[Chem. Pharm. Bull. 12 (9) 1012 ~ 1020] UDC 547.94[582.572.4]

139. Shinsaku Minami*1 and Shojiro Uyeo*2 : Galanthamine Chemistry. VI.*3 The Synthesis of Deoxydemethyllycoramine.

(*Research Laboratory, Dainippon Pharmaceutical Co., Ltd.*1 and *Faculty of Pharmaceutical Sciences, Kyoto University*2)

On the basis of degradative studies and physicochemical methods, we have previously shown that the structure of galanthamine is represented by the formula (I).[1,2]

Although Barton and Kirby[3] have recently published a total synthesis of galanthamine by an elegant route modelled along the lines of a biogenetic hypothesis, a structure proof by this sort of synthesis rests entirely upon the validity of the original degradative studies. We report here the synthesis by an unambiguous route of a derivative (II) of galanthamine which still contains the dihydrofuran, the hydroazepine, and the spirocyclohexane moieties of the original alkaloid.

As starting material we used 2-hydroxy-3-ethoxybenzaldehyde (III) which is commercially available as a by-product in the manufacture of ethylvanillin. Methylation of this with dimethyl sulfate and alkali followed by treatment with nitromethane in an alkaline solution afforded β-nitro-2-methoxy-3-ethoxystyrene (IV), which with butadiene in an autoclave according to the method described by Wildman and Wildman[4] gave 4-nitro-5-(2-methoxy-3-ethoxyphenyl)cyclohexene (V). A Nef reaction on this compound did not proceed smoothly and gave only 20% yield of 6-(2-methoxy-3-ethoxyphenyl)-3-cyclohexenone (VI) which exhibited an infrared absorption of a carbonyl group at 1710 cm^{-1}. On the other hand, when the nitrocyclohexene (V) was first reduced to the nitrocyclohexane (VII) and then submitted to the Nef reaction, 2-(2-methoxy-3-ethoxyphenyl)-cyclohexanone (VIII), identical with the hydrogenation product of VI, was isolated in 52% yield. Since a preliminary experiment indicated that cyanoethylation of the ketone (VIII) gave a mixture of mono- and disubstituted products, from which the monocyanoethyl derivative could not be separated satisfactory, it was necessary to protect the methylene group adjacent to the carbonyl in VIII by converting it into the benzylidene derivative (IX) which upon treatment with acrylonitrile gave the mono-cyanoethylated compound (X) in 84% yield.

Sodium borohydride reduction of X afforded the allylic alcohol (XI) which crystallized on long standing. In this reaction the possibility of some simultaneous saturation of the benzylidene double bond because of its conjugation with the ketonic group could not be ruled out. That, indeed, this took place to some extent giving rise to the saturated alcohol (XII) was revealed by observations made at a later stage of the synthesis (see below).

In an attempt at dealkylation, the alcohol (XI) was heated with pyridine hydrochloride at 200°. The obtained product analyzed for the formula corresponding to the hydroxyhexahydrodibenzofuran (XIII) and was in accord with its infrared spectrum and solubility in aqueous sodium hydroxide, although it gave a negative ferric chloride test. Although this product was the one which we had initially planned to prepare in two steps, its

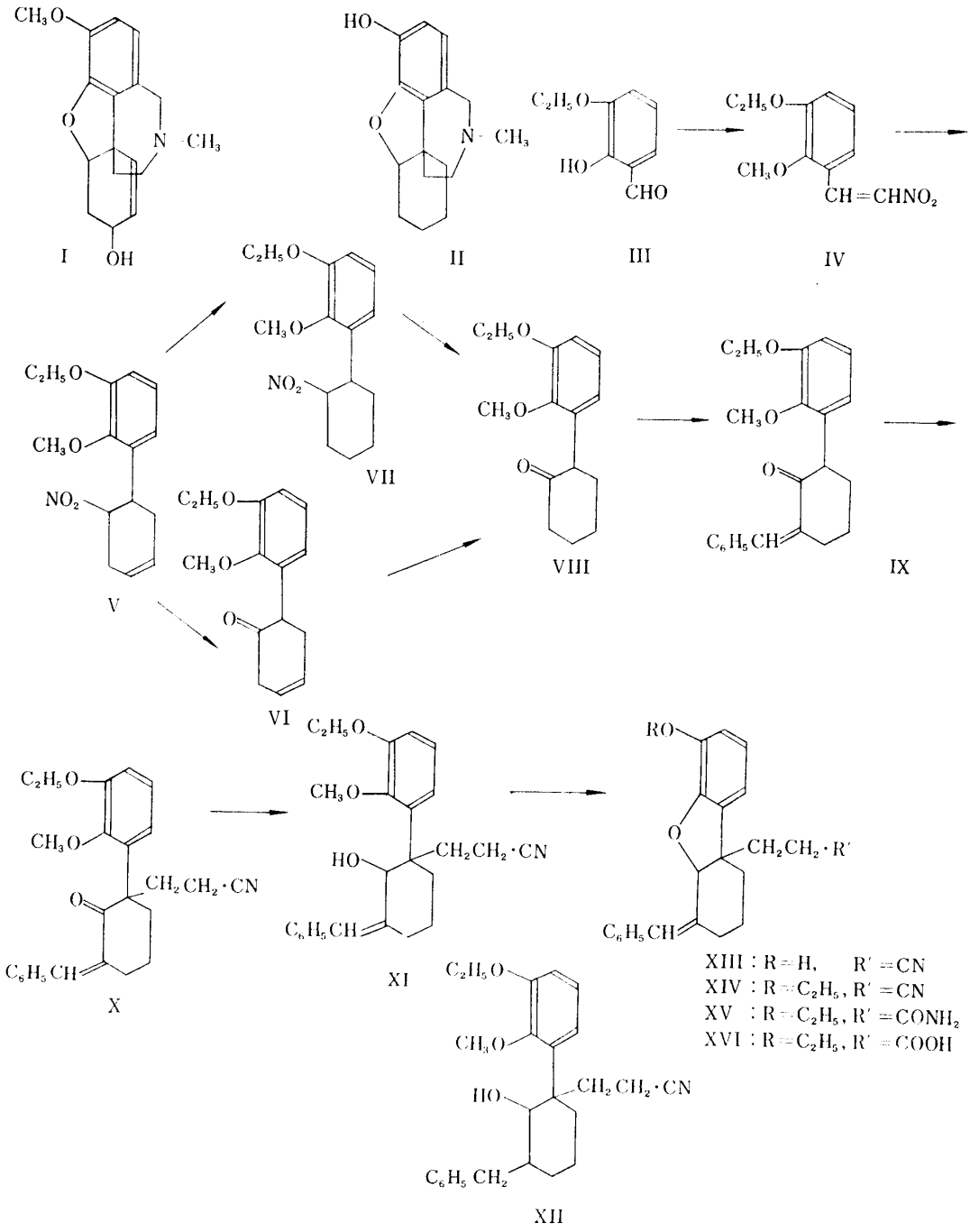
*1 Ebie, Fukushima-ku, Osaka (南 新作).
*2 Konoecho, Sakyo-ku, Kyoto (上尾庄次郎).
*3 Part V : This Bulletin, **12**, 696 (1964).

