Notes

The Structure of Daphmacropodine, a New Alkaloid from *Daphniphyllum macropodum* Miquel, and Its Chemical Conversion into Daphmacrine

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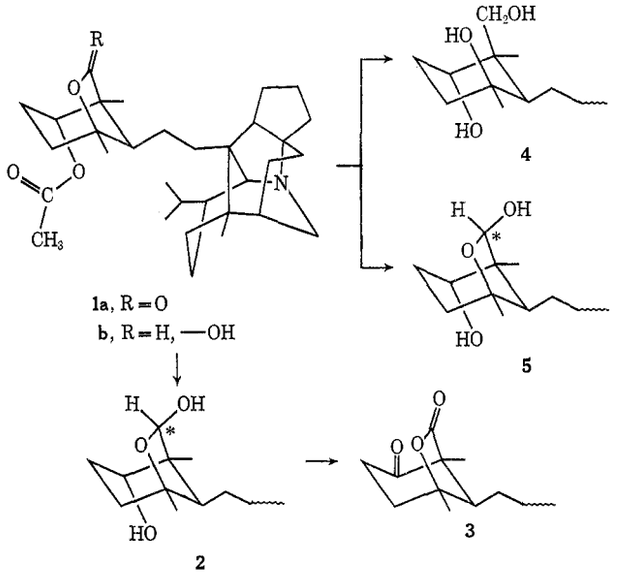
In previous publications,[1a-d] we have reported the isolation from the bark of *Daphniphyllum macropodum* Miquel (Euphorbiaceae) of eight new alkaloids, *viz.*, daphnimacropine,[1a] macrodaphnidine (yuzurimine),[1b,2] daphniphyllamine (daphniphylline),[1b,2] daphmacrine,[1b,d,3] macrodaphniphyllidine,[1b] macrodaphnine,[1b,c] macrodaphniphyllamine,[1b] and daphmacropodine,[1b] and have elucidated the structures of all of them, except for daphmacropodine. These alkaloids possess unusual structures and apparently belong to a new group of alkaloids.

Chart I



The present paper describes the structure of the remaining alkaloid, daphmacropodine,[4] from this same plant, and its chemical interrelation with daphmacrine (**1a**).[1b,d,3]

Daphmacropodine (**1b**), $C_{32}H_{51}O_4N$, crystallized from acetone to show mp 214°, $[\alpha]D$ +4.9° (*c* 1.11, $CHCl_3$), hydrobromide mp 215–218° (from acetone). It showed an ester carbonyl band at 1740 cm^{-1} in the infrared spectrum. The mass spectrum gave peaks at *m/e* 513 (M^+), 498 ($M^+ - CH_3$), 470 [$M^+ - (CH_3)_2CH$], 453 ($M^+ - CH_3COOH$), 430, 412, 407, 392, 364, 300, 286, 272, and 230. The fragment peaks at *m/e* 286, 272, and 230 are typical of daphniphyllamine and related alkaloids.[1b] The nmr spectrum ($CDCl_3$, 100 Hz) displayed signals at τ 9.10 (3 H) and 8.99 (3 H) (doublets, J = 6.5 Hz, one isopropyl), 9.02 (3 H), 8.96 (3 H), and 8.68 (3 H) (singlets, three quaternary methyls), 7.92 (3 H, singlet, one acetoxyl), and 5.26 (1 H, triplet, J_{AX+BX} = 8 Hz, equatorial proton adjacent to the acetoxyl group). A one-proton singlet at τ 5.22 suggested the presence of a hemiacetal grouping [HO(**H**)C(OC)R].[5]

Mild alkaline hydrolysis of daphmacropodine (**1b**) and subsequent chromatography afforded a deacetyl derivative (**2**), $C_{30}H_{49}O_3N$. The hemiacetal structure shown in **1b** was confirmed by oxidation of this derivative with Jones reagent[6] at 0°. The crude product obtained was converted into the hydrochloride and chromatography furnished a pure keto lactone (**3**) as the hydrochloride, ir (KBr) 1766 (γ-lactone) and 1716 cm^{-1} (six-membered ketone). Reduction of daphmacropodine (**1b**) with lithium aluminum hydride in ether–dioxane yielded a triol (**4**), $C_{30}H_{51}O_3N$, mp 238.5–239° (from ethanol–acetone). Chromatography of the mother liquors of this triol[7] yielded a second alcohol (**5**), $C_{30}H_{49}O_3N$, mp 204–205° (from acetone). The infrared spectrum of this alcohol proved to be different from that of the deacetyl derivative **2** obtained by alkaline hydrolysis of daphmacropodine (**1b**), and it is assumed that they are anomers which differ in the configuration at the asterisked carbon.[8] On reduction with lithium aluminum hydride, daphmacropodine (**1b**) yielded the same two alcohols, **4** and **5**.

