153. *Phenol Oxidation and Biosynthesis. Part V.* The Synthesis of Galanthamine.*

By D. H. R. Barton and G. W. Kirby.

N-(3-Hydroxy-4-methoxyphenyl)-*N*-methyl-4-hydroxyphenethylamine, the theoretical biogenetic precursor of the alkaloid narwedine, has been synthesised. Oxidation of this diphenol under various conditions affords racemic narwedine in small yield. The narwedine has been resolved by a special technique of some theoretical interest. By reduction of (−)-narwedine with lithium aluminium hydride (−)-galanthamine and (−)-epigalanthamine have been synthesised. This work also constitutes a synthesis of the alkaloid (−)-lycoramine.

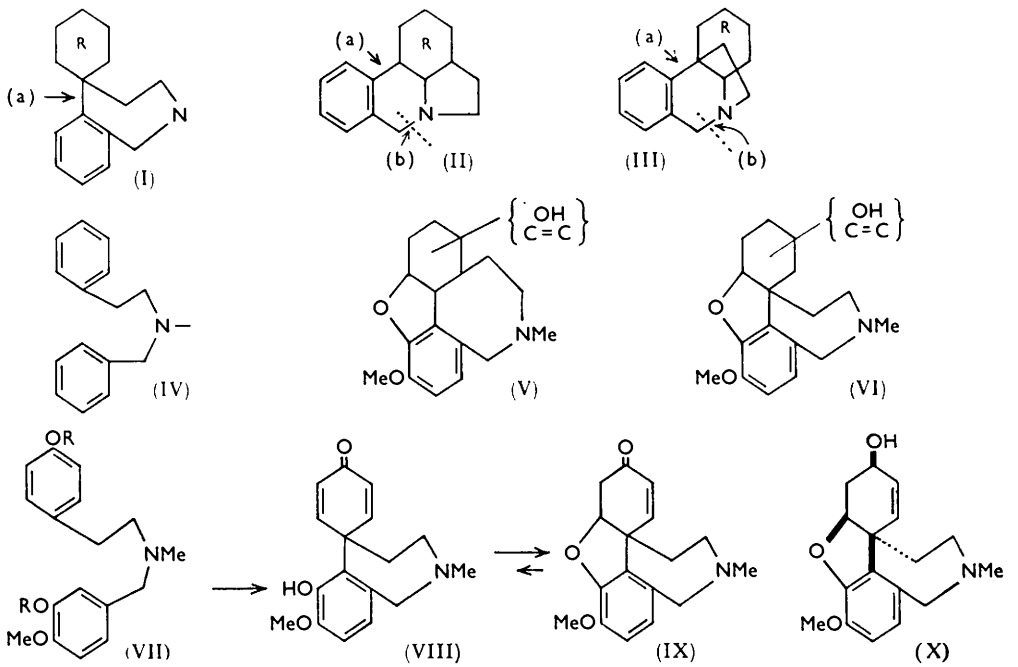
Various discrepancies between the results recorded in the present paper and in the literature are discussed.

The role that the coupling of phenoxide radicals can play in explaining the biosynthesis of natural products is by now well appreciated.[2,4,5] Amongst the many types of compounds which can, at least formally, be derived in this manner the *Amaryllidaceae* alkaloids provide an outstanding example.[2,4] These alkaloids have been intensively studied during the last decade and an authoritative summary of their chemistry has been given recently by Wildman.[6] In brief, three main classes of *Amaryllidaceae* alkaloids can be distinguished,

* The papers in refs. 1—4 are regarded as earlier Parts of this series.

[1] (Part I) Barton, Deflorin, and Edwards, *J.*, 1956, 530.
[2] (Part II) Barton and T. Cohen, "Festschrift Arthur Stoll," Birkhäuser, Basle, 1957, p. 117.
[3] (Part III) Barton and Scott, *J.*, 1958, 1767.
[4] (Part IV) Barton, Fourth Welch Foundation Conference, Houston, Texas, Nov. 1960, in the press.
[5] Erdtman and Wachtmeister, "Festschrift Arthur Stoll," Birkhäuser, Basle, 1957, p. 144.
[6] Wildman, "The Alkaloids," eds. Manske and Holmes, Academic Press, New York, 1960, Vol. VI, p. 290; for leading references see Fales and Wildman, *J. Amer. Chem. Soc.*, 1960, **82**, 3368; Goosen and Warren, *J.*, 1960, 1097; Kitagawa, Uyeo, and Yokoyama, *J.*, 1959, 3741.

having the carbon skeletons shown in (I), (II), and (III). One can visualise in each skeleton one aromatic and one hydroaromatic ring (R). According to biogenetic theory these systems are all derived from a precursor (IV) having two phenolic rings with the phenolic hydroxyl groups at such positions as to direct *ortho*- and/or *para*-coupling between the rings. The biogenesis then involves a pairing of radicals such that the bonds marked (a) are formed. In a later stage of the biosynthesis the bonds marked (b) may be broken and



re-formed elsewhere. In addition, later rearrangements of the carbon skeleton are possible.[7] We do not elaborate the theory further at this juncture since it has already been discussed in adequate detail elsewhere.[2,4]

With the biogenetic theory as a background we have initiated a programme of research, first, to examine the synthesis of these alkaloids along the lines of the biogenetic hypothesis and, secondly, to determine by tracer experiments in the plant how near to the truth our assumptions may be. In the present paper we present our first accomplishments in synthesis. Later papers [8] will deal with the second aspect of our work, a theme to which several other groups have also been giving informative attention.[9]

The alkaloid galanthamine, $C_{17}H_{21}NO_3$, has been investigated by a number of workers.[10] By 1956 the constitutional proposals for galanthamine could be represented by the generalised expressions (V) and (VI). Based on the concept of biogenesis indicated by the formulæ (VII)—(IX), reactions which have analogy in the biosynthesis of usnic acid,[1] it was possible to propose [2] the constitution (X) as the correct one for galanthamine. In

[7] Inubushi, Fales, Warnhoff, and Wildman, *J. Org. Chem.*, 1960, **25**, 2153.

[8] See Barton and Kirby, *Proc. Chem. Soc.*, 1960, 392; Barton, Kirby, Taylor, and Thomas, *Proc. Chem. Soc.*, 1961, 254.

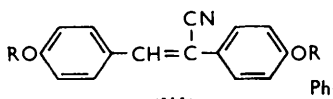
[9] Battersby, Binks, and Wildman, *Proc. Chem. Soc.*, 1960, 410; Battersby, Binks, Breuer, Fales, and Wildman, *Proc. Chem. Soc.*, 1961, 243; Battersby, Fales, and Wildman, *J. Amer. Chem. Soc.*, 1961, **83**, 4098; Warren, personal communication; Suhadolnik, personal communication.

