentic dimethyl dipicolinate,[10] mp 121—123°, was established by the IR spectrum (ν_{max}^{KBr} 1740, 1575, 1290, 1245 cm^{-1}), mass spectrum (M^+ *m/e* 195), gaschromatography (r.t.

10) J.F. Powell, *Biochem. J.*, **54**, 210 (1953).

1.3 min QF-1, column temp. 160°), and mixture melting point determination.

Reaction of O,N-Dimethyllythranidine (III) with $POCl_3$——To a solution of 1.09 g of O,N-dimethyllythranidine (III) in 10 ml of pyridine was added 3 ml of $POCl_3$. The mixture was heated under reflux for 4 hr, poured into ice–water, made alkaline with Na_2CO_3, and extracted with $CHCl_3$ to yield 1.14 g of non–crystalline material. It was hydrogenated over 12% Pd–C in 100 ml of MeOH to give 1.01 g of syrup. Then, it was chromatographed successively on neutral alumina and silica gel to give 34 mg of amorphous dichloro–derivative X, whose TLC on silica gel showed its homogeneity, and 189 mg of crystalline monochloro-derivative IX, mp 156—163°. The latter was recrystallized from EtOH for three times to yield analytical sample, mp 168.5—170°. *Anal.* Calcd. for $C_{28}H_{38}O_2NCl$: C, 73.74; H, 8.40; N, 3.07; Cl, 7.78. Found: C, 73.90; H, 8.67; N, 2.81; Cl, 7.97. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1605, 1500. NMR δ_{ppm}: 2.33 (3H, s, >N–CH_3), 3.76 (6H, s, $OCH_3\times2$), 4.22 (1H, m, >CHCl), 6.80—7.27 (6H, arom. H). Mass Spectrum *m/e*: 455 : 457 (3 : 1)(M^+).

Reductive Dehalogenation of Monochloro-Derivative IX. Bisdeoxy-O,N-dimethyllythranidine (XI)——To a solution of 150 mg of IX in 20 ml of isopropyl alcohol was added 2.0 g of sodium piece by piece, and the mixture was heated at 50—80° for 20 min and refluxed for an additional hour. After addition of water, it was concentrated to remove isopropyl alcohol and extracted with ether after addition of water. The extract on usual treatment afforded amorphous substance, which was crystallized on treatment with EtOH. Recrystallization of the crystals (70 mg) from $CHCl_3$–EtOH gave bisdesoxy-O,N-dimethyllythranidine (XI), mp 127—129°. *Anal.* Calcd. for $C_{28}H_{39}O_2N$: C, 79.76; H, 9.32; N, 3.32. Found: C, 79.49; H, 9.60; N, 3.24. IR ν_{max}^{KBr} cm^{-1}: 1605, 1500. UV λ_{max}^{MeOH}: 187 mμ (ε 3820). NMR δ_{ppm}: 2.34 (3H, s, >N–CH_3), 2.68 (6H, m, >CH–N–CH<, ph-CH_2–$\times2$), 3.76 (6H, $OCH_3\times2$), 6.80—7.25 (6H, arom. H).

Reductive Dehalogenation of Dichloro-Derivative X——To a solution of 34 mg of X in 5 ml of *n*-propyl alcohol was added 600 mg of sodium piece by piece, and the mixture was heated under reflux for 1 hr. After addition of water, the mixture was concentrated *in vacuo* to remove *n*-propyl alcohol and treated with ether and water. The ethereal layer was washed and dried over $MgSO_4$. Evaporation of ether gave 23 mg of oily material which was crystallized on addition of small amount of XI. The crystals were recrystallized from MeOH–ethyl acetate to yield 13 mg of bisdeoxy-O,N-dimethyllythranidine (XI).

Amidoacetal XIV from O-Methyllythranidine (II)——A solution of 580 mg of O-methyllythranidine (II) in 20 ml of ethyl orthoformate was heated under reflux for 6 hr in the presence of 30 mg of TsOH. After addition of 100 ml of benzene, the solution was washed successively with NH_4OH and water, and dried over $MgSO_4$. Evaporation of the solvent afforded 492 mg of a mass partially crystallized. Addition of EtOH and filtration gave 255 mg of crystals. From their mother liquor, the second crop of crystals (79 mg) was obtained. Combined crystals were recrystallized twice from $CHCl_3$–EtOH to give pure amidoacetal XIV, mp 227.5—229.5°. *Anal.* Calcd. for $C_{28}H_{35}O_4N$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.81; H, 7.56; N, 3.21. IR ν_{max}^{KBr} cm^{-1}: 1610, 1580, 1500. NMR δ_{ppm}: 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.88 (2H, m, >CH–O–$\times2$), 5.26 (1H, s, $\begin{matrix}-O\\-O\end{matrix}$>CH–N), 6.76—7.95 (6H, arom. H).

Amidoacetal XIII from Lythranidine (I)——A solution of 500 mg of the acetic acid salt of lythranidine (I) in 20 ml of ethyl orthoformate was heated under reflux for 1.5 hr in the presence of 30 mg of TsOH. After addition of benzene the mixture was washed successively with aqueous Na_2CO_3 and water, and dried over $MgSO_4$. Evaporation of the solvent gave 510 mg of an oil which was chromatographed on neutral alumina. The ethereal eluate gave 78 mg of a crystalline mass which was recrystallized from MeOH–benzene to afford amidoacetal XIII, mp 262—264°. *Anal.* Calcd. for $C_{27}H_{33}O_4N$: C, 74.46; H, 7.64; N, 3.22. Found: C, 74.16; H, 7.66; N, 3.12. IR ν_{max}^{KBr} cm^{-1}: 3350, 1615, 1580, 1500. NMR δ_{ppm}: 3.88 (3H, s, OCH_3), 3.89 (2H, m, >CH–O–$\times2$), 5.29 (1H, s, $\begin{matrix}-O\\-O\end{matrix}$>CH–N), 6.77—8.17 (6H, arom. H).

Oxidation of O-Methyldeacetyllythramine (XVI-A) with CrO_3——One g of O-methyldeacetyllythramine (XVI-A) was added to the complex prepared from 1.0 g of CrO_3 and 10 ml of pyridine, and stirred overnight. The mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over $MgSO_4$. Evaporation of $CHCl_3$ gave 0.8 g of micro crystalline powder, which was recrystallized from $CHCl_3$–EtOH to afford 640 mg of XVII, mp 245—247°. *Anal.* Calcd. for $C_{28}H_{35}O_4N$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.92; H, 8.10; N, 2.94. IR ν_{max}^{KBr} cm^{-1}: 1705, 1605, 1505, 1495. NMR δ_{ppm} (at 100 Mc): 3.69 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.33, 4.27 (each 1H, AB type, $J=8$ cps), 6.64—7.26 (6H, arom. H). Mass Spectrum *m/e*: 449 (M^+).

Deuteration of XVII——A hundred and forty mg of XVII was dissolved in a solution of 100 mg of sodium in 15 ml of MeOD, followed by addition of 1 ml of D_2O. The solution was heated under reflux for 4 hr. Filtration of undissolved material and addition of D_2O to the filtrate gave crystals which were collected and washed with aqueous MeOH to afford, 57 mg of deutrated XVII, mp 247—249°. Mass Spectrum *m/e*: 453 (M^+).

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