1) S. Uyeo : Handbook XVIth I.U.P.A.C. Congress, Paris, 1957, p. 207.
2) J. Koizumi, S. Kobayashi, S. Uyeo : This Bulletin, **12**, 696 (1964).
3) D.H.R. Barton, G.W. Kirby : Proc. Chem. Soc., **1960**, 392; J. Chem. Soc., **1962**, 806.
4) W.C. Wildman, R.B. Wildman : J. Org. Chem., **17**, 581 (1952).

isolation in a pure state was so tedious and the yield was so low (12%) that another approach was investigated.

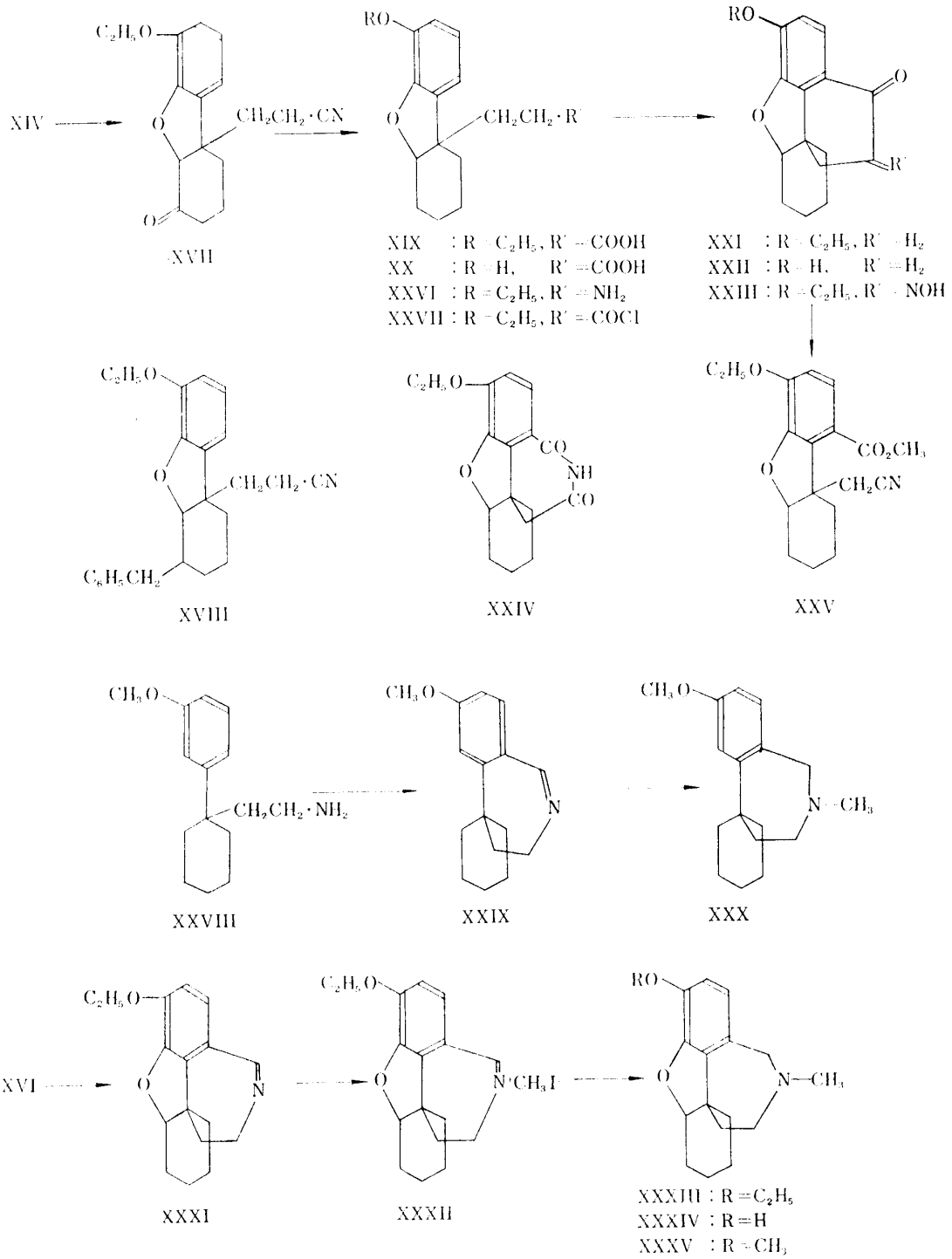
Treatment of the alcohol (XI) with phosphorus tribromide gave a good yield of a product which contained unexpectedly neither a bromine nor a hydroxyl group. Analysis indicated that the compound was represented by the formula (XIV) containing an oxide ring and an ethoxyl group. This structure was proved by converting it into the deethylated compound upon heating with pyridine hydrochloride. The phenol thus obtained was identical with the compound (XIII) already obtained above.

