[CONTRIBUTION FROM THE LABORATORY OF METABOLISM, NATIONAL HEART INSTITUTE, BETHESDA, MD.]

Narcissamine. A Quasi-Racemic Alkaloid

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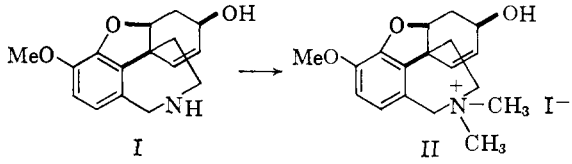
The structure of narcissamine is revised and it is shown to be a quasi-racemic alkaloid consisting of equimolar amounts of (−)-demethylgalanthamine (A) and (+)-demethyldihydrogalanthamine (B). A scheme for its biosynthesis is presented.

Narcissamine, an alkaloid found in a wide variety of Amaryllis,[2-5] has been assigned structure I[3,4] since it forms an O,N-diacetate and is partially converted to (−)-galanthamine methiodide (II) by the action of

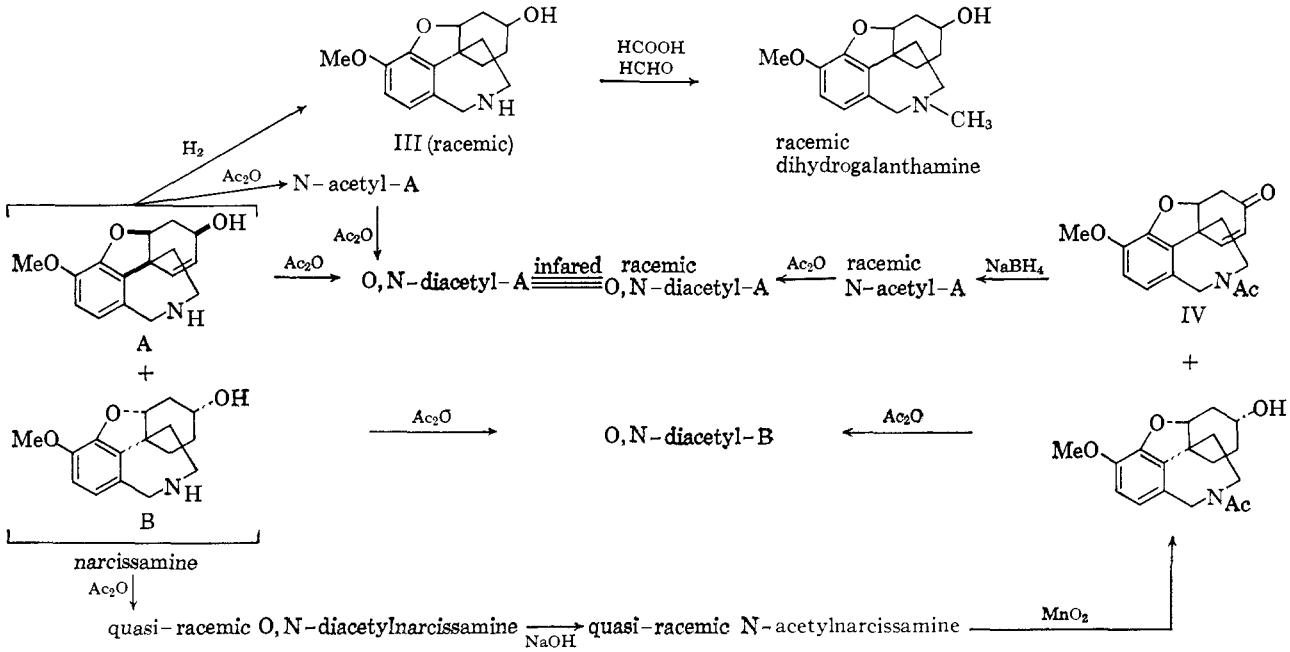


I II

methyl iodide. In spite of this apparently simple relationship, several inconsistencies remain concerning its structure.

Its melting point (158–162° or 197–198°) appeared to indicate polymorphism[3] and its rotation is anomalously low, $[\alpha]^{27}D$ −13°,[3] considering its suggested relationship to (−)-galanthamine, $[\alpha]^{26}D$ −100°. In addition, its rotatory dispersion curve exhibits an anomalous shape compared to that of the latter alkaloid (Fig. 1). Narcissamine proved to be very difficult to purify by the usual chromatographic procedures and crystallization from benzene or water was an unusually slow process.

