The Products of Treatment of Acetylandromedol and 10-Deoxyacetylandromedol with Cupric Sulfate in Acetone

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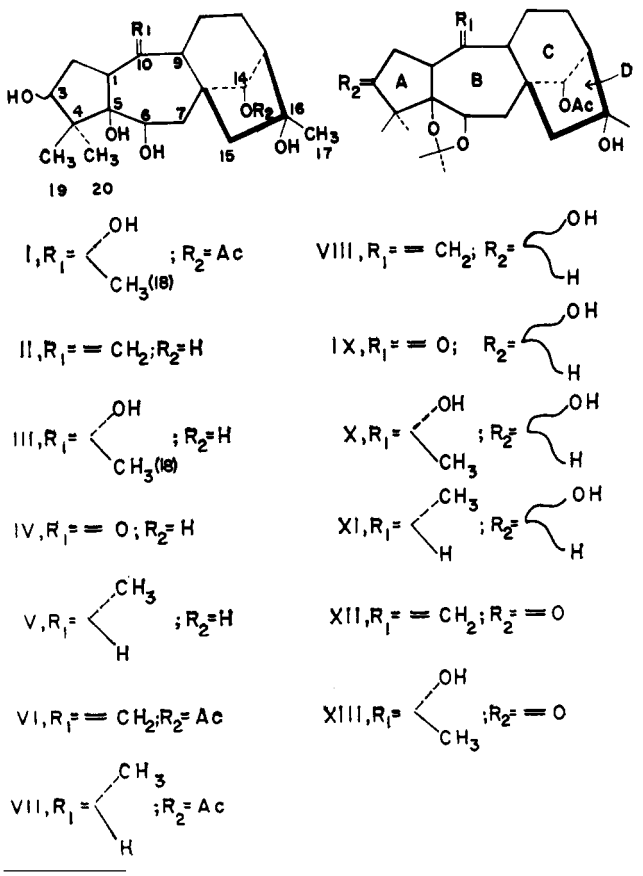
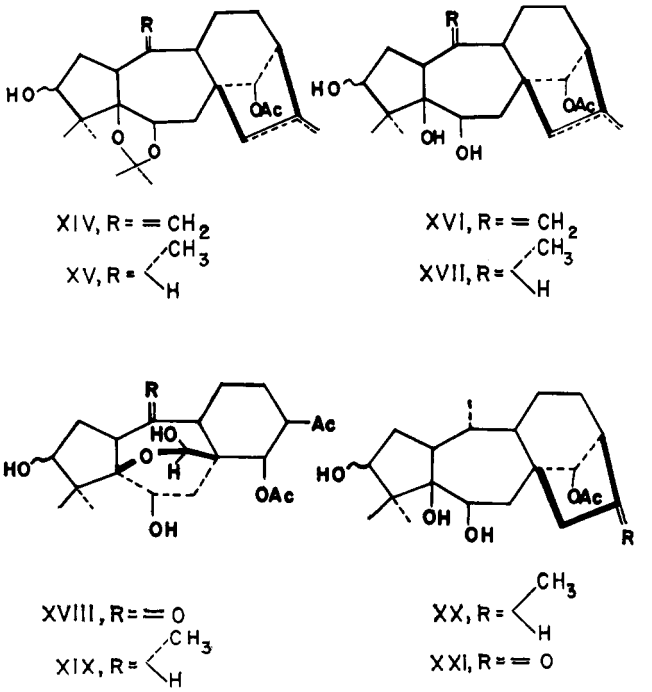
Acetylandromedol (I) is a potent hypotensive agent with pharmacological properties markedly resembling those of the protoveratrines.[1] Structural and stereochemical studies of this unusual diterpene have therefore been of interest not only to further the knowledge of the chemistry of natural products but for medicinal chemical reasons as well. A reaction which has been invaluable in these investigations, namely, treatment of the compound with cupric sulfate in acetone to effect simultaneous blocking of the two adjacent *cis* hydroxyls and dehydration, was first employed by Wood, Stromberg, Keresztesy, and Horning.[2] The usefulness of this procedure stems from the extreme sensitivity of I to other acidic agents commonly employed to introduce blocking groups or effect dehydration. For instance, efforts to introduce double bonds by the usual methods of dehydration led to ether formation[3] or to intractable tars. The cupric sulfate in acetone reaction enabled Meguri[4] to establish unequivocally the relationship between acetylandromedol (I) and the naturally occurring relative which was later shown to be $\Delta^{10(18)}$-andromedenol (II),[5] and it was used by Kakisawa, *et al.*,[6,7] to block the 5- and 6-hydroxyls and permit ring-size determinations by converting secondary hydroxyls to carbonyl groups without the complicating acyloin rearrangement of the otherwise resulting α-ketol system. In this laboratory it made possible the preparation of derivatives needed in connection with the determination of the absolute stereochemistry of I *via* evidence communicated earlier.[8] The purpose of this report is to present additional details concerning the preparation and characterization of these derivatives.