The same phenolic compound was also isolated as a minor by-product when the mother liquors from the ethoxy-compound (XIV) were chromatographed on acid-washed alumina. Also obtained was the amide (XV) identified by a direct comparison with the



product prepared by hydrolysis of the nitrile (XIV) to the acid (XVI) followed by treatment with thionyl chloride and then with aqueous ammonia.

Oxidation of XIV with ozone or preferably with potassium permanganate under mild conditions gave the ketone (XVII) which exhibited a carbonyl band at 1720 cm^{-1} and a nitrile absorption at 2240 cm^{-1} in the infrared spectrum, and was characterized as its semicarbazone. When a crude sample of the allylic alcohol (XI) was used for oxide ring formation and the resulting product consisting mainly of XIV was oxidized, a saturated compound, $C_{24}H_{27}O_2N$, was isolated together with the ketone (XVII). Since this non-ketonic compound was found to be identical with the hydrogenation product (XVIII) of the



benzylidene derivative, some saturation of the benzylidene double bond must have occurred during the treatment of α,β-unsaturated ketone (X) with sodium borohydride, as mentioned above.

Reduction of the carbonyl group in XVII by the Huang-Minlon modification of the Wolff-Kishner method gave the carboxylic acid (XIX) as a result of concomitant saponification of the cyano group in the alkaline medium. A by-product in this reaction was the O-deethylated carboxylic acid (XX), since treatment of the crude Wolff-Kishner product with polyphosphoric acid afforded, along with the expected cyclohexanone (XXI), a small amount of a phenolic ketone (XXII) whose structure was secured by ethylation with diazoethane to afford the cyclohexanone (XXI). A similar partial dealkylation of an alkoxyl group during the course of Wolff-Kishner reaction has previously been observed by Gates and Tschudi.[5]

The initial attempt to enlarge the six-membered ring in XXI was to carry out a Beckmann rearrangement of the isonitroso derivative (XXIII) but the product obtained was the nitrile (XXV) rather than the desired XXIV. An alternative route to a benzazepine would be an application of the Bischler-Napieralski or the Pictet-Spengler reaction, but since no precedent was found in the literature, the possibility of preparation of the amine (XXIX) was first examined using the more readily available 1-(*m*-methoxyphenyl)-cyclohexanepropylamine (XXVIII)[6] as a model. As reported in a separate paper by Tomita and Minami,[7] while the Pictet-Spengler reaction on this compound was unsuccessful under the conditions used by them, treatment of the formate of this amine (XXVIII) with phosphorus pentoxide in boiling toluene gave the expected benzazepine (XXIX) in 12.3% yield, which was characterized as its hydrochloride and the methiodide. The base regenerated from the hydrochloride showed an infrared absorption of a C=N double bond at 1647 cm^{-1} and bands at 883 and 820 cm^{-1} assigned to 1,2,4-trisubstituted benzene ring. The methiodide exhibited two strong ultraviolet absorption bands at 240 and 322 mμ in accord with the expected structure and gave on sodium borohydride reduction a base (XXX) whose hydrochloride showed in the ultraviolet absorption spectrum bands at 273 and 280 mμ characteristic of an isolated benzene ring.

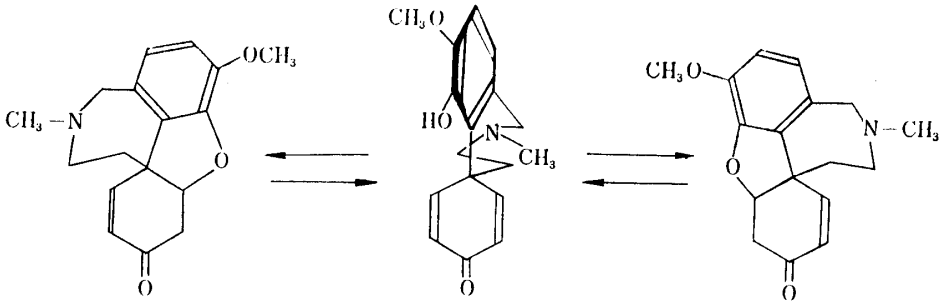
In view of this successful model experiment, we carried out the Bischler-Napieralski reaction on the amine (XXVI) prepared from the acid (XIX) by a Curtius reaction. It gave a base (XXXI) characterized as its methiodide. The infrared spectrum of this methiodide (XXXII) exhibited absorptions at 1660 cm^{-1} (C=N) and 869 and 800 cm^{-1} (1,2,3,4-tetrasubstituted benzene ring) and the ultraviolet spectrum showed bands at 256 and 318 mμ in agreement with the expected structure. Reduction of the methiodide (XXXII) with sodium borohydride afforded a base (XXXIII) which was isolated as its perchlorate. The ultraviolet spectrum of this salt exhibited a band at 288 mμ (ε 3160) corresponding to an alkoxybenzene derivative. Finally the oily base (XXXIII) was deethylated with 48% hydrobromic acid to give a phenol (XXXIV), $C_{16}H_{21}O_2N$, m.p. 225~226°.

That the compound thus obtained was identical with deoxydemethyllycoramine (XXXIV) from the natural sources was established not only by comparison of the respective infrared spectra in chloroform, but also by a mixed melting point determination and identity of the infrared spectra of the synthetic sample and the racemic deoxydemethyllycoramine derived from galanthamine as follows. It has been shown previously[2] that *levo*-rotatory natural galanthamine gave a racemic ketone, *dl*-galanthaminone (XXXVIIa, b) upon manganese dioxide oxidation. The explanation*4 for this result lay in the

*4 We are indebted to Dr. W. I. Taylor (CIBA Pharmaceutical Co., Summit, New Jersey, U. S. A.) for this suggestion and valuable discussions in a private communication (July 2, 1956).