With the advent of the high-resolution techniques of gas[6] and thin layer chromatography the compound has revealed its nature as a 1:1 complex of two closely related alkaloids. Gas chromatography on a 50:50 SE-30/QF-1[7] column showed the main peak to be slightly bifurcated at the maximum. Thin layer chromatography finally allowed complete separation (at 1-mg. levels) of the complex into its constituents and repeated separations afforded a few milligrams of both components. One compound (A, m.p. 156–158°) exhibited the optical rotatory dispersion curve (Fig. 1) initially expected for narcissamine, closely following the curve of natural (−)-galanthamine.[8] The other compound [B, m.p. 77–78° (hydrated), 134° (anhydrous)] exhibited rotation in the positive sense and followed a curve expected for the hypothetical enantiomer of (−)-dihydrogalanthamine [(−)-lycoramine] (Fig. 1). Algebraic summation of the curves of A and B yielded a curve (Fig. 1, dashed line) nearly identical with that of narcissamine itself and afforded an explanation of the anomalous shape of the latter. When both compounds were recombined, in approximately a 1:1 ratio, the melting point was raised to a value identical with that of narcissamine (197–198°). These



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(2) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 163 (1956).

(3) H. M. Fales, L. D. Giuffrida, and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 4145 (1956).

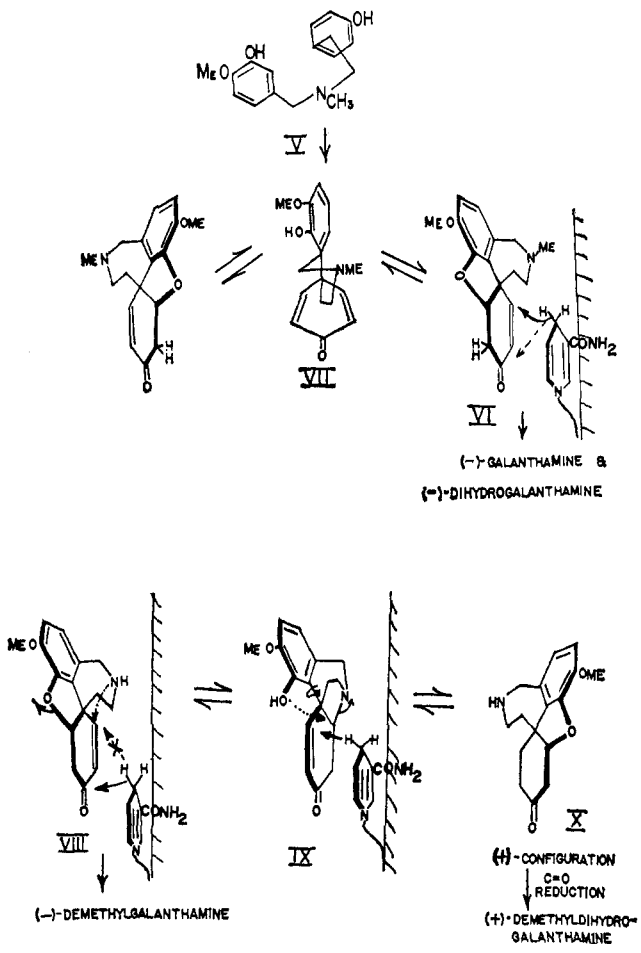
(4) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **90**, 57 (1957).

(5) H.-G. Boit, W. Dopke, and A. Beitner, *ibid.*, **90**, 2197 (1957).

(6) H. A. Lloyd, H. M. Fales, P. F. Highet, W. J. A. VandenHeuvel, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3791 (1960).

(7) W. J. A. VandenHeuvel, E. O. A. Haahti, and E. C. Horning, *ibid.*, **83**, 1513 (1961).

(8) The curve of (−)-desoxydihydrogalanthamine [*cf.* S. Uyeo and K. Koizumi, *Pharm. Bull.* (Tokyo), **1**, 139, 202 (1963)] is included since it shows the rotatory effect of the quaternary carbon and ether linkages free from the hydroxyl group. The fact that this is nearly identical with the curve of (−)-galanthamine emphasizes the small contribution of the axial allylic alcohol in the latter case. This substantiates Barton and Kirby's assignment (see below) of the absolute configuration of (−)-galanthamine as I on the basis of Mills' rule.