Treatment of acetylandromedol (I) with cupric sulfate in acetone gave its 5,6-acetonide (X), $\Delta^{10(18)}$-acetylandromedenol (VI), $\Delta^{10(18)}$-acetylandromedenol-5,6-acetonide (VIII), a mixture of dienes (XVI), and a mixture of diene acetonides (XIV). Similarly, 10-deoxyacetylandromedol (VII), prepared by catalytic hydrogenation of VI, yielded 10-deoxyacetylandro-





(1) N. C. Moran, P. E. Dresel, M. E. Perkins, and A. P. Richardson; *J. Pharmacol. Exptl. Therap.*, **110**, 415 (1954).

(2) H. B. Wood, Jr., V. L. Stromberg, J. C. Keresztesy, and E. C. Horning, *J. Am. Chem. Soc.*, **76**, 5689 (1954).

(3) W. H. Tallent, M. L. Riethof, and E. C. Horning, *ibid.*, **79**, 4548 (1957).

(4) H. Meguri, *J. Pharm. Soc. Japan*, **79**, 1060 (1959).

(5) J. Iwasa, Z. Kumazawa, and M. Nakajima, *Chem. Ind.* (London), 511 (1961).

(6) H. Kakisawa, M. Kurono, S. Takahaski, and Y. Hirata, *Tetrahedron Letters*, 59 (1961); H. Kakisawa, *J. Chem. Soc. Japan*, **82**, 1216 (1961).

(7) The Japanese investigators[6] prefer the names grayanotoxin I, II, and III for acetylandromedol (I), $\Delta^{10(18)}$-andromedenol (II), and andromedol (III), respectively. The reasons cited earlier (ref. 3) for using nomenclature based on andromedol (III) as the parent compound are still valid. In addition, the grayanotoxin nomenclature obscures the extensive pharmacological studies, most if not all of which would be found indexed under "andromedotoxin." Such is the case, for example, with the reports of N. C. Moran, *et al.* [*J. Pharmacol. Exptl. Therap.*, **110**, 415 (1954); **111**, 454 (1954); **118**, 55 (1956)], as well as with H. H. Swain and D. A. McCarthy [*ibid.*, **121**, 379 (1957)], P. Polewka and M. Buhler [*Arch. Exptl. Pathol. Pharmakol.*, **236**, 262, 263 (1959)], and F. M. Carey, J. J. Lewis, J. L. MacGregor, and M. Martin-Smith [*J. Pharm. Pharmacol.*, **11**, 269T (1959)].

(8) W. H. Tallent, *J. Org. Chem.*, **27**, 2968 (1962). The results are in complete agreement with those of Kakisawa, *et al.* [*Tetrahedron Letters*, 215 (1962)]. K. H. Overton has pointed out in a private communication that the statement [*Ann. Rept. Progr. Chem.* (Chem. Soc. London), **59**, 299 (1962)] to the effect that different conclusions were reached regarding the stereochemistry at C-14 is incorrect. It should be noted that the stereochemistry of substituents on ring D cannot be shown in the two dimensional structural formulas by the use of broken lines for α or downward and solid lines for β or upward orientation because the ring is approximately perpendicular to the plane of the paper.

medol-5,6-acetonide (XI), a mixture of D-ring olefins (XVII), and a mixture of D-ring olefin acetonides (XV). Ozonization of XVII provided the 17-norketone (XXI) as well as the 10-deoxy-15,16-seco compound (XIX), both of which were key compounds in the determination of the absolute stereochemistry of I. The structure of the 10-deoxy intermediate (VII) was established by reductive deacetylation to 10-deoxyandromedol (V), which was also obtained by catalytic hydrogenation of the above-mentioned $\Delta^{10(18)}$-andromedenol (II). The stereochemistry at C-10 for the two hydrogenation products (V and VII) was assigned on the basis of inspection of models, which leaves little doubt that the epimers indicated would be the ones preferentially formed. Each of the mixtures of olefins (XIV–XVII) exhibited a sharp and constant melting point and gave a single spot on thin layer chromatograms. They were all shown, however, by various combinations of evidence from n.m.r., gas chromatography, and ozonization products to be approximately 3:1 mixtures of exocyclic and endocyclic D-ring double-bond isomers.