5) M. Gates, G. Tschudi : J. Am. Chem. Soc., 78, 1380 (1956).
6) T. Takahashi, M. Hori, A. Kanbara : This Bulletin, 7, 917 (1959).
7) M. Tomita, S. Minami : Yakugaku Zasshi, 83, 1022 (1963).

realization that the facile racemization was the result of an equilibrium between the initial oxidation product (XXXVIIa), its symmetrical retro-Michael product, the dienone (XXXVI) and its optical antipode (XXXVIIb).



XXXVIIa XXXVI XXXVIIb

Hydrogenation of the double bond in *dl*-galanthaminone and subsequent removal of the carbonyl group by the Wolff-Kishner method gave racemic deoxylycoramine (XXXV) which on treatment with hydrobromic acid furnished *dl*-demethyldeoxylycoramine (XXXIV), m.p. 225~226°, identical in all respects with the synthetic sample obtained above.

Experimental

β-Nitro-2-methoxy-3-ethoxystyrene (IV)——A solution of 2-methoxy-3-ethoxybenzaldehyde (18 g.) and nitromethane (6.2 g.) in hot EtOH (70 ml.) was cooled to −10° and despite of separation of crystals a solution of KOH (7.4 g.) in EtOH (22 ml.) and H_2O (13 ml.) was added dropwise with stirring, maintaining the temperature below 0° by cooling in a freezing mixture. When a small sample of the mixture became completely soluble in H_2O, the whole was poured into ice-cold *N* H_2SO_4 (330 ml.) and the precipitate which formed was collected and crystallized from MeOH to give the nitrostyrene (IV) (21 g.) as yellow needles, m.p. 77~78°. *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.22; H, 5.82; N, 6.14.

4-Nitro-5-(2-methoxy-3-ethoxyphenyl)cyclohexene (V)——A solution of the nitrostyrene (IV) (44 g.), butadiene (80 g.), and a trace of hydroquinone in toluene (150 ml.) was heated in an autoclave at 110~120° for 75 hr. The mixture was evaporated to dryness under reduced pressure and the residue crystallized from MeOH to give the cyclohexene (V) as needles (48.5 g.), m.p. 104~105°. *Anal.* Calcd. for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.71; H, 6.84; N, 4.78.

6-(2-Methoxy-3-ethoxyphenyl)-3-cyclohexenone (VI)——A solution of the nitrocyclohexene (V) (2.8 g.) in EtOH-EtONa prepared from Na (0.46 g.) in EtOH (50 ml.) was added dropwise with stirring to a mixture of conc. HCl (12 ml.), EtOH (100 ml.), and H_2O (120 ml.) at 0°. Stirring was continued at 0° for 1 hr. and at room temperature for an additional 2 hr. H_2O (300 ml.) was added to the mixture and the whole extracted with Et_2O (300 ml.).

The ethereal extract was washed with aq. Na_2CO_3, and H_2O, dried and evaporated to give a yellowish brown oil. Trituration with MeOH gave the cyclohexenone (VI) (0.5 g.) as needles, m.p. 86° (from MeOH), IR: ν_{max}^{KBr} 1710 cm^{-1} (C=O). *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.82; H, 7.34.

1-(2-Methoxy-3-ethoxyphenyl)-2-nitrocyclohexane (VII)——The nitrocyclohexene (V) (15 g.) in dioxane (70 ml.) was catalytically hydrogenated in the presence of Adams catalyst (0.2 g.) at room temperature under atmospheric pressure until H_2 uptake ceased (1.3 L.). The catalyst was filtered off, the solvent evaporated under reduced pressure, and the residue crystallized from MeOH to give the nitrocyclohexane (VII) (14.1 g.) as needles, m.p. 94°. *Anal.* Calcd. for $C_{15}H_{21}O_4N$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.51; H, 7.52; N, 4.86.

2-(2-Methoxy-3-ethoxyphenyl)cyclohexanone (VIII)——1) The nitrocyclohexane (VII) (5.6 g.) was added to a solution of Na (1 g.) in EtOH (110 ml.) and kept at room temperature for 1 hr. until all crystals disappeared. The solution was added dropwise to a stirred mixture of conc. HCl (24 ml.), H_2O (240 ml.) and EtOH (200 ml.) at 0°. Stirring was continued for 1 hr. at 0° and a further 3 hr. at room temperature. After dilution of the mixture with an equal amount of H_2O followed by extraction with AcOEt, the organic layer was washed with aq. Na_2CO_3, and H_2O, dried and evaporated to give an oil which on

distillation at 128～130°(bath-temp.)/0.005 mm. gave the ketone (Ⅷ) as a crystalline mass, m.p. 40°, IR : ν_{max}^{liquid} 1709 cm^{-1}(C=O). *Anal.* Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found : C, 72.34; H, 7.94. The semicarbazone had m.p. 175～176°(from MeOH). *Anal.* Calcd. for $C_{16}H_{23}O_3N_3$: C, 62.93; H, 7,59; N, 13.76. Found : C, 63.00; H, 7.62; N, 13.69.

2) The cyclohexenone (Ⅵ) (1 g.) in EtOH (20 ml.) was catalytically hydrogenated in the presence of 10% Pd-C (50 mg.) at room temperature and atmospheric pressure. The catalyst was removed by filtration, the filtrate evaporated, and the oily residue was distilled at 128～130°(bath-temp.)/0.005 mm. to give the hexanone (Ⅷ) (0.95 g.), identical with the product of the same structure obtained above.

2-Benzylidene-6-(2-methoxy-3-ethoxyphenyl)cyclohexanone (IX)——The cyclohexanone (Ⅷ) (5.8 g.) and benzaldehyde (3 ml.) in MeOH (27 ml.) containing NaOH (1.8 g.) were kept at room temperature for 2 days. The crystals which separated during the time was collected and washed with MeOH. The benzylidene derivative (Ⅸ) was recrystallized from MeOH to give prisms, m.p. 80° (5.4 g.), IR : ν_{max}^{Nujol} 1665 cm^{-1} (conjugated C=O). *Anal.* Calcd. for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found : C, 78.32; H, 7.10.