[10] (*a*) Proskurnina and Yakovleva, *Zhur. obshchei Khim.*, 1955, **25**, 1035; 1956, **26**, 172; (*b*) Uyeo and Kobayashi, *Pharm. Bull.* (*Japan*), 1953, **1**, 139; (*c*) Uyeo and Koizumi, *ibid.*, p. 202; (*d*) Kobayashi, Shingu, and Uyeo, *Chem. and Ind.*, 1956, 177; Kobayashi and Uyeo, *J.*, 1957, 638; (*e*) Fales, Giuffrida, and Wildman, *J. Amer. Chem. Soc.*, 1956, **78**, 4145.

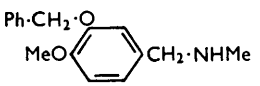
the meantime the probable accuracy of this formula has been strengthened by the isolation of the alkaloids belladine [11] (VII; R = Me) and narwedine [12] (IX) and by experiments not yet published in detail.[13]

In order to confirm the formula (X) for galanthamine we undertook its synthesis. Since nothing was known of the relative and absolute stereochemistry of the molecule these had to be established also during the synthetic work.

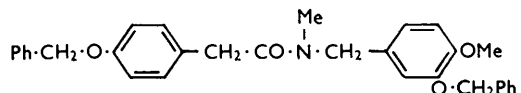
The base (VII; R = H) was readily synthesised by the following route. *p*-Hydroxybenzaldehyde was converted into its cyanohydrin. Concomitant reduction and hydrolysis of this nitrile with hydriodic acid [14] gave a convenient synthesis of *p*-hydroxyphenylacetic acid suitable for large-scale preparations. A by-product for the reaction is assigned the constitution (XI; R = H), being characterised as its diacetate (XI; R = Ac). No doubt it is formed by condensation of *p*-hydroxybenzaldehyde, either present as impurity in the cyanohydrin or formed therefrom by acid-catalysed reversal, with 4-hydroxybenzyl cyanide, the reduction product of the cyanohydrin. The *p*-hydroxyphenylacetic acid was benzylated and converted into *p*-benzyloxyphenylacetyl chloride essentially as described earlier.[15]



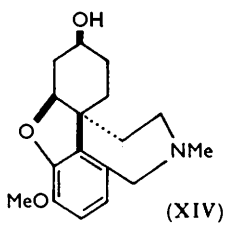
(XI)



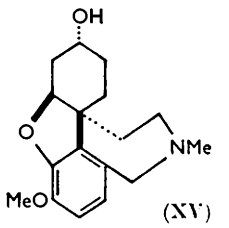
(XII)



(XIII)



(XIV)



(XV)

In the meantime *O*-benzylisovanillin [16] was treated with methylamine in methanol and the resulting imine (infrared control) was reduced *in situ* with potassium borohydride. The resulting amine (XII), purified through its hydrochloride, was obtained in a nicely crystalline form. *p*-Benzyloxyphenylacetyl chloride with two mol. of the amine (XII) in benzene gave the amide (XIII) in excellent yield. Reduction of this amide with lithium aluminium hydride then afforded the tertiary amine (VII; R = CH_2Ph). Hydrogenolysis of the amine over palladised charcoal in methanol containing hydrochloric acid furnished the desired diphenol (VII; R = H), whose constitution was confirmed by treatment with diazomethane which gave belladine (VII; R = Me), characterised as its hydrochloride. A prior synthesis of belladine has been recorded.[17]

Oxidation of the diphenol (VII; R = H) with slightly alkaline potassium ferricyanide was studied in some detail. The major product in all cases was a chloroform-insoluble polymer. Even in very dilute solution extensive polymerisation was observed. It was hoped that oxidation of the diphenol on solid surfaces might prove more successful since adsorbed phenoxide radicals might have a better opportunity to couple intramolecularly than those freely diffusing in solution. Active manganese and lead dioxide were used but again polymerisation was the major process observed. Similar results were obtained by using anodic oxidation.

[11] Warnhoff, *Chem. and Ind.*, 1957, 1385.
[12] Boit, Döpke, and Beitner, *Chem. Ber.*, 1957, **90**, 2197.
[13] Uyeo, Handbook XVIth I.U.P.A.C. Congress, Paris, 1957, p. 207.
[14] Czaplicki, Kostanecki, and Lampe, *Ber.*, 1909, **42**, 831.
[15] Mozingo and Folkers, " Chemistry of Penicillin," Princeton Univ. Press, 1947, p. 568.
[16] Späth, Orechoff, and Kuffner, *Ber.*, 1934, **67**, 1214.
[17] Surrey, Mooradian, Cutler, Suter, and Buck, *J. Amer. Chem. Soc.*, 1949, **71**, 2421.

It was clear from these experiments that narwedine (IX), if being formed at all, could not be present in yields much greater than 1%. In order to determine if any was produced at all we adopted the following simple device. The synthesis of the diphenol (VII; R = H) was repeated with [^{14}C]methylamine instead of ordinary methylamine. The *N*-methyl-labelled diphenol was then oxidised under various conditions, and the products were diluted with unlabelled racemic narwedine. The narwedine was recovered and rigorously purified. After determination of its radioactivity the yield of narwedine formed in the oxidation step was easily calculated. The results are tabulated below, and details are given in the Experimental section.

The effectiveness of intermolecular coupling in reducing the yield of the desired narwedine (IX) was shown by two tracer experiments with ferricyanide as oxidising agent. In one a very dilute solution of the diphenol (VII; R = H) was run slowly into an excess of ferricyanide. In another the ferricyanide was added slowly to a relatively concentrated solution of the diphenol. The conditions of the second experiment favour polymerisation and, in agreement with this, the yield of narwedine (IX) dropped by a factor of about 25.

Oxidation of the diphenol (VII; R = H) to narwedine (IX).

Method	Yield (%) of narwedine: By tracer method	Isolated chemically
Manganese dioxide	0·50	0·3
Lead dioxide	—	0·2
Silver oxide	0·10	—
Dil. solution of (VII; R = H) added to excess of aq. $K_3[Fe(CN)_6]$	0·92	1·4 *
Aq. $K_3[Fe(CN)_6]$ added slowly to solution of (VII; R = H)	0·037	—

* The solution of (VII; R = H) was added more slowly than in the tracer experiment.

For preparative work active manganese dioxide appeared to be a convenient reagent. The yield, by the tracer determination, was 0·50%. By working up the product as detailed in the Experimental section pure racemic narwedine (IX) was isolated in 0·3% yield. In a more elaborate preparative experiment with ferricyanide as oxidant the yield of narwedine actually isolated was increased to 1·4%. No doubt further improvement in yield could be achieved by increasing the dilution of the reactants still more.

The racemic narwedine needed for comparison with the synthetic material was obtained by oxidising (−)-galanthamine (X) with manganese dioxide [12] or chromium trioxide. The (−)-narwedine (IX) thus obtained was readily racemised either by chromatography over alumina or by warming it in ethanol. The racemisation must proceed through the symmetrical dienone (VIII). Racemic narwedine served as a convenient relay in the synthesis of galanthamine.