Studies designed to further characterize the acetonides (VIII, X, XI, XIV, and XV) are reported in detail in the Experimental section, and molecular rotatory dispersion data for several ketones are given. Also reported are the double carbonyl band infrared frequencies for the 14-acetoxy group in compounds containing the 16-hydroxy group as cited earlier.[8] These are due to interaction between the two groups similar to that described by Bruice and Fife[9] for *exo*-2-acetoxy-*syn*-7-hydroxynorbornane.

Finally, one aspect of the n.m.r. data in Table I requires explanation. The n.m.r. spectra of the three acetonides containing unsaturation at C-10, namely VIII, IX and XIV, all integrated for two nonexchangeable hydrogens (see Table I, footnote *a*) in the region where the 3-hydrogen absorbs. This would seem to suggest that two secondary hydroxyl groups are present in these compounds, but oxidation of $\Delta^{10(18)}$-acetylandromedenol-5,6-acetonide (VIII) with the Jones reagent[10,11] gave a monoketone (XII). The infrared spectrum ($\lambda_{CHCl_3}^{C=O}$ 5.72 μ) confirmed that this ketone is a cyclopentanone, and the shift of a 4-methyl n.m.r. band confirmed that XII is in fact 3-keto-$\Delta^{10(18)}$-acetylandromedenol-5,6-acetonide. The n.m.r. spectrum still showed a band at 220–230 c.p.s. which now is integrated for one hydrogen, and it is postulated that in these compounds the C-1 hydrogen absorption is shifted into this region due to the cumulative deshielding effects of the double bond at C-10 and the carbon-to-oxygen bond at C-5. This phenomenon, which is not observed in the case of nonacetonide $\Delta^{10(18)}$-olefins, reflects the different A-ring conformation in the more rigid acetonides.

Experimental[12]

Isolation of Acetylandromedol (I) and Andromedol (III).—Undried *Kalmia angustifolia* leaves and stems (82 kg.) collected in New Hampshire in August were ground and extracted according to the published procedure.[2] The residue of the final chloroform solution (239 g.) was dissolved in ethyl acetate and allowed to stand. Over a period of several days the solution yielded a total of 8.92 g. of **acetylandromedol** (I) in three crops, m.p. 255–258°, 254–257°, and 251–255°, respectively, when a rate of heating was used such that highly purified material melted at 261–263°.[13] While the material was recrystallized in portions as needed rather than all at once, normally one recrystallization from ethyl acetate gave about an 80% recovery of material melting at 258–260° or higher and having an infrared spectrum (KBr) identical with that of a sample retained from a previous study.[3]

Chromatography of the residue of the mother liquors from the 8.92 g. of crude product on Davison No. 950 silica gel and elution with 2% methanol in ethyl acetate afforded an additional 4.51 g. of acetylandromedol (making a total of 13.43 g. or 0.016%) and 6.10 g. (0.007%) of **andromedol** (III) (eluted with 5% methanol in ethyl acetate). Crystallization of the andromedol from ethyl acetate gave a solvate as revealed by a carbonyl band at 5.71 μ in the infrared spectrum (KBr), and the ethyl acetate could not be removed completely by drying. Acetonitrile was found to be an excellent solvent for the crystallization, however, and material obtained from it melted at 229–223°[13] and had an infrared spectrum (KBr) identical with that of a sample obtained earlier[3] by alkaline hydrolysis of acetylandromedol.