1-(2-Methoxy-3-ethoxyphenyl)-2-oxo-3-benzylidene)cyclohexanepropionitrile (X)——The benzylidene derivative (Ⅸ) (7 g.), acrylonitrile (2 ml.) and MeONa (0.2 g.) in benzene (30 ml.) were heated on a water bath for 1.5 hr. After cooling, the benzene layer was washed with dilute AcOH and H_2O, dried and evaporated to give the oxocyclohexanepropionitrile derivative (X) (6.5 g.) as prisms, m.p. 135°(from MeOH), IR ν_{max}^{Nujol} cm^{-1} : 2230 (C≡N), 1675 (conjugated C=O). *Anal.* Calcd. for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found : C, 76.93; H, 6.77; N, 3.97.

1-(2-Methoxy-3-ethoxyphenyl)-2-hydroxy-3-benzylidenecyclohexanepropionitrile (XI)——To the oxocyclohexanepropionitrile (X) (2 g.) in tetrahydrofuran (40 ml.) was added a solution of $NaBH_4$ (0.5 g.) in H_2O (2 ml.) and the whole kept at room temperature overnight. After acidification with AcOH, the mixture was concentrated, diluted with H_2O, and extracted with AcOEt. The extract was washed with H_2O, dried and evaporated to dryness giving an oil which crystallized on long standing to give the hydroxy cyclohexanepropionitrile (Ⅺ) (2 g.), m.p. 113～114°, prisms from absolute EtOH, IR ν_{max}^{KBr} cm^{-1} : 3450 (OH), 2240 (C≡N). *Anal.* Calcd. for $C_{25}H_{29}O_3N$: C, 76.69; H, 7.47. Found : C, 76.56; H, 7.60. The hydrate had m.p. 65～67°(from 94% EtOH). *Anal.* Calcd. for $C_{25}H_{29}O_3N \cdot H_2O$: C, 73.32; H, 7.63. Found : C, 73.30; H, 8.16.

4-Benzylidene-6-hydroxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XIII)——An intimate mixture of the cyclohexanol (Ⅺ) (0.4 g.) and pyridine·HCl (3 g.) was heated under N_2 in an oil bath at 200°. After cooling, 10% aq. NaOH (20 ml.) was added and the whole was washed with Et_2O (50 ml.). The ethereal washings were extracted with 5% aq. NaOH. The alkaline aqueous layer and the aqueous extract were combined and acidified with dil. HCl, and the oil which separated was taken up in $CHCl_3$ (70ml.). The $CHCl_3$ extract was washed with satd. aqueous NaCl, dried and evaporated to give an oil (0.1 g.) which was chromatographed in benzene over acid-washed Al_2O_3 (10 g.). The benzene-AcOEt (5:1) eluate gave the hexahydrodibenzofuran (XIII) (0.09 g.) which crystallized from benzene as needles, m.p. 162～162.5°, IR ν_{max}^{KBr} cm^{-1} : 3400 (OH), 2250 (C≡N). *Anal.* Calcd. for $C_{22}H_{21}O_2N$: C, 79.73; H, 6.39; N, 4.23. Found : C, 79.58; H, 6.32; N, 4.33.

4-Benzylidene-6-ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XIV)——A mixture of the cyclohexanol (Ⅺ) (1 g.) and freshly distilled phosphorus tribromide (2 ml.) was warmed on a water bath for 30 min. The gelatinous reaction mixture was concentrated under reduced pressure at 100° to remove the excess phosphorus tribromide, and the residue was dissolved in Me_2CO (30 ml.). The Me_2CO solution was poured into ice water and the white crystalline substance deposited was taken up in AcOEt (50 ml.). The AcOEt solution was washed with 10% aq. Na_2CO_3, and satd. aqueous NaCl, dried and evaporated to give a yellowish brown oil. Trituration with MeOH gave the hexahydrodibenzofuran (XIV) (0.6 g.) which crystallized from MeOH as needles, m.p. 134～135°, UV : λ_{max}^{EtOH} 243 mμ (ε 21,900). *Anal.* Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01; N, 3.90; OC_2H_5, 12.54. Found : C, 80.05; H, 6.83; N, 4.17; OC_2H_5, 12.54. Chromatography of the mother-liquors from the above product in benzene over alumina, and elution of the column with benzene (100 ml,) gave XV as prisms, m.p. 166～167°, which was identical with an authentic sample as obtained below. Further elution with $CHCl_3$ (200 ml.) gave XIII as needles, m.p. and mixed m.p. 160°.

Deethylation of XIV——An intimate mixture of the ethoxyhexahydrodibenzofuran (XIV) (1 g.) and the freshly prepared pyridine·HCl (6 g.) was heated under N_2 in an oil bath at 200°. After cooling, 5% aq. NaOH (30 ml.) was added to the reaction mass, the mixture washed with Et_2O and ethereal layer again washed with 5% aq. NaOH (10 ml.). The alkaline solution and the washings were combined, acidified with dil. HCl and the resulting phenolic product was taken up in AcOEt (50 ml.). The AcOEt extract was washed thoroughly with saturated aqueous solution of NaCl, dried (Na_2SO_4) and evaporated to give XIII which on crystallization from benzene formed needles (0.06 g.), m.p. and mixed m.p. 163°.

4-Benzylidene-6-ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionic Acid (XVI)——A mixture of the tetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XIV) (1.4 g.), diethylene glycol (30 ml.) and 30% aq. NaOH (10 ml.) was heated under reflux for 7 hr. After cooling, the reaction mixture was diluted with H_2O, washed with Et_2O, acidified with dil. HCl and the oil which separated was taken up in AcOEt.

The extract was washed with saturated aqueous solution of NaCl, dried (Na_2SO_4) and evaporated, to give a crystalline mass, which on recrystallization from MeOH gave the acid (XVI) (1.2 g.) as prisms, m.p. 141~142°. *Anal.* Calcd. for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found : C, 75.98; H, 6.93.