Reduction of (±)-narwedine with lithium aluminium hydride gave two stereoisomeric alcohols, m. p. 121—123° and m. p. 199°, which were readily separated by chromatography and were both reconverted into narwedine by manganese dioxide. Infrared comparison with (−)-galanthamine proved that the lower-melting isomer was (±)-galanthamine. The other must, therefore, be (±)-epigalanthamine. The two alcohols differed markedly in their physical properties. (±)-Galanthamine was more soluble in non-polar solvents such as carbon tetrachloride and benzene; it was much more easily eluted from alumina. These properties suggested that (±)-galanthamine might show intramolecular hydrogen bonding and its epimer intermolecular bonding. This was confirmed by a study of the infrared hydroxyl frequencies in chloroform. (±)-Galanthamine showed a band at 3575 cm.$^{-1}$, some 55 cm.$^{-1}$ lower than the main hydroxyl band of (±)-epigalanthamine (the concentrations used for the measurements were so dilute as to exclude intermolecular hydrogen bonding [18]).

These facts have an important bearing on the stereochemistry of (±)-galanthamine.

[18] Cf. Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

The oxide ring in narwedine (and hence in galanthamine) must have the more stable, *cis*-fused, configuration because (—)-narwedine racemises but does not epimerise under basic conditions.[19] The intramolecular hydrogen bonding shown by galanthamine must be between the hydroxyl group and the oxygen of the oxide ring. This is a well known phenomenon [20] and it proves that the two groupings must be *cis* to each other. The relative stereochemistry of galanthamine must, therefore, be as indicated in (X). A different stereochemistry has been proposed by Uyeo and Nakagawa [21] but in a personal communication Professor Uyeo has kindly informed us that he now accepts the conclusions that we have drawn from the evidence summarised above.*

Fales, Giuffrida, and Wildman [10e] have reported that " Base IX " ($[\alpha]_D$ —222°) described by Kondo, Ishiwata, and Okajama [22] is epimeric with (—)-galanthamine ($[\alpha]_D$ —120°). The difference in rotation between the two epimers can be interpreted according to Mills's generalisation [23] to indicate that (—)-galanthamine has the absolute configuration already indicated in (X).

Comparison of the physical properties of dihydro- (XIV) and dihydroepi-galanthamine (XV) confirmed the stereochemical conclusions reached above as to the configurations of the hydroxyl group. (±)-Dihydroepigalanthamine, m. p. 185—190°, and (—)-dihydrogalanthamine (lycoramine [10b]), m. p. 120—121°, both obtained by catalytic hydrogenation of the corresponding allylic alcohols, showed hydroxyl bands at 3615 and 3580 $cm.^{-1}$, respectively, in chloroform. Dihydrogalanthamine was much more easily eluted from alumina than its epimer. The facts are in agreement with the configurations given in (XIV) and (XV).

Boit, Döpke, and Beitner [12] have described a new alkaloid, irenine, m. p. 128°, $[\alpha]_D$ +120°, which they consider to be dihydroepigalanthamine (XV). In order to synthesise this compound in optically active form we reduced (—)-dihydronarwedine (lycoraminone [10c]) by the Ponndorf–Meerwein procedure, obtaining, as the major product, a crystalline alcohol, m. p. 180—192°, $[\alpha]_D$ —95°, that had an infrared spectrum (in chloroform) identical with that of (±)-dihydroepigalanthamine. Similar Ponndorf–Meerwein reduction of (±)-narwedine gave mainly (±)-epigalanthamine. It is difficult to reconcile our results with those of Boit, Döpke, and Beitner [12] and it is clear that irenine, if it exists, is not dihydroepigalanthamine.†

In order to effect the synthesis of natural (—)-galanthamine it was necessary to resolve either (±)-narwedine or (±)-galanthamine. Our interest in carrying this to completion was specially stimulated whilst the work was actually in progress by Russian reports [24] that (—)-galanthamine had valuable applications in Soviet medicine.

The standard methods of resolution were uniformly unsuccessful when applied to both (±)-narwedine and (±)-galanthamine. An interesting resolution was, however, secured in an unexpected manner. It was observed that during oxidation of (—)-galanthamine to (—)-narwedine by manganese dioxide in chloroform the optical rotation became more negative as the reaction proceeded. The rotation of the total product was also more

* The occurrence of intramolecular hydrogen bonding in galanthamine has also been demonstrated by Dr. W. C. Wildman whom we thank cordially for his personal communication to this effect.

† Boit and his collaborators [12] record the conversion of (—)-epigalanthamine (" Base IX ") into irenine by hydrogenation. They also report the hydrogenation of narwedine to a mixture of lycoramine and irenine. Irenine [12] has m. p. 128°, $[\alpha]_D$ +120° (in $CHCl_3$). We find for dihydroepigalanthamine, m. p. 180—192°, $[\alpha]_D$ —95° (in $CHCl_3$). The same conclusion as to the non-identity of irenine and dihydroepigalanthamine has been reached by Professor Uyeo (personal communication).

[19] Cf. Arkley, Dean, Robertson, and Sidisunthorn, *J.*, 1956, 2322.

[20] See Büchi, Crombie, Godin, Kaltenbronn, Siddialingaiah, and Whiting, *J.*, 1961, 2843; and references there cited.

[21] Uyeo, 4th Symposium on Natural Product Chemistry of the Chemical and Agricultural Chemical Societies of Japan, 1960, p. 28.

[22] Kondo, Ishiwata, and Okajama, *J. Pharm. Soc. Japan*, 1933, **53**, 149.

[23] Mills, *J.*, 1952, 4977; see also Jeffs, Warren, and Wright, *J.*, 1960, 1090; Uyeo and Nakagawa, *J.*, 1959, 3736.