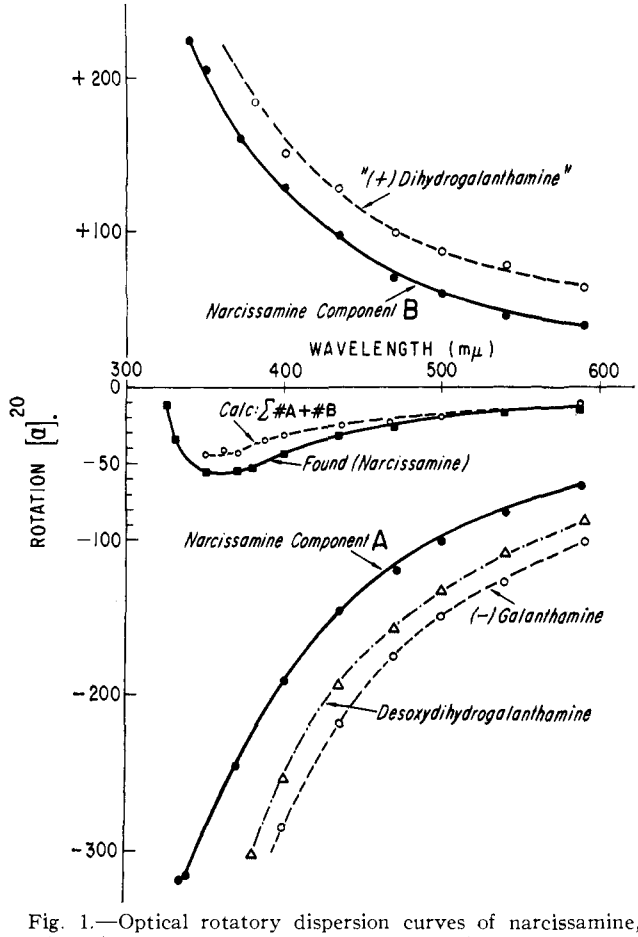


Fig. 1.—Optical rotatory dispersion curves of narcissamine, narcissamine components A and B, galanthamine, (+)-dihydrogalanthamine, and desoxydihydrogalanthamine.

facts suggested that narcissamine was a quasi-racemic complex, but the nature of the complex was ascertained only by consideration of its reduction product. On catalytic hydrogenation, in agreement with the results of Boit and Ehmke,[2] exactly 0.5 equiv. of hydrogen was absorbed and the fully racemic, optically inactive N-demethyldihydrogalanthamine (III) was obtained and characterized as its O,N-diacetate. The racemate was then methylated with formaldehyde and formic acid to give a compound identical in infrared spectrum in chloroform with natural (−)-dihydrogalanthamine, establishing its structure as given. At this point the n.m.r. spectrum of narcissamine was investigated and the olefinic proton area at 6.02 δ was found to be one-half of that expected by comparison with the single aromatic proton peak at 6.60 δ. In addition, the methoxyl group at 3.80 δ was very slightly split at the maximum indicating the presence of two compounds. It is apparent that narcissamine is a quasi-racemic[9] compound containing equimolar amounts of (−)-demethylgalanthamine (A) and (+)-demethyldihydrogalanthamine (B) [(+)-demethyllycoramine]. Compounds A and B were independently converted to their O,N-diacetates to confirm the presence of OH and NH functions by absorption at 5.78 and 6.08 μ in the infrared.

O,N-Diacetylnarcissamine, formed by the direct acetylation of narcissamine and reported earlier,[2] melted sharply at 209–210° and is undoubtedly a similar quasi-racemate. On short treatment with dilute sodium hydroxide the O-acetyl group is cleaved and a third quasi-racemate, N-acetylnarcissamine, is formed which melts sharply at 167–168° and also shows one-half the theoretical number of olefinic protons in its n.m.r. spectrum. This mixture of secondary alcohols was oxidized with manganese dioxide furnishing the N-acetyl-unsaturated ketone IV which was found to be optically inactive as expected on the basis of the easy racemization of the closely related galanthaminone (see below). Under these conditions, the nonallylic alcohol (+)-N-acetyldihydrogalanthamine remained unoxidized and was recovered in pure form. Further acetylation gave an O,N-diacetate identical with that of component B itself, confirming its nature.

The corresponding N-acetyl derivative of A was obtained *via* a Schotten–Baumann acetylation of narcissamine, the unsaturated alcohol selectively crystallizing from the reaction solvent. It was identified by further acetylation to the same O,N-diacetyl derivative as that produced by A itself.

Possession of the quasi-racemic N-acetylnarcissamine allowed an examination of the stereochemistry of components A and B. At high dilution in carbon tetrachloride only one strongly bonded hydroxyl band is observed at 3580 cm.$^{-1}$ (half-intensity band-width

(9) The term "quasi-racemate" was originated by A. Fredga, *Arkiv. Kemi. Mineral. Geol.*, **18B**, 4 (1944), and defines the formation of a crystalline compound when two closely related, but not identical, compounds bearing an enantiomorphic relationship to each other are combined in a 1:1 ratio. Fredga has recently thoroughly reviewed the whole subject of quasi-racemates; *cf. Tetrahedron*, **8**, 126 (1960). The authors are indebted to one of the referees for pointing out the existence of a quasi-racemate "J-2" consisting of an equimolecular mixture of dalbergione and 4''-methoxydalbergione of opposite absolute configuration: W. B. Eyton, W. D. Ollis, I. O. Sutherland, L. M. Jackman, O. R. Gottlieb, and M. T. Mogalhães, *Proc. Chem. Soc.*, 301 (1962).