Isolation of $\Delta^{10(18)}$-Andromedenol (II).—Rechromatography of 28 g. of residue of the mother liquor from crystallization of acetylandromedol (I) from the silica gel column fractions on 900 g. of silicic acid (Mallinckrodt A.R. No. 2847) and elution with 5% methanol in chloroform provided 1.8 g. of a crystalline mixture of acetylandromedol (I) and $\Delta^{10(18)}$-andromedenol (II). This mixture was resolved by countercurrent distribution. In a typical experiment 0.6 g. of the mixture was subjected to distribution with a 30-tube, 5-ml.-per-phase Craig-Post apparatus, and a solvent system prepared by mixing equal volumes of cyclohexane, ethyl acetate, ethanol, and water. After 120 transfers the acetylandromedol remained in the apparatus with its peak at tube 19, while withdrawal fractions 65–90 provided 208 mg. of **$\Delta^{10(18)}$-andromedenol** (II), m.p. 201–203° (from ethyl acetate), lit.[14] m.p. 198°, $[\alpha]^{23}D$ −42.1° (*c* 1.0, ethanol), lit.[14] $[\alpha]D$ −43°. Comparison of the infrared spectrum (Nujol) with the one reproduced in the literature[4] confirmed the identification. The ultraviolet spectrum showed a peak at 200 mμ (ϵ 5700).

Anal. Calcd. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.22; H, 9.13.

Ozonization of $\Delta^{10(18)}$-Andromedenol (II).—An ozone–oxygen mixture containing 23 mg. of ozone/l. of gas was passed through 25 ml. of an ethyl acetate solution containing 254.4 mg. of $\Delta^{10(18)}$-andromedenol (II) at Dry Ice–acetone bath temperature at the rate of 1 l./minute. After 6 min. the consumption of ozone was complete, and the solvent was saturated as evidenced by a deep blue color. The excess ozone was removed by passing nitrogen through the solution. Fifty milligrams of 5% palladium on charcoal was added, and the ozonide was decomposed by hydrogenation at atmospheric pressure and room temperature. Removal of the catalyst and concentration of the filtrate provided 208.2 mg. (82%) of crystalline **18-norketone** (IV), m.p. 239–241°. Recrystallization of 90 mg. of the ketone from ethyl

(9) T. C. Bruice and T. H. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962).

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

(11) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(12) All melting points were taken on a Kofler stage. Square glass plates (8 in.) coated to a thickness of 250 μ with silica gel G (Merck AG) were used for thin layer chromatograms. Of the several solvent systems tried, pure ethyl acetate was found to give the best resolution of mixtures in every case examined in this series of compounds. The Godin vanillin–perchloric acid spray [see ref. 3 and P. Godin, *Nature*, **174**, 134 (1954)] was used to detect the spots. Ozonizations were effected with ozone generated by a Welsbach T-23 ozonator, and the course of the reaction was followed with the aid of a Welsbach Model C ozone meter. Infrared spectra were obtained with a Beckman IR 4 spectrophotometer and ultraviolet spectra with a Beckman DK-2 spectrophotometer. For detecting the high frequency ultraviolet band due to an isolated double bond, 0.005% solutions in J. T. Baker No. 9400 reagent grade ethyl alcohol were used. The slits were completely opened at 190–195 mμ. In accordance with the suggestion of T. H. Applewhite and R. A. Micheli [*Tetrahedron Letters*, 560 (1961)] the instrument and technique were calibrated with cyclohexene [λ_{max} 202.5 mμ (ϵ_{max} 1280)] and cholesteryl acetate [λ_{max} 202.0 mμ (ϵ_{max} 4950)]. For detecting the weak ultraviolet band of ketones, 0.05% solutions were used. The author wishes to thank Mr. A. J. Damascus and his assistants of this laboratory for all the infrared and ultraviolet spectra and specific rotation determinations, Mrs. Katherine L. Warren of the National Heart Institute for the optical rotatory dispersion data, and Mr. Charles W. Beazley of Micro-Tech Laboratories, Skokie, Ill., for the analytical data.

(13) See ref. 2 for comment on the variation of the melting point of acetylandromedol (I) with the rate of heating. Andromedol (III) exhibits a similar but even greater variation.

(14) J. Iwasa, Z. Kumazawa, and M. Nakajima, *Agr. Biol. Chem.* (Tokyo), **25**, 782 (1961).