The above experimental results revealed the hemiacetal nature and also the close relation of daphmacropodine (**1b**) to daphmacrine (**1a**), whose lactonic structure and absolute configuration have been established by X-ray crystallographic analysis.[1d,3]

The crude product from Jones oxidation[6] of daphmacropodine (**1b**) was converted into a lactone hydrobromide, mp >300° (*ca.* 315°) (from acetone–ether), which was identical with daphmacrine (**1a**) hydrobromide.

Experimental Section

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer

(1) (a) N. Kamijo, T. Nakano, S. Terao, and K. Osaki, *Tetrahedron Lett.*, 2889 (1966); (b) T. Nakano and Y. Saeki, *ibid.*, 4791 (1967); (c) T. Nakano and B. Nilsson, *ibid.*, 2883 (1969); (d) T. Nakano, Y. Saeki, C. S. Gibbons, and J. Trotter, *Chem. Commun.*, 600 (1968).

(2) N. Sakabe, H. Irikawa, H. Sakurai, and Y. Hirata, *Tetrahedron Lett.*, 963, 965, 5363, 6309 (1966); *ibid.*, 553 (1967).

(3) Note that the absolute configuration of this alkaloid has also been established: C. S. Gibbons and J. Trotter, *J. Chem. Soc. B*, 840 (1969).

(4) A brief description of this alkaloid has been presented at the 5th International Symposium on the Chemistry of Natural Products, London, July 1968. Also see ref 1b.

(5) D. Lavie, M. K. Jain, and I. Kirson, *J. Chem. Soc. C*, 1347 (1967).

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(7) T. Nakano and S. Terao, *J. Chem. Soc.*, 1417 (1966).

(8) The relative configurations at this carbon of these two anomers and daphmacropodine (**1b**) itself have not been studied because of the small amounts available.

337 spectrometer for potassium bromide disks. Rotations were measured at 26° with a Kreis polarimeter 0.01 for solutions in chloroform. Nmr spectra were obtained for solutions in deuteriochloroform with a Varian HA-100 spectrometer, with tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU 6E at 70 eV using a direct inlet system. Thin layer chromatograms were prepared on silica gel G and developed with chloroform–ethylamine (usually 100:2–5, v/v); the spots were observed either by spraying with Dragendorff's reagent or by exposure to iodine vapor. All extracts were dried over anhydrous sodium sulfate or magnesium sulfate before evaporation. Microanalyses were carried out by A. Bernhardt, Microanalytical Laboratory, 5251 Elbach über Engelskirchen, West Germany.

Alkaline Hydrolysis of Daphmacropodine (1b).—The alkaloid (100 mg) was heated under reflux with 1 *N* methanolic sodium hydroxide (10 ml) for 1.5 hr. After addition of water, the product was extracted with chloroform and the chloroform extract was washed with water, dried, and evaporated. The crude product (92 mg) thus obtained was chromatographed over Merck standardized alumina (activity II–III). Elution with 2–5% methanol in chloroform yielded the deacetyl derivative **2** (35 mg). After recrystallization from acetone, it showed mp 130–135°.

Anal. Calcd for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.15; H, 10.26; N, 3.10.

Oxidation of the Deacetyl Derivative 2 with Jones Reagent.[6]—The deacetyl derivative **2** (50 mg) in acetone (3 ml) was oxidized with stirring at 0° with Jones reagent (0.08 ml). After 10 min, methanol was added to destroy the excess reagent. The solution was diluted with water and basified with aqueous ammonia, and the product was extracted with chloroform. Washing of the chloroform extract with water, drying, and evaporation yielded a crude product (49 mg). This was converted into the hydrochloride and purified by chromatography over Mallinckrodt silicic acid (3 g). Elution with 10% methanol in chloroform yielded a keto lactone (**3**) (25 mg) as the hydrochloride, mp 179–180° (from acetone–ether), mass spectrum *m/e* 467 (M^+ − HCl), 452, 424, 369, 302, 290, 286, 272, and 230.

Anal. Calcd for $C_{30}H_{45}O_3N \cdot HCl$: C, 71.40; H, 9.19; N, 2.77. Found: C, 71.25; H, 8.89; N, 2.51.

Reduction of Daphmacropodine (1b) with Lithium Aluminum Hydride.—A solution of the alkaloid (300 mg) in anhydrous dioxane (6 ml) was added dropwise at room temperature to a stirred suspension of lithium aluminum hydride (150 mg) in anhydrous ether (80 ml). After 4 hr, a mixture of ethyl acetate (5 ml) and chloroform (15 ml) was added and the solution was stirred for 40 min. Then ethyl acetate (5 ml) saturated with water (1 ml) was added and stirring was continued for a further 20 min. The solution was filtered and the filtrate was concentrated *in vacuo* and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to yield crystals (290 mg) which gave two spots on tlc. Purification by recrystallization from ethanol–acetone yielded a triol (**4**) (139 mg), mp 238–239°, mass spectrum *m/e* 473 (M^+), 455 ($M^+ - H_2O$), 440 [$M^+ - (H_2O + CH_3)$], 424 [$M^+ - (H_2O + CH_2OH)$], 412 {$M^+ - [H_2O + (CH_3)_2CH]$}, 372, 300, 286, 272, and 230.