[24] See " The Evening News " (London), March 3rd, 1960, p. 13.

negative than that of (−)-galanthamine itself. Crystallisation of the product from acetone gave (−)-material, m. p. 184—190°, $[\alpha]_D$ typically −88°. However, crystallisation from ethanol afforded a dextrorotatory product, m. p. 184—190°, $[\alpha]_D$ typically +36°. These two products had infrared and ultraviolet spectra identical with that of (±)-narwedine and indeed gave essentially quantitatively, and at the same rate, (±)-narwedine when kept in ethanol. One must conclude (see below) that the products are partly racemic (−)- and (+)-narwedine, respectively. The apparently spontaneous generation of (+)-narwedine during crystallisation from ethanol was shown to be due to the presence of small amounts of unoxidised (−)-galanthamine. During the crystallisation from ethanol the initially lævorotatory narwedine is racemised completely (through the basicity of narwedine itself). Whilst crystallisation actually proceeds the (−)-galanthamine induces the separation of substantially pure (+)-narwedine in partly resolved form. This conclusion was confirmed by crystallisation of (±)-narwedine in the presence of (−)-galanthamine. By using a 2 : 1 ratio of (±)-narwedine to (−)-galanthamine, (+)-narwedine with $[\alpha]_D$ +306° was obtained. Crystallisation from benzene raised this rotation to a constant value of +405° which we regard as characteristic of the pure enantiomer. In preparative work the addition of triethylamine facilitated the interconversion of the (+)-, (−)-, and (±)-forms of narwedine. Reduction of optically pure (+)-narwedine with lithium aluminium hydride gave, as expected, a mixture of (+)-galanthamine and (+)-epigalanthamine which could be separated as already demonstrated for the racemic compounds. Since preliminary experiments showed that (+)-epigalanthamine was as good a resolving agent, *mutatis mutandis*, as (−)-galanthamine, it was convenient to take the mixture of (+)-galanthamine and (+)-epigalanthamine and use it directly to resolve (±)-narwedine to furnish natural (−)-narwedine. Reduction of the latter then completed the conversion of (±)-narwedine into (−)-galanthamine [and (−)-epigalanthamine]. The optical resolution, in principle, affords 100% conversion into either enantiomer. In practice we have been able to obtain substantially more than 50% of the desired enantiomer. Our synthetic goals had thus been attained.

The resolution of (±)-narwedine described above was sufficiently without precedent to justify a more detailed examination of the process. The phenomenon was not one of resolution induced by seeding. Crystallisation from ethanol in the absence of galanthamine gave no significant resolution even on addition of (+)- or (−)-narwedine crystals to a saturated solution of the racemate. The extent of resolution was dependent upon the amount of galanthamine added, although the latter was not incorporated into the optically active narwedine that separated.

Two possible explanations can be considered. If the (−)-galanthamine were to form reversibly a complex with (−)-narwedine in solution then the crystals separating from the solution would be enriched in the (+)-isomer. However, the rotation of a solution of (−)-galanthamine and (±)-narwedine was exactly that calculated for the (−)-galanthamine present so that complex-formation, to a major extent, is almost certainly excluded. Also, modification of the functional groups of (−)-galanthamine did little to affect its "activating" power. (−)-*O*-Acetylgalanthamine, (−)-dihydrogalanthamine (lycoramine), (+)-epigalanthamine, and (−)-galanthamine methotoluene-*p*-sulphonate could all be used for the resolution. Codeine, brucine, quinine, veratrine, and crinine were without effect. It is difficult to visualise a narwedine–galanthamine complex whose stability depends critically upon the gross structure of galanthamine but not on the nature of the functional groups. An alternative explanation invokes adsorption of galanthamine on the surface of growing narwedine crystals. An adsorbed (−)-galanthamine layer on (+)-narwedine crystals might either favour deposition of (+)-narwedine (behaving like a biological membrane) or, more probably, inhibit deposition of (−)-narwedine. It is well known that small amounts of foreign molecules may modify profoundly crystal growth.[25]

[25] See *Discuss. Faraday Soc.*, 1949, **5**.

Boit, Döpke, and Beitner [12] have described the isolation of narwedine with $[\alpha]_D$ +100° from extracts of " Texas " daffodils. The low specific rotation might be explained by racemisation during isolation but the sign of rotation, on the assumption of a biogenetic relationship with (—)-galanthamine, should, of course, be (—), not (+). In collaboration with Mr. J. B. Taylor we have repeated this extraction. After chromatography over alumina we obtained a mixture of narwedine and (—)-galanthamine. Crystallisation of the narwedine from benzene gave pure material but with $[\alpha]_D$ +52°. However, crystallisation of (±)-narwedine from benzene in the presence of 50% by wt. of (—)-galanthamine also gave pure narwedine with a similar positive rotation. On the present evidence the sign of rotation of narwedine from " Texas " daffodils is still in doubt, and the possibility that the compound exists in the plant in the racemic form, or is racemised during extraction, cannot be excluded. Indeed, natural narwedine may still belong to the (—)-series and the positive rotation reported by Boit and his collaborators [12] may be due simply to the resolution phenomenon described in the present paper.

The use of solid oxidants for effecting phenol coupling has been independently reported in elegant syntheses by Davidson and Scott,[26] by Brown, Clark, Ollis, and Veal,[27] and by Hassall and Lewis.[28]

Experimental

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$, ultraviolet adsorption spectra to EtOH, and infrared absorption spectra to $CHCl_3$ solutions. Light petroleum refers to the fraction of b. p. 60—80°. Activated manganese dioxide was obtained from British Drug Houses Ltd.

p-*Hydroxyphenylacetic Acid.*[14]—*p*-Hydroxybenzaldehyde (40 g.) was converted into its cyanohydrin [29] which was powdered and added to hydriodic acid (90 ml.; *d* 1·94) with stirring. Heat was evolved as the cyanohydrin dissolved and the mixture was cooled to maintain its temperature at *ca.* 40°. The resulting solution was refluxed for 40 min., cooled, and poured into 10% aqueous sodium metabisulphite (600 ml.). The small amount of insoluble material which separated was filtered off and examined separately. The filtrate was extracted with ether (4 × 150 ml.), and the ethereal solution washed with water, dried ($MgSO_4$), treated with charcoal, and evaporated. Water (10 ml.) was added to the pasty residue which was then kept at 5° for 1 hr. The crystals which separated (19 g.) were collected and recrystallised from water to give *p*-hydroxyphenylacetic acid as needles (17 g., 34%), m. p. 149—152°.

The insoluble by-product (see above) crystallised from aqueous ethanol and aqueous acetic acid to afford αβ-*di*-p-*hydroxyphenylacrylonitrile* (XI; R = H), $\lambda_{max.}$ 239 and 347 mμ (ε 14,300 and 27,300, respectively), $\lambda_{infl.}$ 300 mμ (ε 9200) (Found: C, 75·5; H, 4·5; N, 5·5. $C_{15}H_{11}NO_2$ requires C, 75·9; H, 4·7; N, 5·9%). With acetic anhydride in pyridine this gave the *diacetate* (XI; R = Ac) which crystallised from ethanol as plates, m. p. 160° (Found: C, 71·0; H, 4·7; N, 4·5. $C_{19}H_{15}NO_4$ requires C, 71·0; H, 4·7; N, 4·4%).

p-*Benzyloxyphenylacetic Acid.*[15]—To a solution of *p*-hydroxyphenylacetic acid (5 g.) in ethanol (40 ml.) containing potassium hydroxide (5 g.) was added benzyl chloride (5 g.), and the resulting mixture refluxed under nitrogen for 5 hr. The solvent was evaporated and the residue shaken with water and ether. Acidification of the aqueous layer with hydrochloric acid gave *p*-benzyloxyphenylacetic acid which crystallised from aqueous ethanol as plates (5·3 g., 67%), m. p. 120—122°.