= 35 cm.$^{-1}$), clearly indicating that both hydroxyls in the mixture are *cis*-1,3-diaxially oriented with respect to the ether bridge as in the cases of galanthamine and dihydrogalanthamine.[10]

Sodium borohydride reduction of the fully racemic unsaturated ketone IV obtained previously yielded the racemic N-acetyl unsaturated alcohol identical in its infrared spectrum in chloroform solution with the optically active N-acetyl unsaturated alcohol obtained directly from narcissamine. Further acetylation furnished the racemic O,N-diacetyl derivative of A which was identical in chloroform with that of its optically active counterpart.

This may be the second quasi-racemate isolated from natural sources.[9,11] Since it is a crystal phenomenon it probably does not exist as such in the plant tissues. Our interest in the condition lies in the fact that the same plant[2,4] contains both of the corresponding N-methyl derivatives (−)-galanthamine and (−)-dihydrogalanthamine (lycoramine). However, these are both unquestionably in the same (−)-antipodal series and so do not form a quasi-racemic complex. Although component A may be a precursor or direct metabolite of its N-methyl derivative, (−)-galanthamine, component B cannot be so related to (−)-dihydrogalanthamine because of its antipodal nature. It is suggested that *neither* of the narcissamine components are, in fact, metabolic precursors of galanthamine and its dihydro derivative. Barton and Kirby have shown that the O,N-dimethylnorbelladine (V) is converted to galanthamine in plants and it seems likely that the naturally occurring (−)-narwedin (VI) is an intermediate.[12] The latter is easily racemized (its half-life in alcohol is 18 min. at 25°)[12] presumably through the dienone VII. This has been confirmed by proton n.m.r. studies (see Experimental).

If a right-handed enzyme surface acting through the dihydropyridine nucleotide (TPNH or DPNH) selected VI as shown, 1,2-reduction of the unsaturated ketone would furnish the unsaturated alcohol (−)-galanthamine while 1,4- followed by 1,2-reduction would yield the related saturated alcohol (−)-dihydrogalanthamine.

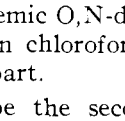
In the case of the N–H analog of (−)-narwedin (VIII), 1,2-reduction of the unsaturated ketone might occur on a similar enzyme surface to yield (−)-demethylgalanthamine (component A) analogous to (−)-galanthamine. However, 1,4-reduction on this side may be inhibited by prior formation of the relatively stable structure IX. If this is the case, 1,4-reduction may still be possible on the *opposite* side of the cyclohexenone ring. Inversion of configuration will then occur when the resulting saturated ketone undergoes β-elimination of the tertiary nitrogen followed by rotation of the aromatic ring and readdition of the phenolate anion as shown in X. The reaction is completed when the inverted saturated ketone X is reduced to the inverted (+)-demethyldihydrogalanthamine (component B). The foregoing is admittedly speculative and tracer studies are in progress to determine whether one enzyme system is indeed responsible for the formation of both components of narcissamine.

(10) D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.*, 39 (1960); D. H. R. Barton, G. W. Kirby, J. B. Taylor, and G. M. Thomas, *ibid.*, 254 (1961).

(11) H. M. F. is indebted to Dr. J. T. Potts of this laboratory for pointing out that the original Narcissus exhibited an analogous quasi-racemism as he gazed into a pool at his reflected image.

(12) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962).

Experimental[13]

Narcissamine isolated from *Narcissus pseudonarcissus*. L. (King Alfred daffodils) as described previously[3] melts sharply at 197–198° after extensive recrystallization from ethyl acetate (reported m.p. 195–196°,[2] 193–199°[3]),[14] $[\alpha]^{23}D$ −13°, $[\alpha]^{23}_{436}$ −33.5° (*c* 0.74, chloroform); $[\alpha]^{23}D$ −17°, (*c* 0.25, chloroform); see also Fig. 1. The proton n.m.r. spectrum shows absorption at 3.80 and 3.83 (3H doublet, OCH_3), 6.02 (1H broad singlet, 
0.5 , see text) and 6.60 δ (2H singlet, aromatic H). After equilibrating with D_2O[15] the band at 2.12 δ (2H broad singlet) disappeared and was thus assigned to both NH and OH groups.

The previously reported[3] figures are in better agreement with those calculated for the complex. *Anal.* Calcd. for $C_{16}H_{19}NO_4 \cdot C_{16}H_{21}NO_4$: C, 70.05; H, 7.35; N, 5.11. Found: C, 70.07; H, 7.27; N, 4.92.