Anal. Calcd for $C_{30}H_{51}O_3N$: C, 76.06; H, 10.85; N, 2.96. Found: C, 75.89; H, 10.66; N, 2.79.

The mother liquor of the above triol was chromatographed on neutralized Mallinckrodt silicic acid[7] (10 g). Elution with 1–2% ethanol in chloroform yielded a second alcohol (70 mg) (**5**), mp 204–205° (from acetone), mass spectrum *m/e* 471 (M^+), 456 ($M^+ - CH_3$), 453 ($M^+ - H_2O$), 438 [$M^+ - (H_2O + CH_3)$], 428 [$M^+ - (CH_3)_2CH$], 412, 388, 306, 300, 294, 286, 272, and 230.

Anal. Calcd for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.27; H, 10.28; N, 2.69.

The ir spectrum of this alcohol was found to be different from that of the deacetyl derivative **2**.

Reduction of Daphmacrine (1a) with Lithium Aluminum Hydride.—To a stirred suspension of lithium aluminum hydride (100 mg) in anhydrous ether (10 ml) was added dropwise at room temperature a solution of the alkaloid (98 mg) in anhydrous ether (10 ml). After 1 hr, anhydrous ether (30 ml) was added and the mixture was stirred at room temperature overnight. The excess reagent was decomposed by addition of a saturated aqueous solution of sodium sulfate. After basification with aqueous ammonia, the product was extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to yield a crude product (95 mg) which gave two spots on tlc. After recrystallization from acetone, a triol (**4**) (44 mg), mp 238–239°, was separated. The mother liquor of this triol was chromatographed on neutralized silicic acid[7] and elution with 1% methanol in chloroform afforded a second alcohol (**5**) (12 mg), mp 202–203° (from acetone). These two alcohols were also obtained by the lithium aluminum hydride reduction of daphmacropodine (**1b**) (see above).

Oxidation of Daphmacropodine (1b) with Jones Reagent.[6]—The alkaloid (80 mg) in acetone (8 ml) was treated with Jones reagent (0.2 ml) at 0° for 10 min. Methanol was added to decompose the excess reagent. The solution was then basified with aqueous ammonia and the product (80 mg) was isolated in the usual way. The product was converted into the hydrobromide and purified by chromatography on Mallinckrodt silicic acid (1.0 g). Elution with 1% methanol in chloroform furnished a lactone (**1a**) as the hydrobromide (50 mg), mp >300°.

Anal. Calcd for $C_{32}H_{49}O_4N \cdot HBr$: C, 64.84; H, 8.50; N, 2.36. Found: C, 64.56; H, 8.32; N, 2.17.

Its ir spectrum was identical with that of daphmacrine hydrobromide.

Registry No.—**1a**, 19775-48-5; **1a** HBr, 39729-20-9; **1b**, 39729-21-0; **1b** HBr, 39729-22-1; **2**, 39729-23-2; **3** HCl, 39729-24-3; **4**, 39729-25-4; **5**, 39729-26-5; lithium aluminum hydride, 16853-85-3.

An Improved Synthesis of Aminoethanethiols

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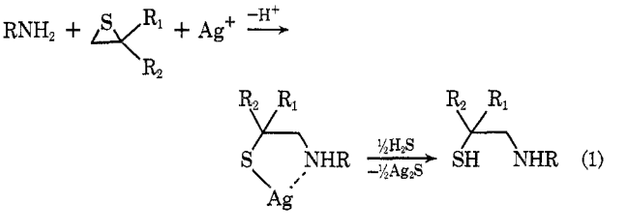
Of the variety of synthetic routes used to prepare aminoethanethiols, one of the most direct involves the addition of amines to episulfides or episulfide precursors.[1] Although this reaction is general, applying to both aromatic and aliphatic amines, it suffers from the fact that it often requires elevated temperatures in sealed tubes and that the yields are dependent on solvent polarity.[1,2a,d] A further disadvantage of this reaction is that the product aminoethanethiols are further mercaptoethylated on sulfur or nitrogen to give bismercaptoethylated products or polymers resulting from polymercaptoethylation.[2] The addition of excess amine has been successfully used to obviate these side reactions,[1,2a] but has also necessitated separating the excess amine from the product.

We have found that the mercaptoethylation of primary aliphatic amines can be carried out near room temperature with equimolar amounts of episulfide and amine in aqueous media containing amine–silver ion complex. Although only little effort has been spent



(1)

(1) D. D. Reynolds and D. L. Johnson, *Mech. React. Sulfur Compounds*, **5**, 103 (1970).

(2) (a) R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962); (b) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2672 (1947); (c) N. S. Isaacs, *Can. J. Chem.*, **44**, 395 (1966); (d) E. Tobler, *Ind. Eng. Chem., Prod. Res. Develop.*, **8**, 415 (1969).