3-*Benzyloxy*-4-*methoxy*-N-*methylbenzylamine* (XII).—To a solution of *O*-benzylisovanillin [16] (10 g.) in methanol (25 ml.) was added 30% aqueous methylamine (6 ml.). After 1 hr. at room temperature potassium borohydride (3 g.) was added slowly and the resulting suspension set aside for 2 hr. The solvent was evaporated and the residue shaken with water and ether. Evaporation of the ether layer gave the oily amine which was dissolved in methanol (15 ml.), treated with 6N-hydrochloric acid (10 ml.), and kept at 5° for 1 hr. The *hydrochloride* (7·8 g., 68%) separated as needles, m. p. 212° (Found: C, 65·6; H, 7·0; N, 5·0. $C_{16}H_{20}ClNO_2$ requires

[26] Davidson and Scott, *Proc. Chem. Soc.*, 1960, 390.
[27] Brown, Clark, Ollis, and Veal, *Proc. Chem. Soc.*, 1960, 393.
[28] Hassall and Lewis, *J.*, 1961, 2312.
[29] Ladenburg, Folkers, and Major, *J. Amer. Chem. Soc.*, 1936, **58**, 1292.

C, 65·4; H, 6·8; N, 4·8%). Decomposition of the hydrochloride with sodium carbonate and extraction with ether gave the *amine* (XII), m. p. 61—64° (from light petroleum) (Found: C, 74·5; H, 7·2; N, 5·7. $C_{16}H_{19}NO_2$ requires C, 74·7; H, 7·4; N, 5·4%). Acylation in the usual way gave the *benzamide*, m. p. 79—80° (Found: C, 76·45; H, 6·7. $C_{23}H_{23}NO_3$ requires C, 76·4; H, 6·4%).

N-(3-*Benzyloxy*-4-*methoxybenzyl*)-N-*methyl*-p-*benzyloxyphenylacetamide* (XIII).—To a suspension of *p*-benzyloxyphenylacetic acid (5 g.) in benzene (5 ml.) was added oxalyl chloride (5 ml.), and the mixture warmed until all the acid had dissolved. After 1 hr. at room temperature the solvent and the excess of oxalyl chloride were evaporated and the remaining acid chloride was redissolved in benzene (20 ml.). This solution was added dropwise with stirring to a solution of the amine (XII) (10·6 g.) in benzene (50 ml.). After 2 hr. the precipitated amine hydrochloride was filtered off (5·4 g. after recrystallisation), and the filtrate successively washed with N-hydrochloric acid, water, N-sodium hydrogen carbonate, and water, dried, and evaporated. The crude product crystallised on addition of light petroleum. Recrystallisation from ether gave the *amide* (8·5 g., 85%), m. p. 91—93° (Found: C, 77·6; H, 6·4; N, 2·75. $C_{31}H_{31}NO_4$ requires C, 77·3; H, 6·5; N, 2·9%).

4-*Benzyloxy*-N-(3-*benzyloxy*-4-*methoxybenzyl*)-N-*methylphenethylamine* (VII; R = Ph·CH_2). —The amide (XIII) (2 g.) was extracted (Soxhlet) into a refluxing suspension of lithium aluminium hydride (2 g.) in ether (100 ml.). The excess of reagent was decomposed with ethyl acetate, and water was added. The ether layer was separated and the pasty aqueous layer further extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal solutions gave the *amine* (VII; R = Ph·CH_2) which crystallised from ethanol as prisms (1·7 g., 88%), m. p. 74° (Found: C, 79·9; H, 7·1; N, 3·15. $C_{31}H_{33}NO_3$ requires C, 79·6; H, 7·1; N, 3·0%).

4-*Hydroxy*-N-(3-*hydroxy*-4-*methoxybenzyl*)-N-*methylphenethylamine* (VII; R = H).—A solution of the amine (VII; R = Ph·CH_2) (1·5 g.) in methanol (50 ml.) containing concentrated hydrochloric acid (0·4 ml.) was hydrogenated over 10% palladised charcoal (0·15 g.). After 2 hr. the solution was filtered, evaporated to 15 ml., and diluted with ether, the amine (VII; R = H) separating as its *hydrochloride* (1·0 g., 76%), m. p. 230° (decomp.) (Found: C, 63·2; H, 7·0; N, 4·5. $C_{17}H_{22}ClNO_3$ requires C, 63·1; H, 6·8; N, 4·3%). Decomposition of the hydrochloride with aqueous sodium hydrogen carbonate and extraction with ether afforded the *amine* (VII; R = H) which crystallised from ethanol–light petroleum as prisms, m. p. 133—135° (Found: C, 71·3; H, 7·5; N, 5·2. $C_{17}H_{21}NO_3$ requires C, 71·05; H, 7·4; N, 4·9%). The phenolic amine (80 mg.) with diazomethane, in the usual way, gave an oily amine which, on treatment with ethanolic hydrogen chloride and ether, afforded belladine hydrochloride (53 mg.), m. p. 182—185° (lit.,[17] 181—182°) (Found: C, 64·7; H, 7·7; N, 4·1. Calc. for $C_{19}H_{26}ClNO_3$: C, 64·8; H, 7·45; N, 4·0%).

Preparation of the Amine (VII; R = H) *labelled with* ^{14}C.—The preparation followed that described above with slight modifications. To a solution of [^{14}C]methylamine hydrochloride (40 mg.) in methanol (4 ml.) containing *O*-benzylisovanillin (175 mg.) was added aqueous 4N-sodium hydroxide (0·4 ml.) and, after 2 hr., the product was reduced with sodium borohydride (50 mg.). The amine was isolated in the usual way and, without recrystallisation, was acylated with *p*-benzyloxyphenylacetyl chloride (from 50 mg. of acid). The resulting amide was reduced directly with lithium aluminium hydride, and the amine (VII; R = Ph·CH_2) hydrogenated without being recrystallised. The final product was obtained as its crystalline hydrochloride in 30% overall yield. The labelled amine (XII) was recovered from the acylation step and used again.

Oxidation of the Labelled Amine (VII; R = H).—(a) *With manganese dioxide and silver oxide.* A solution of the labelled amine (100 mg., $8·7 \times 10^6$ counts per min.*) in chloroform (30 ml.) was shaken with active manganese dioxide (600 mg.) at room temperature for 3 hr. Narwedine (20 mg.) was added and the solution filtered and evaporated. The product was chromatographed on alumina (grade III) (5 g.), narwedine being eluted with ethyl acetate–benzene (1 : 4). This material was further purified by rechromatography, crystallisation from ether, sublimation, and finally conversion into its hydrochloride and methiodide. The activity of the alkaloid remained constant [$2·1(5) \times 10^3$ counts per min. per mg.] within the limits of experimental error during publication and corresponded to a yield of 0·50% of narwedine in the oxidation step.