O,N-Diacetylnarcissamine (quasi-racemate) was prepared as described previously from pyridine and acetic anhydride. Recrystallization from ethanol furnished long prisms, m.p. 209–210°, $[\alpha]^{23}D$ +20°, $[\alpha]^{23}_{436}$ +49.8° (*c* 0.86, chloroform); reported m.p. 208–209°, $[\alpha]^{22}D$ +19.3°, $[\alpha]^{22}_{436}$ +44.2° (*c* 0.62, chloroform). The reported analytical figures[3] are in fair agreement with the complex. *Anal.* Calcd. for $C_{20}H_{23}NO_5 \cdot C_{20}H_{25}NO_5$: C, 67.02; H, 6.75; N, 3.91. Found: C, 67.11; H, 6.42; N, 4.01.

N-Acetylnarcissamine (quasi-racemate) was prepared by heating 200 mg. of the above quasi-racemic diacetate with an excess of 5% sodium hydroxide on the steam bath for 1 hr. Extraction with chloroform gave the crude product which was crystallized from ethyl acetate to give 100 mg. of crystals, m.p. 167–168°, $[\alpha]^{25}D$ −8.9°, $[\alpha]^{25}_{436}$ −23.4° (*c* 0.47, chloroform). The product shows absorption at 6.12 μ (N-acetyl) and at 3580 cm.$^{-1}$ (half-intensity band-width = 35 cm.$^{-1}$) at high dilution in carbon tetrachloride. The latter is characteristic of a somewhat strained hydrogen-bonded hydroxyl group.[16] The proton n.m.r. shows peaks at 2.10 (3H singlet, CH_3—C(=O)—N), 3.86 (*3H* singlet, CH_3O), *6.00* (1H broad singlet, *0.5* H>C=C<*H*, see text), and 6.69 δ (2H doublet, aromatic H). In benzene the N-acetyl methyl group peak is split into two bands of equal height at 3.36 and 3.44 δ.

Anal. Calcd. for $C_{18}H_{21}NO_4 \cdot C_{18}H_{22}NO_4$: C, 68.33; H, 7.01. Found: C, 68.19; H, 7.05.

Upon treatment with acetic anhydride and pyridine the compound was converted to the original quasi-racemic O,N-diacetylnarcissamine identical in all respects with the latter.

Action of Manganese Dioxide on N-Acetylnarcissamine.—A solution of 146 mg. of N-acetylnarcissamine was mixed with 1.56 g. of activated manganese dioxide in chloroform and allowed to stir overnight. Filtration left an oil which still exhibited hydroxyl absorption at 2.80 μ as well as a new carbonyl band at 5.94 μ. Chromatography over alumina with ethyl acetate produced 65 mg. of crude **N-acetyldemethylgalanthaminone (IV)**. Elution with 2% ethanol in ethyl acetate produced 63 mg. of unoxidized crude (+)-**N-acetyldemethyldihydrogalanthamine.**

The unsaturated ketone IV, m.p. 175–177°, was recrystallized from acetone–water, and shows bands in the infrared at 5.94 (unsaturated carbonyl) and 6.08 μ (N-acetyl), λ_{max}^{EtOH} 263 mμ (ϵ

(13) All melting points are corrected and were observed on a Kofler microscope hot stage equipped with polarizer. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and the authors wish to record their gratitude to Mr. Alicino for his excellent work often performed on samples well below the usual 3–4 mg. Ultraviolet absorption spectra were recorded with a Cary Model 11 MS spectrophotometer in absolute alcohol and infrared spectra were recorded with Perkin–Elmer Model 21 and Beckman Model IR-7 spectrophotometers. Except where noted, infrared spectral band assignments were recorded in chloroform solution, but all identities were confirmed by KBr pellet spectra. Optical rotatory dispersions were carried out on a Rudolph spectropolarimeter. N.m.r. spectra were recorded with a Varian A-60 spectrometer at 60 Mc. in deuteriochloroform with tetramethylsilane as an internal standard. All spectral work was performed by Mrs. K. S. Warren.

(14) Material obtained earlier, melting at 158–163°, may have been a small amount of component A rather than a polymorph as suggested.

(15) H. M. Fales and A. V. Robertson, *Tetrahedron Letters*, **3**, 111 (1962).

(16) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **85**, 784 (1963).

4910), λ_{sh}^{EtOH} 300 mμ (ε 2500), $[\alpha]^{26}D$ 0.0°, $[\alpha]^{25}_{436}$ 0.0° (*c* 0.81, chloroform).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.90; H, 6.40; N, 4.53.