TABLE I

N.M.R. DATA[a]

Compound	4-Methyl	10-Methyl	16-methyl	Isopropylidene Methyls	1-H	3-H	6-H	14-H	15-H	17- and/or 18-vinyl H
I	58, 70	81	79			215	215	329		
VI	58, 72		83			210–233	210–233	321		301, 307
VII	57, 70	70	80			205–225	205–225	317		
VIII	50, 63		81	81	210–225	210–225	251–258	303		303
IX	52, 65		80	80	220	220	260–268	295		
X	51, 64	85	80	80, 88		215	250–257	351		
XI	48, 62	68 + 73	80	80, 92		213 + 218	248–255	310		
XII	57, 65		78	82	220–230		254–261	300		306, 311
XIII	58, 63	85	81	80, 89			251–259	354		
XIV	51, 64			79	207	207	244–252	283	309	309
XV	50, 63	69 + 74		80, 92		205–225	248–257	296	318	291, 296
XVI	59, 73					220	220	295	328	298, 301, 309
XVII	58, 72	72				220	220	303	303	292
XVIII	61, 73		133			210 + 214	246, 255	322	295	
XIX	61, 71	71 + 76	132			205–225	260–271	322	295	
XX	58, 71	71	71			220	220	305		
XXI	60, 72	72				215–228	215–228	320		

[a] Mr. A. J. Damascus of this laboratory determined the nuclear magnetic resonance spectra using a Varian A-60 spectrometer. The data are given in c.p.s. downfield from the reference band due to tetramethylsilane added as an internal standard. Tetradeuteriomethanol was used as solvent for compounds I and XVIII. Deuteriochloroform was used for all others. All of the bands listed were still present after deuterium oxide exchange by the method of H. M. Fales and A. V. Robertson [*Tetrahedron Letters*, 111 (1962)], and in every case the integration curve was in agreement with the assignments given. In addition to those listed, each of the spectra contained a methyl band due to the O-acetyl group. This was at 118 c.p.s. in the case of XVIII and between 121 and 127 c.p.s. for all others. A different designation is used in the table to distinguish between two separate bands given in the same column (*e.g.*, 50, 63 for the two 4-methyl groups for XV) and two bands reflecting splitting due to coupling (*e.g.*, 69 + 74 for the 10-methyl of XV; this doublet is not resolved when one of the 4-methyl bands occurs at the same frequency as its more intense component) as well as broad multiplets with no definite maximum (*e.g.*, 210–233 for the 3- and 6-hydrogen bands for VI). In the case of the acetonides VIII–XV, the band due to the 6-hydrogen was a quartet of varying distinctness. In the case of the seco compounds XVIII and XIX, the 16-methyl and 15-H bands indicated refer to ones due to the methyl group and the hydrogen atom derived from those so numbered in the parent compounds.

acetate gave 70 mg. of material, m.p. 240–242° (lit.[14] m.p. 234–235°), $[\alpha]^{24}D$ −113.0° (*c* 0.5, ethanol), lit.[14] −112°, $[\alpha]^{24}_{320}$ −2580°, negative Cotton effect, $\lambda^{C=O}_{KBr}$ 5.90 μ, λ_{max} 280 mμ (ε 35).

Anal. Calcd. for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.09; H, 8.76.

Hydrogenation of $\Delta^{10(18)}$-Andromedenol (II).—A solution of 209 mg. of $\Delta^{10(18)}$-andromedenol (II) in ethanol was hydrogenated with 5% palladium on charcoal (20 mg.) at room temperature and atmospheric pressure. The hydrogen uptake (1.1 moles) was complete in 2 hr. The catalyst was removed by filtration, and the solvent was removed under vacuum. Crystallization of the residue from ethyl acetate gave 163.5 mg. (78%) of **10-deoxyandromedol (V)**, m.p. 268–270°, lit.[14] m.p. 260–261°, $[\alpha]^{24}D$ +7.9° (*c* 1.0, ethanol), lit.[14] +7.0.

Anal. Calcd. for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.42; H, 9.30.

Efforts to crystallize the other epimer from the mother liquor were unsuccessful.

Twenty-Four-Hour Cupric Sulfate–Acetone Reaction with Acetylandromedol (I).—To 2 g. of acetylandromedol in 600 ml. of acetone, previously dried by refluxing 2 hr. over calcium chloride and then distillation from it, was added 40 g. of anhydrous cupric sulfate (Mallinckrodt No. 4760). The mixture was refluxed on a steam bath for 24 hr. with the exclusion of moisture. The cupric sulfate was removed by suction filtration and washed thoroughly with hot acetone. The residue of the combined filtrates was chromatographed on 40 g. of silicic acid. Elution with 1% methanol in chloroform provided 645 mg. (32%) of **acetylandromedienol acetonides (XIV)**, m.p. 208–210° (from cyclohexane), lit.[2] 208–210°, $[\alpha]^{26}D$ −34.0° (*c* 1.0, ethanol); and 141 mg. (8%) of **acetylandromedienols (XVI)**, m.p. 158–159° (from cyclohexane), $[\alpha]^{26}D$ −18.0° (*c* 1.0, ethanol).