4-Benzylidene-6-ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionamide (XV)——The acid (XVI) (0.35 g.) obtained above was warmed with freshly distilled $SOCl_2$ (2 ml.) at 70~80° for 30 min. After removal of the excess $SOCl_2$ under reduced pressure, the remaining acid chloride was dissolved in dry tetrahydrofuran (10 ml.) and the solution was added dropwise with stirring to 23% aq. NH_3 (10 ml.) at 0°. Stirring was continued at room temperature for 1.5 hr. and the mixture was extracted with AcOEt (30 ml.). The extract was washed with 5% aq. Na_2CO_3, and satd. aqueous NaCl, dried and evaporated. Chromatography of the resulting oil (0.2 g.) in benzene on acid-washed Al_2O_3 (10 g.) and elution with benzene (300 ml.) gave the acid-amide (XV) which was crystallized from MeOH as prisms, m.p. 166~167°, (0.18 g.). *Anal.* Calcd. for $C_{24}H_{27}O_3N \cdot \frac{1}{2}H_2O$: C, 74.59; H, 7.25. Found : C, 74.38; H, 7.09.

4-Oxo-6-ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XVII)——a) By oxidation with $KMnO_4$: The benzylidenetetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XIV) (2 g.) in Me_2CO (150 ml.) containing a few drops of H_2O was oxidized by adding in portions powdered $KMnO_4$ (2 g.) at 5~7° during 5 hr. and the mixture was kept at 7° overnight. After acidification with dil. H_2SO_4, aq. $NaHSO_3$ was added to the mixture until the precipitated MnO_2 dissolved, and the mixture was concentrated under reduced pressure to dryness. The resulting oily residue was taken up in AcOEt (50 ml.), which was washed with 10% aq. Na_2CO_3 (30 ml.) and satd. aqueous NaCl, dried (Na_2SO_4) and evaporated to give an oil (1.6 g.) which was chromatographed in $CHCl_3$ on SiO_2 gel. The first $CHCl_3$ eluate which gave a negative Zimmermann test afforded the unchanged starting material (XIV) (0.6 g.). The second $CHCl_3$ eluate showed a positive Zimmermann test and gave the ketone (XVII) which crystallized from MeOH as prisms, m.p. 149~150° (0.6 g.), UV : λ_{max}^{EtOH} 278 mμ (ε 1600). *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found : C, 71.20; H, 6.70; N, 5.01. The semicarbazone had m.p. 227° (decomp.), from MeOH. *Anal.* Calcd. for $C_{18}H_{22}O_3N_4$: C, 63.14; H, 6.48; N, 16.36. Found : C, 63.01; H, 6.52; N, 16.40.

b) By oxidation with ozone : The benzylidenetetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XIV) (2 g.) in CH_2Cl_2 (20 ml.) and MeOH (10 ml.) was ozonized by introducing 4.5 L O_2 stream containing O_3 (32 mg./L) at −70° in a dry ice-acetone-bath. Triethylphosphite was added at −70° and the mixture was kept at room temperature overnight. The solvents were removed under reduced pressure, the clear oily residue was dissolved in $CHCl_3$, and the organic layer was washed with dil. aqueous $NaHCO_3$ and evaporated, to give an oil (0.8 g.) which was chromatographed in $CHCl_3$ on SiO_2 gel (10 g.). The first $CHCl_3$ eluate gave the unchanged starting material (XIV) (0.3 g.) and the second $CHCl_3$ eluate afforded the ketone (XVII) (0.2 g.) as prisms, m.p. and mixed m.p. 149~150° (from MeOH).

Since at first the cyclohexanol (XI) was not obtained crystalline, a crude oily sample (XI) was treated with PBr_3 to give the benzylidenedibenzofuran (XIV) which in contrast to the pure sample had m.p. 127~129° and ε 13,800 at 243 mμ after repeated crystallization from MeOH. When this sample (2 g.) was oxidized with $KMnO_4$ and worked up in the same manner as mentioned above, there was obtained, along with the ketone (XVII) (0.6 g.), a compound (0.02 g.), m.p. 118°, UV : λ_{max}^{EtOH} 280 mμ (ε 2,400), which was identical in all respects with a sample of 4-benzyl-6-ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionitrile (XVIII), m.p. 118°, prepared by hydrogenation of the benzylidene derivative (XIV) by the usual method. *Anal.* Calcd. for $C_{24}H_{27}O_2N$: C, 79.74; H, 7.53; N, 3.88; OC_2H_5, 12.54. Found : C, 79.04; H, 7.62; N, 3.68; OC_2H_5, 12.54.

6-Ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-propionic Acid (XIX)——A mixture of XVII (1 g.), 80% hydrazine hydrate (0.5 ml.) and diethylene glycol (8 ml.) was heated in an oil bath at 160~170° for 1 hr. After cooling, KOH (1 g.) was added and the mixture was again heated at 190° for a further 2 hr., then poured onto ice and washed with Et_2O to remove water-insoluble material. Acidificatioh of the alkaline layer with dil. HCl deposited crystals which were extracted with AcOEt. The extract was washed with satd. aqueous NaCl, dried (Na_2SO_4) and evaporated, to give a crystalline mass which on recrystallization from MeOH afforded the acid (XIX) (0.6 g.) as prisms, m.p. 128°. *Anal.* Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found : C, 70.07; H, 7.64.