* Activities were measured on thin films (0·5—1·0 mg. per cm.^{2}) by using a gas-flow (methane) proportional counter and are not corrected for self-absorption.

In a similar experiment a solution of the labelled phenolic amine (100 mg.) in chloroform (50 ml.) was shaken with freshly precipitated silver oxide (1 g.) for 24 hr. The yield of narwedine in the experiment was 0·10%.

(b) *With potassium ferricyanide.* A solution of the labelled phenolic amine hydrochloride (21 mg.; $1·0 \times 10^7$ counts per min.) in water (100 ml.) was delivered through a fine capillary submerged in a vigorously stirred solution of potassium ferricyanide (0·4 g.) in water (80 ml.) containing N-sodium hydrogen carbonate (20 ml.) during 1·5 hr. A solution of (±)-narwedine (15 mg.) in a little dilute hydrochloric acid was added to the ferricyanide solution at the beginning of the experiment, which was carried out under nitrogen. One hour after all the phenol had been added the mixture was extracted with chloroform (4 × 20 ml.), and the extracts were washed with water, dried (Na_2SO_4), and evaporated to give a brown gum (17 mg.). This material was chromatographed on alumina (grade III) (5 g.), narwedine (9 mg.) being eluted with ethyl acetate–benzene (3 : 7). The alkaloid was further purified by chromatography, recrystallisation from ether, and conversion into its methiodide. The total activity of the purified alkaloid ($9·2 \times 10^4$ counts per min.) corresponded to a 0·92% yield of narwedine from the oxidation.

(c) *With potassium ferricyanide: reverse addition.* The labelled phenolic amine hydrochloride (100 mg.; $5·0 \times 10^6$ counts per min.) was dissolved in water (10 ml.), ethanol (5 ml.), and N-aqueous sodium hydrogen carbonate (10 ml.) containing (±)-narwedine (15 mg.), and the resulting solution was swept free from air with nitrogen. A solution of potassium ferricyanide (400 mg.) in water (10 ml.) was then run in with stirring during 30 min., and after 1 hr. the product was extracted with chloroform (4 × 20 ml.). Evaporation of the chloroform gave a gum which was chromatographed in the usual way, to give narwedine (10 mg.) having a total activity [$1·8(6) \times 10^3$ counts per min.] corresponding to a 0·037% yield of narwedine from the oxidation.

Oxidation of the Phenol (VII; R = H) *with Manganese and Lead Dioxide.*—A solution of the phenolic amine (from 0·5 g. of hydrochloride) in chloroform (200 ml.) was shaken with active manganese dioxide (1·5 g.) at room temperature for 3 hr. and then filtered. The filtrate was evaporated, the gummy residue was extracted with hot benzene, and the extracts were chromatographed on alumina (grade III) (5 g.). Elution was followed by the ultraviolet absorption of the eluate at 280 mμ, 2 ml. fractions being collected. Benzene (10 ml.), ethyl acetate–benzene (1 : 9; 12 ml.), and ethyl acetate–benzene (1 : 4; 12 ml.) removed only traces of material. Elution with ethyl acetate–benzene (3 : 7) gave (±)-narwedine (1·3 mg., 0·3%), m. p. 187—189° (a little softened at 175°), having an infrared spectrum (Nujol mull) identical with that of (±)-narwedine obtained from galanthamine (see below). This experiment was performed twice more and the combined products (1·9 mg.) were rechromatographed, giving material (1·4 mg.) of m. p. and mixed m. p. 187—189° with an ultraviolet spectrum ($\lambda_{max.}$ 225, 265, and 295 mμ; ε 16,600, 3600, and 1200; $\lambda_{min.}$ 248 and 289 mμ; ε 2300 and 1100) identical with that of the authentic alkaloid. (±)-Narwedine methiodide showed a similar ultraviolet spectrum ($\lambda_{max.}$ 225, 260, and 295 mμ; ε 16,600, 4100, and 2300) after subtraction of the corresponding curve for triethylmethylammonium iodide.

A similar experiment with active lead dioxide [30] gave crude (±)-narwedine (0·8 mg.) which proved difficult to purify. After chromatography and sublimation it had m. p. 178—186°. Its ultraviolet spectrum differed slightly from that of pure material.

Oxidation of the Phenol (VII; R = H) *with Ferricyanide.*—A solution of the phenolic amine hydrochloride (250 mg.) in water (1·5 l.) was added to a solution of potassium ferricyanide (8 g.) in water (1·6 l.) containing N-sodium hydrogen carbonate (400 ml.) during 70 hr. as described for the tracer experiment (b) (see above). The mixture was extracted with chloroform (5 × 100 ml.), and the chloroform solution then extracted with 5N-hydrochloric acid (5 × 50 ml.), the solution being filtered occasionally to remove polymer which separated. The aqueous extract was made alkaline with sodium carbonate and re-extracted with chloroform (5 × 20 ml.), and the chloroform solution dried and evaporated to yield a yellow gum (10 mg.). This material was treated with hot benzene, and the extract was chromatographed as described above, to give (±)-narwedine (3·0 mg., 1·4%). After sublimation at 140°/10^{-4} mm. the product had m. p. 186—190° undepressed when mixed with authentic narwedine. The ultraviolet and infrared spectra were identical with those of authentic material.

Narwedine from (−)-*Galanthamine.*—(*a*) (−)-Galanthamine was oxidised with active

[30] Kuhn and Hammer, *Chem. Ber.*, 1950, **83**, 413.

manganese dioxide by the procedure of Boit, Döpke, and Beitner,[12] the crude product being chromatographed to remove coloured impurities and (−)-galanthamine. After crystallisation from 95% ethanol narwedine was obtained as prisms, m. p. 187—190°, showing no detectable rotation in chloroform (*c* 1·0).

(*b*) To a solution of (−)-galanthamine (43 mg.) in acetone (15 ml.) containing water (3 ml.) was added 6N-sulphuric acid (0·1 ml.), followed by chromic oxide (12 mg.) in acetone (3 ml.). The mixture was left overnight and the solvent evaporated. The residue was dissolved in water, treated with a slight excess of sodium hydrogen carbonate, and extracted with chloroform. This extract was evaporated and the residue chromatographed in benzene on alumina (grade III) (10 g.). Elution with ethyl acetate–benzene (1 : 9) gave an unidentified crystalline compound (7 mg.); elution with ethyl acetate–benzene (1 : 4) gave (±)-narwedine (23 mg.), m. p. 187—190°.