The compound exhibits peaks in the proton n.m.r. spectrum at 2.12 (3H singlet, OAc), 3.87 (3H singlet, OCH_3), 6.75 (2H singlet, aromatic protons), and a broad quartet at 2.97 δ (2H, J_1 = ~10 c.p.s., J_2 = 3 c.p.s.; $—CH_2C(=O)—$). The olefinic proton adjacent to the ketone appears at 6.06 δ (1H doublet, J = 11 c.p.s.) while the β-proton is at 6.90 δ (1H doublet, J = 11 c.p.s.). The β-proton doublet is further split into two triplets (J = ~2 c.p.s.) by long-range coupling, presumably to the nearby methylene of the ethylamine side chain. On addition of perdeuterioacetic acid to the deuteriochloroform the spectrum did not immediately change, but after being heated at 100° (sealed tube) overnight the broad quartet at 2.97 δ owing to the α-methylene group had disappeared. The olefinic protons were unchanged in appearance indicating that migration of the oxide bridge is not catalyzed by acetic acid. Addition of excess trimethylamine (sealed tube) caused an immediate loss of the doublet owing to the α-olefinic proton at 6.06 δ and concomitant collapse of the β-protons to a broad singlet at 7.05 δ indicating that migration of the oxide linkage is catalyzed by base as suggested earlier by Barton and Kirby.[12]

The unoxidized dihydro component (+)-**N-acetyldemethyldihydrogalanthamine**, m.p. 178–180°, was recrystallized from ethyl acetate, and depressed the melting point of the ketone IV on admixture. The material shows absorption at 2.85 (hydroxyl) and 6.08 μ (N-acetyl), $[\alpha]^{24}D$ +5.1°, $[\alpha]^{24}_{436}$ +34° (*c* 0.55, chloroform).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.34. Found: C, 68.44; H, 7.59.

A small sample of this material was acetylated further with pyridine and acetic anhydride, requiring 48 hr., and yielding (+)-**N-diacetyldemethyldihydrogalanthamine**, m.p. 177–179°, identical in all respects with the material obtained from acetylation of isolated (+)-demethyldihydrogalanthamine (see below).

(−)-**N-Acetyldemethylgalanthamine.**—A solution of 100 mg. of narcissamine was stirred with a large excess of 10% sodium hydroxide, and 1 ml. of acetic anhydride was added slowly at room temperature. Acetic acid was added to acidify the solution and after several days the derivative crystallized in rectangular prisms. Recrystallization from ethyl acetate gave material, m.p. 209–211°, showing bands at 6.12 (N-acetyl) and 2.85 μ (hydroxyl).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71. Found: C, 68.39; H, 6.78.

On further acetylation with pyridine–acetic anhydride (−)-O,N-diacetyldemethylgalanthamine (the O,N-diacetate of A) was obtained melting at 234–235° and identical in all respects with the latter.

When treated with manganese dioxide in chloroform a small sample was completely oxidized (absence of the 2.90 μ hydroxyl band) to the racemic N-acetyldemethylgalanthaminone (IV), m.p. 175–177°, obtained earlier from oxidation of the quasiracemic N-acetylnarcissamine.

Separation of the Components of Narcissamine. a. Gas Chromatography.—A doublet was observed when narcissamine was gas chromatographed at 234° on a 12 ft. × 3.4 mm. i.d. glass column containing 1% of a 50/50 (w./w.) mixture of General Electric silicone SE-30 and Dow-Corning QF-1 polymers on 100–140 mesh Applied Science Laboratories Gas Chrom-P packing. The pressure was 21 p.s.i. (argon) and the first component eluted at 6.10 min., the second at 6.35 min. Under the same conditions (−)-galanthamine eluted at 5.34 min. and (−)-dihydrogalanthamine at 5.55 min., so it is reasonable to assume that the unsaturated alcohol (A) is the earliest component of the former doublet.

b. Thin Layer Chromatography.—Narcissamine was separated into its two components by horizontally spotting a maximum of 1 mg. on an 0.5 mm. thick silica gel "G" plate, 8 × 8 in., and eluting with a mixture of chloroform, ethyl acetate, and methanol in a volume ratio of 10:10:30, respectively. Component A shows a slightly higher R_f (0.11) than component B (R_f 0.07). Efforts to increase the movement of either spot with a wide variety of solvents failed, and it was necessary to resort to the use of many plates to acquire enough material for characterization. The compounds were identified with a light spray of Dragendorff reagent; then the spots were scraped off the plates, and the bases were eluted from the silica with ammoniacal chloroform containing 2% ethanol. Evaporation left an oil in each case which was evaporatively distilled at 150° (1 μ) and recrystallized from appropriate solvents. In this way, component A, (−)-**demethylgalanthamine**, was obtained and recrystallized from ethyl acetate; m.p. 156–158°, $[\alpha]^{23}D$ −62°, $[\alpha]^{23}_{436}$ −146° (*c* 0.28, chloroform); see Fig. 1. The compound exhibits an infrared spectrum (KBr) which differs from that of either narcissamine or its other component (B). The ultraviolet spectrum shows a maximum at 285 mμ and the general shape is identical with that of narcissamine. Insufficient material was on hand to determine accurately the extinction coefficient.

The material was quite hygroscopic and because of its instability and the paucity of material only one analysis was obtained.