The infrared spectrum ($CHCl_3$) of the **acetylandromedienol acetonides (XIV)** was identical with a copy of the one obtained in connection with the initial preparation,[2] the description of which failed to mention a very weak C=C band at 6.00 μ in addition to the one at 6.11 μ. A sharp band at 2.76 μ in the potassium bromide disk spectrum confirmed the presence of a hydroxyl group. The ultraviolet spectrum showed a maximum at 205 mμ (ε 9910).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.91; H, 8.38.

The melting point and infrared spectrum were unchanged by recrystallization from cyclohexane or methanol–water, and thin layer chromatography showed only one spot. Nevertheless, gas chromatography[15] revealed two components with retention times of 4.75 (major peak) and 5.43 min. (minor peak) when 10-p.s.i. inlet carrier-gas pressure and a column 6 ft. long maintained at 244° were used.

The **acetylandromedienols (XVI)** had $\lambda^{C=O}_{CHCl_3}$ 5.78 μ, $\lambda^{C=C}_{CHCl_3}$ 6.00 and 6.10 μ, λ_{max} 205.5 mμ (ε 10,190).

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.31; H, 8.52.

Conversion of Acetylandromedienol Acetonides (XIV) to Acetylandromedienols (XVI).—To a solution of 200 mg. of the acetonides (XIV) in 4 ml. of methanol were added 2 ml. of water and 2 ml. of acetic acid. The methanol was boiled off and the water–acetic acid solution was heated on a steam bath for 3 hr., with sufficient water being added periodically to maintain a slight turbidity. The solution was then diluted with water and neutralized with sodium bicarbonate, and the product was extracted with chloroform and crystallized from cyclohexane to give 57 mg. (32%) of product, m.p. 156–158°, undepressed by mixture with acetylandromedienols (XVI) from the 24-hr. cupric sulfate–acetone reaction. The infrared spectra of the two samples were identical.

Ozonization of Acetylandromedienols (XVI).—Starting with 116 mg. of XVI in 25 ml. of ethyl acetate, the reaction was conducted and the ozonides decomposed as described above for $\Delta^{10(18)}$-andromedenol (II). Thin layer chromatography showed the presence of two compounds in the crude reaction product, which was dissolved in a mixture of ethyl acetate and cyclohexane and allowed to stand. After several days, 21 mg. (17%) of crystals of the minor component, the 10-keto-15,16-seco compound (XVIII), formed; m.p. 216–218°; $\lambda^{C=O}_{KBr}$ 5.70, 5.80, and 5.84 μ.

(15) The author is indebted to Dr. R. J. Highet of the National Heart Institute for the gas chromatographs. For these experiments Dr. Highet used columns prepared from Chromosorb-W coated with 0.75% of General Electric silicone polymer SE-30. Argon was used as carrier gas.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 61.45; H, 7.37. Found: C, 61.18; H, 7.43.

Hydrogenation of Acetylandromedienols (XVI).—The conditions used were the same as described above for $\Delta^{10(18)}$-andromedenol (II). The reaction was stopped when 1 mole of hydrogen had been absorbed, and an unsuccessful effort was made to isolate a crystalline monoene (hopefully XVII). Thin layer chromatography of the partially hydrogenated material gave three spots, two of which corresponded to those for starting material and subsequently obtained completely hydrogenated product (XX), respectively. When 204.5 mg. of the partially hydrogenated material was subjected to further hydrogenation, an additional mole of the gas was absorbed, and 114 mg. (56%) of **10,16-dideoxyacetylandromedol (XX)** was obtained, m.p. 176–177° after crystallization from cyclohexane, $[\alpha]^{26}D$ +20.0° (*c* 0.7, ethanol), $\lambda^{C=O}_{CHCl_3}$ 5.79 μ, no ultraviolet absorption down to 190 mμ.

Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.56; H, 9.58.

Efforts to obtain additional crystals from the mother liquor were unsuccessful.