Reduction of (±)-Narwedine with Lithium Aluminium Hydride.—(±)-Narwedine (128 mg.) was extracted (Soxhlet) into a refluxing suspension of lithium aluminium hydride in ether (15 ml.) during 2 hr. The excess of reagent was decomposed with ethyl acetate, and water added. The ether layer was separated and the pasty residue extracted with chloroform. Evaporation of the combined ether and chloroform extracts, after drying (Na_2SO_4), gave a partially crystalline mass which was chromatographed in benzene on alumina (grade III) (20 g.). Elution with ethyl acetate–benzene (1 : 1) gave (±)-galanthamine (78 mg.) which crystallised from ether as needles (50 mg.), m. p. 121—123°. Its infrared spectra in chloroform and in carbon tetrachloride were those of (−)-galanthamine. The column was washed with chloroform, and elution with ethanol–chloroform (1 : 19) then gave (±)-*epigalanthamine* (50 mg.). Crystallisation from ethanol yielded needles, m. p. 199° (Found: C, 71·0; H, 7·6; N, 4·6. $C_{17}H_{21}NO_3$ requires C, 71·05; H, 7·4; N, 4·9%).

Oxidation of both (±)-galanthamine and (±)-epigalanthamine with manganese dioxide in chloroform gave (±)-narwedine (identified by its infrared spectrum), whereas (−)-dihydrogalanthamine (see below) was only slowly attacked, the infrared spectrum of the crude product showing a cyclohexanone band at 1715 cm.$^{-1}$.

The reduction of (±)-narwedine with sodium borohydride gave a mixture of alcohols which proved difficult to separate by chromatography. Infrared spectral examination of crude fractions suggested the presence of (±)-galanthamine and (±)-dihydrogalanthamine.

Reduction of (±)-Narwedine with Aluminium Isopropoxide.—A solution of (±)-narwedine (100 mg.) in dry propan-2-ol (10 ml.) containing aluminium isopropoxide (from 100 mg. of aluminium) was heated under reflux for 2 hr., acetone (detected by dinitrobenzene in ethanolic sodium hydroxide) being slowly distilled off. The solvent was evaporated and the residue decomposed with water and then extracted with chloroform. Evaporation of the chloroform gave crystals (92 mg.) which separated from 95% ethanol as needles (60 mg.), m. p. 199°, having an infrared spectrum in chloroform identical with that of (±)-epigalanthamine. (−)-Galanthamine was unaffected by aluminium isopropoxide under these conditions, even in the presence of a trace of acetone.

(±)-Dihydroepigalanthamine.—(±)-Epigalanthamine (58 mg.) was hydrogenated in ethanol (20 ml.) over 10% palladised charcoal (60 mg.). Hydrogen uptake (5 ml.) ceased after 2·5 hr. The solution was filtered and evaporated, and the residue chromatographed on alumina (grade III) (5 g.). Elution with ethyl acetate, then chloroform, gave only traces of material, but ethanol–chloroform (1 : 49) gave (±)-*dihydroepigalanthamine* (40 mg.) which crystallised from ethyl acetate as needles, m. p. 185—190° (Found: C, 70·3; H, 7·8; N, 4·9. $C_{17}H_{23}NO_3$ requires C, 70·6; H, 8·0; N, 4·8%).

(−)-Dihydrogalanthamine (Lycoramine).—(−)-Galanthamine (200 mg.) was hydrogenated as described by Uyeo and Kobayashi [10b] and the crude product purified by chromatography on alumina (grade III), (−)-dihydrogalanthamine being eluted with ethyl acetate–benzene (7 : 3). The alkaloid crystallised on treatment with ether as needles (120 mg.), m. p. 118—121° (lit.,[10b] 120—121°).

(−)-Dihydronarwedine (Lycoraminone).—To a solution of lycoramine (76 mg.) in acetone (15 ml.) was added 6N-sulphuric acid (0·3 ml.), followed by water dropwise to afford a clear solution. Chromic oxide (19 mg.) in water (1 ml.) and acetone (5 ml.) was then added and the mixture kept at room temperature for 12 hr. After evaporation of the acetone the product was treated with an excess of aqueous sodium hydrogen carbonate and extracted with chloroform. The chloroform extracts were evaporated and the residue was chromatographed on

alumina (5 g.) (grade III). Elution with ethyl acetate–benzene (4 : 6) gave (−)-dihydronarwedine (20 mg.), which crystallised from ether as plates, m. p. 131—134° (lit.,[10b] 130—132°).

(−)-*Dihydroepigalanthamine* (*Epilycoramine*).—(−)-Dihydronarwedine (20 mg.) was reduced with aluminium isopropoxide in propan-2-ol in the usual way (see above). The product (13 mg.) was chromatographed on alumina (grade III) (3 g.), (−)-dihydroepigalanthamine (7 mg.) being eluted with ethanol–chloroform (1 : 49). This material crystallised from ethyl acetate as plates, m. p. 180—192°, $[\alpha]_D$ −95° (*c* 0·25), having an infrared spectrum in chloroform identical with that of the racemic compound obtained from (±)-epigalanthamine.

Infrared Spectra.—Spectra were measured in chloroform (distilled over P_2O_5) by means of a Grubb–Parsons spectrometer with a calcium fluoride prism at two concentrations: A, 17 mg. per ml.; B, 3·3 mg. per ml. The hydroxyl stretching frequences are tabulated, main bands being in bold type. The weak bands near 3700 cm.$^{-1}$ were not shown by galanthamine or dihydrogalanthamine in carbon tetrachloride solution. In chloroform containing a trace of ethanol epigalanthamine and its dihydro-derivative showed broad associated hydroxyl absorption near 3450 cm.$^{-1}$, whereas galanthamine and dihydrogalanthamine did not.

Compound	A (cm.$^{-1}$)	B (cm.$^{-1}$)
(−)-Galanthamine	**3575**	3700, 3620sh, **3575**
(±)-Epigalanthamine	**3630**	3705, **3625**
(−)-Dihydrogalanthamine	**3580**	3690, **3630**, 3590
(±)-Dihydroepigalanthamine	**3615**	3700, **3615**

Oxidation of (−)-*Galanthamine with Manganese Dioxide.*—A solution of (−)-galanthamine (100 mg.) in chloroform (20 ml.) was shaken with active manganese dioxide (1·0 g.) for 30 min. The solution was filtered and evaporated, to give a partly crystalline product (75 mg.), $[\alpha]_D$ −131° (*c* 1·0). Two crystallisations from 95% ethanol gave material (25 mg.), m. p. 184—190°, $[\alpha]_D$ +36° (*c* 1·0). In a similar experiment the crude product was treated with acetone; the crystals which separated crystallised from acetone to give a compound (26 mg.), m. p. 180—190°, $[\alpha]_D$ −88° (*c* 1·0). These dextro- and lævo-rotatory compounds had identical infrared (Nujol) and ultraviolet spectra, and they racemised in ethanol at the same rate (see below) to give (±)-narwedine.

Racemisation of Narwedine.—Mixtures of (+)-narwedine (5 mg.) and various organic bases were dissolved in chloroform (*ca.* 0·05 ml.), and the solutions made up to 1 ml. with 95% ethanol. Racemisation was followed polarimetrically at 25° to at least 90% completion. The racemisation half-times, *t*, are tabulated.