Anal. Calcd. for $C_{16}H_{19}NO_3 \cdot 0.5\ H_2O$: C, 68.06; H, 7.14. Found: C, 68.26; H, 7.07.

The other component (+)-**demethyldihydrogalanthamine** (B) was isolated in a similar fashion and evaporatively distilled at 150° (1 μ) to provide an oil, which slowly crystallized in the air as it absorbed moisture. The hydrate melted at 77–87° as it lost water, then recrystallized and melted again at 134°. In spite of the hygroscopic nature of both A and B, when they were mixed in approximately equal amounts on a cover glass the mass sintered below 100° and recrystallized at 130°. The bulk of the material formed prisms identical with those of narcissamine and finally melted sharply at 197–198°. Component B also exhibits an infrared spectrum (KBr) different from that of narcissamine or A and an ultraviolet maximum and shape identical with that of narcissamine; $[\alpha]^{23}D$ + 38.2°, $[\alpha]^{23}_{436}$ +97.5° (*c* 0.28, chloroform); see Fig. 1.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.99; H, 7.90.

O,N-Diacetyl Derivatives of A and B.—Because of the sensitive nature of the secondary amino alcohols A and B, as well as their scarcity, they were individually converted to their O,N-diacetyl derivatives with an excess of pyridine and acetic anhydride. The acetylation mixtures after standing at room temperature 48 hr. were decomposed with aqueous bicarbonate and extracted with chloroform to recover the products.

(−)-**O,N-Diacetyldemethylgalanthamine,** m.p. 234–235°, was recrystallized from ethanol, and shows bands at 5.78 (O-acetyl) and 6.08 μ (N-acetyl) in the infrared.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 66.96; H, 6.31.

(+)-**O,N-Diacetyldemethyldihydrogalanthamine** was recrystallized from ethanol and sublimed at 150° (0.1 mm.), m.p. 177–179°. It exhibits bands at 5.78 (O-acetyl) and 6.08 μ (N-acetyl) in the infrared. On admixture with the former diacetate the material sintered at 150°, recrystallized, and finally melted sharply at 207–209°, which is the melting point of the quasiracemic O,N-diacetylnarcissamine, $[\alpha]^{24}D$ +18°, $[\alpha]^{24}_{436}$ +52° (*c* 0.21, chloroform).

Anal. Calcd. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01. Found: C, 66.85; H, 7.21.

Racemic N-Acetyldemethylgalanthamine.—A solution of 50 mg. of the racemic unsaturated ketone IV was reduced with an ethanolic solution of sodium borohydride. After decomposition of the excess borohydride with dilute hydrochloric acid and treatment with base, the mixture of epimeric alcohols was extracted with chloroform. Crystallization from ethyl acetate gave racemic N-acetyldemethylgalanthamine as the only isolable product, m.p. 156–158°. This shows the same infrared spectrum in chloroform as its optically active counterpart obtained earlier (m.p. 209–211°).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71. Found: C, 68.36; H, 6.81.

Racemic O,N-diacetyldemethylgalanthamine was prepared by acetylating 10 mg. of the above alcohol with pyridine and acetic anhydride. The product was recrystallized from ethyl acetate, m.p. 204–205°, and exhibits the same infrared spectrum in chloroform as its optically active counterpart, m.p. 234–235°, $[\alpha]^{25}D$ 0.0°, $[\alpha]^{25}_{436}$ 0.0° (*c* 0.25, chloroform).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 66.96; H, 6.77.

Hydrogenation of Narcissamine.—Narcissamine (110 mg.) in ethanol with 20 mg. of prereduced 10% palladium-on-charcoal absorbed one-half of the theoretical amount of hydrogen in 1 hr. Filtration from the catalyst left amorphous **dihydronarcissamine** which showed $[\alpha]^{23}D$ −1.7°, $[\alpha]^{23}_{436}$ −4° (*c* 0.64, chloroform), but stubbornly refused to recrystallize. The proton n.m.r. indicates the absence of a band at 6.02 δ previously assigned to the olefinic

protons, confirming its total reduction. Chromatography on alumina still did not permit crystallization, so the material was acetylated with pyridine and acetic anhydride. Prisms of **racemic O,N-diacetyldemethyldihydrogalanthamine** were obtained which were recrystallized from ethyl acetate and sublimed at 150° (0.1 mm.), m.p. 208–209.5°, $[\alpha]^{23}D$ 0.00,° $[\alpha]^{23}_{436}$ 0.00° (*c* 0.19, chloroform). The infrared spectrum in chloroform was identical with its optically active counterpart (m.p. 177–179°). Surprisingly, the compound does not appear to depress the racemic O,N-diacetyldemethylgalanthamine, m.p. 204–205°, but fortunately its infrared spectrum (KBr) exhibits many points of difference.