6-Ethoxy-2,3,4,4*a*-tetrahydro-1*H*-9,9*b*-(1-oxopropano)dibenzofuran (XXI)——A mixture of XIX (0.045 g.) and polyphosphoric acid, prepared from phosphorus pentoxide (1 g.) and 85% phosphoric acid (0.6 ml.) at 100°, was heated on a water bath for 2 hr. The mixture was poured into ice water and the whole extracted with AcOEt (50 ml.). The extract was washed with 10% aq. Na_2CO_3 to remove acidic material, dried and evaporated, to give the ketone (XXI) which was crystallized from MeOH as prisms, m.p. 147.5° (0.023 g.), UV λ_{max}^{EtOH} mμ (ε) : 238 (21,000), 286 (10,500), 318 (7,080). *Anal.* Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.71; H, 7.24. When the crude oily acid (XIX) (0.8 g.) prepared from XVII was directly treated with polyphosphoric acid and worked up in the same manner as mentioned above, there was obtained, after chromatography over acid-washed alumina, the phenolic product (0.02 g.) (XXII) (from $CHCl_3$ eluate), along with the ketone (0.45 g.) (XXI) (from benzene eluate). The phenolic compound (XXII) was recrystallized from AcOEt as prisms, m.p. 198°, IR ν_{max}^{KBr} cm^{-1} : 3300 (OH), 1660

(conjugated C=O), UV λ_{max}^{EtOH} mμ (ε): 238 (20,000), 288 (7,950), 316 (5,020). *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.66; H, 6.89. This was treated with ethereal diazoethane to give 6-ethoxy-2,3,4,4*a*-tetrahydro-1*H*-9,9*b*-(1-oxopropane)dibenzofuran (XXI), m.p. 145°, which was identical in all respects with the sample (XX) obtained above.

6-Ethoxy-2,3,4,4*a*-tetrahydro-1*H*-9,9*b*-(1-oxo-2-hydroxyiminopropano)dibenzofuran (XXIII)——To a stirred solution of metallic K (0.2 g.) in dry Me_3COH (4 ml.), and dry Et_2O (2 ml.), was added the ketone (XXI) (0.5 g.) in portions at room temperature during 30 min. After the addition of isoamyl nitrite (0.5 ml.), the mixture was stirred for a further 3 hr. and kept overnight. The solution was diluted with H_2O (15 ml.), acidified with dil. AcOH, and evaporated under reduced pressure. The residue was extracted with AcOEt and the extract was washed with satd. aqueous NaCl, dried, and evaporated to give the hydroxyimino-compound (XXIII) (0.35 g.) as pale yellow prisms, m.p. 229° (decomp.) (from AcOEt). *Anal.* Calcd. for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.50; H, 6.26; N, 4.52.

Methyl 6-Ethoxy-9*b*-cyanomethyl-1,2,3,4,4*a*,9*b*-hexahydrodibenzofuran-9-carboxylate (XXV)——The foregoing oximino-compound (0.1 g.) (XXIII) was added in portions to a freshly distilled $SOCl_2$ at 0°. The mixture was stirred for 1 hr. at room temperature and evaporated to dryness under reduced pressure to remove the excess $SOCl_2$. The residue was dissolved in MeOH (5 ml.) which was kept at 40° for 30 min. and evaporated. Chromatography of the residue (0.08 g.) in benzene over Al_2O_3 (5 g.) and elution with benzene (100 ml.) gave the abnormal Beckmann rearrangement product (XXV) as prisms, m.p. 123~124°, (from light petroleum), IR ν_{max}^{KBr} cm^{-1}: 2240 (C≡N), 1610 (C=O). UV λ_{max}^{EtOH} mμ (ε): 257 (7,080), 299 (5,370). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71. Found: C, 68.33; H, 6.66.

6-Ethoxy-2,3,4,4*a*-tetrahydro-1*H*-dibenzofuran-9*b*-ethylamine (XXVI)——The tetrahydro-1*H*-dibenzofuran-9*b*-propionic acid (XIX) (0.5 g.) was added with stirring to an excess of freshly distilled $SOCl_2$ (20 ml.) at 0° and the whole was heated on a water bath for 30 min. The excess $SOCl_2$ was removed under reduced pressure, dry benzene was added to the residue, and the solution was again evaporated to dryness under a vacuum. To a chilled solution of the resulting acid chloride (XXVII) in dry tetrahydrofuran (5 ml.) was added dropwise with stirring a solution of NaN_3 (0.15 g.) in H_2O (1 ml.) at 0~5° during 2 hr. The mixture was diluted with H_2O and extracted with Et_2O (100 ml.) which was washed with 5% aq. $NaHCO_3$ and satd. aqueous NaCl, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The resulting oily azide in dry benzene (100 ml.) was heated under reflux on a water bath until evolution of N_2 ceased. After cooling, conc. HCl (5 ml.) was added and the solution was heated with stirring which was continued for 1 hr. after the generation of CO_2 was complete. The mixture was cooled and the benzene layer was separated and extracted with 2 portions of 10% HCl (60 ml.). The aqueous layers were combined, basified with powdered $NaHCO_3$ and the liberated base was isolated in Et_2O (150 ml.), which was washed with satd. aqueous NaCl, dried, and evaporated to give the amine (XXVI) as pale yellow oil (0.2 g.). The hydrochloride formed needles, m.p. 125~126° (from MeOH). *Anal.* Calcd. for $C_{16}H_{23}O_2N \cdot HCl$: C, 64.52; H, 8.12; Cl, 11.90. Found: C, 64.27; H, 8.10; Cl, 11.90.

6-Ethoxy-9*b*-(2-formamidoethyl)-1,2,3,4,4*a*,9*b*-hexahydrodibenzofuran——The foregoing base (XXVI) (0.2 g.) regenerated from its hydrochloride was heated with 100% HCO_2H (0.2 ml.) in an oil bath at 160° for 5 hr. After cooling, the mixture was dissolved in benzene, and the solution was washed successively with dil. aqueous $NaHCO_3$, and dil. HCl, dried ($MgSO_4$) and evaporated to dryness, to give an oily formyl derivative (0.21 g.), which was used in the subsequent experiment without further purification, IR ν_{max}^{liquid} cm^{-1}: 3220 (OH), 1660 (C=O).