Added base	None	(−)-Galanthamine		(±)-Narwedine	NEt_3
Added base (mg.)	—	1·0	3·0	3·0	1·06
t (min.)	21	15	10	15	8

Narwedine racemised in methanol at a concentration of 5 mg. per ml. with a half-time of 18 min. No detectable racemisation occurred during 1 hr. at 25° in chloroform, benzene, or dioxan solution. The rotation of a solution of (+)-narwedine (12 mg.) in 95% ethanol (1 ml.) containing 6N-hydrochloric acid (0·01 ml.) diminished by 8% during 1 hr. at 25°.

Resolution of (±)-*Narwedine.*—Mixtures of (±)-narwedine and various alkaloids were crystallised from either 95% ethanol (A) or 95% ethanol–triethylamine (9 : 1) (B). The narwedine was allowed to crystallise slowly, the supernatant solution was removed with a pipette, and the crystals were washed with a little 95% ethanol, then with ether. The purity of the product was measured by allowing it to racemise completely in ethanol, the resulting rotation then giving the amount of contaminating alkaloid present. In all cases the purity was >95%, the yield of narwedine being *ca.* 80%. The rotations of the narwedine obtained are tabulated. The rotations quoted are typical values but vary somewhat with the rate of

Wt. of (±)-narwedine (mg.)	Added alkaloid (mg.)	Solvent	$[\alpha]_D$ of narwedine
10	(−)-Galanthamine (5)	A	+188°
15	(−)-Galanthamine (5)	A	+117
10	(−)-Galanthamine (5)	B	+306
16	(+)-Epigalanthamine (8) •	B	−340
10	(−)-Lycoramine (3·5)	A	+220
10	(−)-Acetylgalanthamine (4)	A	+344
10	(−)-Galanthamine methotoluene-*p*-sulphonate (8·3) †	B	+137

• $[\alpha]_D$ +211° (*c.* 0·9 in ethanol). † Amorphous compound obtained from (−)-galanthamine and methyl toluene-*p*-sulphonate in methanol.

crystallisation of narwedine. Codeine, quinine, brucine, veratrine (the commercial mixture), and crinine did not resolve narwedine. When (±)-narwedine crystallised from ethanolic triethylamine with (+)-narwedine ($[\alpha]_D$ +405°) as a seed, the product had $[\alpha]_D$ +79° (*c* 1·0).

(+)-*Narwedine.*—(−)-Galanthamine (200 mg.) was oxidised with manganese dioxide (2 g.) in chloroform (40 ml.) in the usual way, and the mixture, containing *ca.* 30% of unchanged galanthamine, was crystallised from 95% ethanol–triethylamine (9 : 1), the hot solution being seeded with (+)-narwedine prepared in a preliminary small-scale experiment. The product (71 mg.), $[\alpha]_D$ +326° (*c* 1·0), crystallised from benzene to give (+)-*narwedine* (55 mg.), m. p. 189—192°, $[\alpha]_D$ +405° (*c* 1·0). Further crystallisation from benzene did not increase the specific rotation.

(+)-*Galanthamine and* (+)-*Epigalanthamine.*—A solution of (+)-narwedine (36 mg.), $[\alpha]_D$ +405° (*c* 1·0), in dioxan (10 ml.) was added slowly to lithium aluminium hydride (40 mg.) in ether (10 ml.) with stirring during 1 hr. at room temperature. Ethyl acetate and water were added to decompose the excess of reagent, and the supernatant liquid was decanted. The remaining paste of aluminium salts was extracted with chloroform, and the combined extracts and supernatant liquid were dried (Na_2SO_4) and evaporated. The residue was chromatographed on alumina (grade III) in the usual way (see above). The galanthamine fraction (13 mg.) crystallised readily under ether, to give partly racemic (+)-galanthamine, m. p. 110—125°, $[\alpha]_D$ +112° (*c* 0·5 in ethanol). The epigalanthamine fraction (9 mg.) had $[\alpha]_D$ +211° (*c* 0·9 in ethanol), but was not investigated further.

(−)-*Narwedine.*—(+)-Narwedine (101 mg.), $[\alpha]_D$ +392° (*c* 1·0), was reduced as described above, to give a mixture of (+)-galanthamine and (+)-epigalanthamine. To the mixture was added (±)-narwedine (100 mg.), and the whole crystallised from ethanolic triethylamine in the usual way, giving narwedine (84 mg.), $[\alpha]_D$ −346° (*c* 1·0). Crystallisation of this material from benzene then gave (−)-narwedine (67 mg.), m. p. 189—192°, $[\alpha]_D$ −400° (*c* 1·0). The mother-liquors from the first crystallisation were then used to resolve more (±)-narwedine (100 mg.), giving (−)-narwedine (77 mg.), $[\alpha]_D$ −391° (*c* 1·0).

(−)-*Galanthamine.*—(−)-Narwedine (130 mg.), $[\alpha]_D$ −396° (*c* 1·0), was reduced with lithium aluminium hydride, and the product chromatographed (as above). The galanthamine fraction was dissolved in a little ether and seeded with natural (−)-galanthamine, to give (−)-galanthamine (76 mg.) as needles m. p. 123—129°, $[\alpha]_D$ −120° (*c* 0·6 in EtOH) {lit., m. p. 127—129°, $[\alpha]_D$ −121·4° (*c* 0·99 in EtOH)}. Recrystallisation from ether gave needles, m. p. 127—130° undepressed on admixture with authentic (−)-galanthamine. The mother-liquors from the first crystallisation gave less pure material (11 mg.), $[\alpha]_D$ −111° (*c* 1·0 in EtOH). The synthetic (−)-galanthamine was converted into its hydrochloride, m. p. and mixed m. p. 253—257° (rapid heating), $[\alpha]_D$ −103° (*c* 0·6 in water).

Isolation of Narwedine from "Texas" Daffodils [with Mr. J. B. Taylor].—"Texas" bulbs (2 kg.) were ground and extracted with ethanolic tartaric acid, the procedure of Fales, Giuffrida, and Wildman [10c] being used. The final chloroform extract was evaporated to low bulk, filtered to remove lycorine, and evaporated to dryness. The residue (740 mg.) was then chromatographed in benzene on alumina (grade III) (50 g.), narwedine and galanthamine being eluted with benzene–ethyl acetate (9 : 1). After rechromatography on alumina (grade III) the narwedine, still mixed with a little galanthamine, crystallised from benzene to give prisms (25 mg.), m. p. and mixed m. p. 188—190°, $[\alpha]_D$ +52° (*c* 1·0).

Crystallisation of an artificial mixture of (±)-narwedine (10 mg.) and (−)-galanthamine (5 mg.) from benzene gave narwedine, $[\alpha]_D$ +40° (*c* 0·35) and $[\alpha]_D$ +57° (*c* 0·42) in two separate experiments.

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