Sixteen-Hour Cupric Sulfate–Acetone Reaction with Acetylandromedol (I).—In a typical reaction 4 g. of acetylandromedol (I) was treated exactly as described above for the 24-hr. reaction except that all quantities were doubled and the reaction time was reduced to 16 hr. Silicic acid chromatography gave four products as follows in order of elution.

$\Delta^{10(18)}$-Acetylandromedenol-5,6-acetonide (VIII), 903 mg. (21%), crystallized from cyclohexane, had m.p. 223–226°, lit.[4] m.p. 226°, $[\alpha]^{26}D$ −16.5° (*c* 1.0, ethanol), $\lambda^{C=O}_{CHCl_3}$ 5.71 and 5.76 μ (sh), $\lambda^{C=C}_{CHCl_3}$ 6.12 μ, λ_{max} 205 mμ (ϵ 5560).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.02; H, 9.03.

Acetylandromedienols (XVI), 152 mg. (4%), crystallized from cyclohexane, had m.p. 158–159°, undepressed by admixture with material from the 24-hr. reaction above. The infrared spectrum was identical with that of material from the 24-hr. reaction.

Acetylandromedol-5,6-acetonide (X), 405 mg. (9%), crystallized from ethyl acetate–cyclohexane, transition point 119–120°, had m.p. 178–180°, $[\alpha]^{26}D$ −9.5° (*c* 1.0, ethanol), $\lambda^{C=O}_{CHCl_3}$ 5.71 and 5.76 μ, no ultraviolet absorption down to 190 mμ.

Anal. Calcd. for $C_{25}H_{40}O_7$: C, 66.34; H, 8.91. Found: C, 66.37; H, 8.84.

$\Delta^{10(18)}$-Acetylandromedenol (VI), 685 mg. (18%), crystallized from ethyl acetate–cyclohexane, had m.p. 178–180°, $[\alpha]^{26}D$ −10.5° (*c* 1.0, ethanol), $\lambda^{C=O}_{CHCl_3}$ 5.71 μ, $\lambda^{C=C}_{CHCl_3}$ 6.11 μ, λ_{max} 204 mμ (ϵ 4230).

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 66.64; H, 8.42.

Ozonization of $\Delta^{10(18)}$-Acetylandromedenol-5,6-acetonide (VIII).—Under conditions described above for $\Delta^{10(18)}$-andromedenol (II), 175 mg. of starting material provided, after hydrogenolysis of the ozonide, 139 mg. (79%) of **10-keto-18-noracetylandromedol-5,6-acetonide (IX)**; m.p. 219–221° after crystallization from ethyl acetate–cyclohexane; $[\alpha]^{24}D$ −74.5° (*c* 1.2, ethanol); $[\alpha]_{309}{}^{24}$ −1720°; negative Cotton effect; $\lambda^{C=O}_{CHCl_3}$ 5.71, 5.76 (sh), and 5.89 μ; λ_{max} 288 mμ (ϵ 33).

Anal. Calcd. for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 66.19; H, 8.32.

Hydrogenation of $\Delta^{10(18)}$-Acetylandromedenol-5,6-acetonide (VIII).—Eighty-seven milligrams of the olefin acetonide (VIII) was hydrogenated under conditions described above for $\Delta^{10(18)}$-andromedenol (II). Even after 12 hr., spectroscopy revealed that some unsaturation was still present. Since 1.05 moles of hydrogen was absorbed, some double bond migration and hydrogenolysis of the carbon-to-oxygen bond at C-6 appeared to have taken place. Crystallization from ethyl acetate–cyclohexane provided 56 mg. of a mixture. After two recrystallizations there was obtained from this 22 mg. of material which, though still melting low (185–190°), had an infrared spectrum identical with that of **10-deoxyacetylandromedol-5,6-acetonide (XI)** characterized in more detail below. Preliminary experiments indicated that use of platinum as a catalyst resulted in extensive double bond migration and hydrogenolysis.