7-Ethoxy-1,2,9,10,11,12-hexahydro-8*a*H-dibenzofuro[1,9*b*,9*a*-*cd*]azepine Methiodide (XXXII)——Phosphorus pentoxide (0.8 g.) was added to a solution of the foregoing N-formyl compound (0.15 g.) in dry toluene and the mixture was heated at 125° for 1 hr. After cooling, the mixture was poured onto ice, basified with 10% aq. NaOH, and shaken repeatedly with Et_2O (100 ml.). The ethereal extracts were combined and extracted with *N* HCl. The aqueous acidic layer was basified by the addition of powdered $NaHCO_3$, and extracted with Et_2O (100 ml.), which was washed with aq. saturated NaCl, dried, and evaporated to give the basic compound (XXXI) (30 mg.) as an oil. This oil was dissolved in MeOH and heated with freshly distilled CH_3I (0.1 ml.) on a water bath for 1 hr. The methanolic solution was concentrated to give the methiodide (XXXII) as yellow crystalline mass which on recrystallization from MeOH formed pale yellow prisms, m.p. 234° (25 mg.), IR ν_{max}^{KBr} cm^{-1}: 1660 (C=N), 869, 800 (1,2,3,4-tetrasubstituted benzene), UV λ_{max}^{EtOH} mμ (ε): 256 (5,250), 318 (11,000). *Anal.* Calcd. for $C_{18}H_{24}O_2NI$: C, 52.30; H, 5.85; N, 3.38; I, 30.70. Found: C, 52.20; H, 5.82; N, 3.38; I, 30.65.

3-Methyl-7-ethoxy-1,2,3,4,9,10,11,12-octahydro-8*a*H-dibenzofuro[1,9*b*,9*a*-*cd*]azepine (XXXIII)——$NaBH_4$ (0.03 g.) was added with stirring in portions to a solution of the methiodide (XXXII) (0.03 g.) in MeOH (20 ml.) at room temperature. After the mixture had been kept overnight, the solvent was evaporated, the residue dissolved in benzene (50 ml.) and the solution was washed with a satd. NaCl solution, dried (Na_2SO_4), and evaporated to give the compound (XXXIII) as an oil, which resisted crystallization after chromatography in benzene over Al_2O_3. The perchlorate crystallized from Me_2CO as needles (25 mg.), m.p. 222°, UV λ_{max}^{EtOH} mμ (ε): 232 (8,130) (shoulder), 288 (3,160). *Anal.* Calcd. for $C_{18}H_{25}O_2N \cdot HClO_4$: C, 55.73; H, 6.75; Cl, 9.14. Found: C, 55.33; H, 6.59; Cl, 9.12.

3-Methyl-1,2,3,4,9,10,11,12-octahydro-8*aH*-dibenzofuro[1,9*b*,9*a*-*cd*]azepin-7-ol (*dl*-Deoxydemethyllycoramine) (XXXIV)——A solution of the base (XXXIII) (0.02 g.) (regenerated from its perchlorate) in 48% HBr (1 ml.) was heated with red P (5 mg.) under reflux at 140~150° in an oil bath for 2 hr. After cooling, the reaction mixture was basified with NaOH, washed with benzene (30 ml.) which was again washed with 20% aq. NaOH. The alkaline layer and the washings were combined, acidified with 4*N* HCl, again basified with powdered $NaHCO_3$ and then repeatedly extracted with AcOEt (150 ml.) which was washed with satd. aqueous NaCl, dried (Na_2SO_4), and evaporated to give *dl*-demethyldeoxylycoramine (XXXIV) as colorless prisms, m.p. 225~226° (decomp.) (from MeOH) (13 mg.). *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found : C, 73.93; H, 8.14; N, 5.25. The IR spectrum of this compound in $CHCl_3$ was superimposable upon that of the optically active deoxydemethyllycoramine from natural sources and a mixed melting point determination with *dl*-deoxydemethyllycoramine prepared from galanthamine as described below showed no depression.

***dl*-Deoxydemethyllycoramine (XXXIV) from Galanthamine**——The *dl*-galanthaminone (0.5 g.), prepared by oxidation of galanthamine with actived MnO_2 in MeOH (50 ml.), was hydrogenated over 10% Pd-C (0.2 g.) until H_2 uptake had ceased (75 ml.). The filtrate from the catalyst was evaporated to dryness to give an oil (0.5 g.) which indicated no α,β-unsaturated carbonyl band in the IR spectrum and was used in the subsequent experiment without further purification. A mixture of the foregoing dihydrogalanthaminone (0.5 g.), diethylene glycol (5 ml.), hydrazine hydrate (freshly distill with KOH) (0.8 ml.) and KOH (0.5 g.) was heated in an oil bath at 150~155° for 1.5 hr. After cooling, the mixture was poured onto ice and the oily product was taken up in $CHCl_3$ (100 ml.), which was washed with satd. aqueous NaCl, dried and evaporated, to give *dl*-deoxylycoramine (XXXV) as an oil (0.42 g.), which indicated no carbonyl IR absorption and gave a negative Zimmermann test. *dl*-Deoxylycoramine (0.42 g.) in 48% HBr (5 ml.) was heated under reflux with a small amount of red P in an oil bath at 140~150° for 2 hr. After cooling, the mixture was diluted with H_2O, filtered, basified with KOH, and extracted with Et_2O (100 ml.). The ethereal extract was shaken with 20% aq. KOH (10 ml.) and the alkaline aqueous layer was acidified with 5*N* HCl, again basified with powdered $NaHCO_3$ and extracted with AcOEt (200 ml.), which was washed with satd. aqueous NaCl, dried (Na_2SO_4), and evaporated, to give *dl*-deoxydemethyllycoramine. Recrystallization from MeOH gave prisms, m.p. 225~226° (decomp.), identical with the synthetic 3-methyl-1,2,3,4,9,10,11,12-octahydro-8*aH*-dibenzofuro[1,9*b*,9*a*-*cd*]azepin-7-ol (XXXIV), as shown by mixed melting point and comparison of the IR spectra (KBr-disk).

Summary

Deoxydemethyllycoramine which is closely related in structure to galanthamine has been synthesized by an unambiguous sequence of reactions providing confirmative evidence for the structure of the alkaloid.

(Received May 7, 1964)