Conversion of Dihydronarcissamine to Racemic Dihydrogalanthamine.—A solution of 150 mg. of the crude hydrogenation product of narcissamine in a mixture of 1 ml. of 90% formic acid and 1 ml. of 37% formalin was heated on the steam bath for 3 hr., basified, and extracted into chloroform. The product was then chromatographed over alumina with 1% ethanol in ethyl acetate and the resulting oil evaporatively distilled at 150° (0.1 mm.). The infrared spectrum of the product is identical in chloroform solution with (−)-dihydrogalanthamine and gas phase chromatography shows a retention time identical with the latter (see above). The material was purified by crystallizing its hydriodide salt from water, recovering the free base with alkali, and evaporatively distilling the product. Still an oil, the product showed $[\alpha]^{23}D$ 0.0°, $[\alpha]^{23}_{436}$ 0.0° (*c* 0.655, chloroform).

Anal. Calcd. for $C_{17}H_{29}NO_3$: C, 70.56; H, 8.01. Found: C, 70.32; H, 7.91.

The compound formed a **methiodide** from acetone which was recrystallized from ethanol–water; m.p. 300° dec. The infrared spectrum (KBr) of the salt is very similar to, but not identical with, that of (−)-dihydrogalanthamine methiodide.

Anal. Calcd. for $C_{18}H_{26}NO_3I$: C, 50.12; H, 6.08; I, 29.43. Found: C, 50.39; H, 6.07; I, 29.34.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASS.]

Terpenes. XIX.[1] Synthesis of Patchouli Alcohol[2]

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(+)-Camphor was converted to (−)-homocamphor by known methods and in a short synthetic sequence the latter was transformed to the tricyclic cyclopentenone **10**. Condensation with methylmagnesium iodide or with triphenylphosphinemethylene followed by hydrogenation yielded β-patchoulene (**12**). Rearrangement of the corresponding epoxide **16** with boron fluoride furnished the desired unsaturated alcohol **18**. This key intermediate was subsequently transformed to patchoulione (**2**) and to α-patchoulene (**23**). A previously accomplished but at that time incorrectly interpreted reconversion of α-patchoulene (**23**) to patchouli alcohol (**28**) completed the synthesis. Some transformations of the natural product **28** are reinterpreted in terms of a new structure determined by the X-ray method.

Patchouli alcohol is a constituent of the East Indian shrub *Pogostemon patchouli* and a major component of commercial patchouli oil. Structure **1** was recently deduced from analytical studies[5] and this paper describes a synthesis of this sesquiterpene alcohol. The planning of our synthetic work was influenced by the finding that patchoulione (**2**), a transformation product of the alcohol, has a powerful ambergris-type odor. Consequently it seemed important to devise a synthetic sequence to the natural product in which patchoulione (**2**) figures as an intermediate. Furthermore, the construction of β-patchoulene (**12**), an olefin with rearranged skeleton, appeared simpler than a synthesis of α-patchoulene (**23**). The success of such a scheme would then depend on the ultimate transformation of β-patchoulene (**12**) to a substance with the tricyclic framework of the natural product. β-Patchoulene (**12**) contains the same bicyclo[1.2.3]-octane skeleton as (−)-homocamphor[6] (**3**) and the first phase of the synthesis was concerned with the attachment of a cyclopentane ring to this readily available starting material. Initial efforts to add a three-carbon chain by Stobbe condensations with diethyl succinate or with tetraethyl phosphonosuccinate[7] failed and addition of the sodium salt of ethyl propiolate[8] resulted in a Michael adduct rather than the desired carbinol. Realizing that the source of these difficulties may lie in the reversibility of these reactions, we turned to an irreversible process and addition of allylmagnesium chloride furnished the desired alcohol **4**. There was little doubt that the adduct had the configuration indicated and this was verified by its further transformations.[9] Treatment of the unsaturated alcohol **4** with diborane[10] followed by oxidation with Jones reagent[11,12] yielded the spirolactone **5** with infrared absorption at 1770 cm.$^{-1}$. Attempts to dehydrate this lactone with polyphosphoric acid[13] led to no useful result, but treatment with zinc chloride in a mixture of acetic acid and acetic anhydride[14] furnished a mixture of two ketones.

The minor product (10%) was optically inactive and had λ^{EtOH}_{max} 247 mμ (ε 14,500); $\nu^{CCl_4}_{max}$ 1665 and 1615 cm.$^{-1}$; n.m.r.[15] at 4.25 (1 H, singlet) and 8.82 τ (6 H,

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(4) Pan American Union Fellow on leave from the Universidad Nacional Autonoma, Mexico, D.F.

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(15) N.m.r. spectra were measured in carbon tetrachloride solution on a Varian Associates A-60 instrument with tetramethylsilane as internal refer-