Oxidation of $\Delta^{10(18)}$-Acetylandromedenol-5,6-acetonide (VIII).—Nitrogen was bubbled through a magnetically stirred solution of 100 mg. of VIII in 15 ml. of acetone (Mallinckrodt A.R. No. 2440) in an ice bath while an 8.0 *N* solution of chromium trioxide in 8.1 *N* sulfuric acid[10,11] was added dropwise until the brown color of the reagent persisted in the supernatant solution instead of turning green within a few seconds. The excess reagent was decomposed by addition of 1 drop of isopropyl alcohol, and the flocculent green precipitate was removed by suction filtration through a pad of Supercel Hyflo. Evaporation of the acetone and crystallization of the residue from ethanol–water gave 62 mg. (62%) of **$\Delta^{10(18)}$-3-ketoacetylandromedenol-5,6-acetonide (XII)**, m.p. 185–188°, $\lambda^{C=O}_{CHCl_3}$ 5.72 μ, $\lambda^{C=C}_{CHCl_3}$ 6.12.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.65; H, 8.56.

Oxidation of Acetylandromedol-5,6-acetone (X).—The procedure used was exactly as described above, and the product, **3-ketoacetylandromedol-5,6-acetonide (XIII)**, crystallized directly from the final acetone filtrate when it was concentrated. The yield was 169 mg. (75%) from 226 mg. of starting material. One recrystallization from ethyl acetate–cyclohexane gave 110 mg. of product, m.p. 200–202° after a change in crystal form at 120–130°, $[\alpha]^{24}D$ −53.0° (*c* 1.3, ethanol), $[\alpha]_{320}{}^{24}$ −1402°, negative Cotton effect, $\lambda^{C=O}_{CHCl_3}$ 5.72 μ, λ_{max} 290 mμ (ϵ 27).

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.91; H, 8.51.

Hydrogenation of $\Delta^{10(18)}$-Acetylandromedenol (VII).—The reaction was conducted as described above for $\Delta^{10(18)}$-andromedenol (II) except that the quantities were quadrupled. Three hours was required for the uptake of 0.9 mole of hydrogen, and the yield from 777 mg. of starting material was 601 mg. (77%) of **10-deoxyacetylandromedol (VII)**. In order to obtain sufficient material for use in cupric sulfate–acetone reactions, the hydrogenation was repeated twice with similar results. When crystallized from ethyl acetate–cyclohexane, the product showed a transition point near 150° in addition to the melting point at 191–193°, but the transition point was absent in crystals from benzene–cyclohexane. The two types of crystals gave different infrared spectra when potassium bromide disks were used, but the solution spectra (chloroform) were identical with the main carbonyl band at 5.71 and a distinct shoulder at 5.76 μ. There was no significant ultraviolet absorption down to 190 mμ, $[\alpha]^{26}D$ +22.5° (*c* 1.0, ethanol).

Anal. Calcd. for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.71; H, 8.99.

Reductive Deacetylation of 10-Deoxyacetylandromedol (VII).—A solution of 139 mg. of VII in 5 ml. of tetrahydrofuran (Du Pont, stabilized with "butylated hydroxyanisole") was added dropwise to a magnetically stirred solution of 100 mg. of lithium aluminum hydride in the same solvent over a period of 3 min. The solution was stirred at room temperature an additional 1.5 hr., then stirred, and refluxed for 30 min. The excess reagent was decomposed by careful dropwise addition of 0.2 ml. of water. Finally 1 drop of 10% sodium hydroxide and another 0.2 ml. of water were added, and the mixture was stirred an additional 15 min. The flocculent precipitate was removed by suction filtration through a pad of Supercel-Hyflo, and the filter cake was washed with hot tetrahydrofuran. The residue from the combined filtrates was crystallized from ethyl acetate to give 80 mg. (64%) of **10-deoxyandromedol (V)** identical in all respects with that obtained above by catalytic reduction of $\Delta^{10(18)}$-andromedenol (II).

Cupric Sulfate–Acetone Reaction with 10-Deoxyacetylandromedol (VII).—In a typical reaction 800 mg. of the starting material was subjected to reaction conditions similar to those used for the reaction with acetylandromedol (I) for 16 hr. with proportionate quantities of reagent and solvent being employed. Thin layer chromatography of the crude reaction product revealed four components in approximately the same relative amounts as the corresponding products subsequently isolated. One of these spots had the same R_f as a reference spot of starting material. A second spot moved the same distance as the hydrogenation product of $\Delta^{10(18)}$-acetylandromedenol-5,6-acetonide (VIII), and still another corresponded to one of the three spots from the mixture obtained by partial hydrogenation of acetylandromedienol (XVI). Silicic acid chromatography provided three products and 216 mg. (27%) of unreacted starting material. Two of the products have melting points very similar to that of the starting material, but combinations of each of them with VII and with each other gave depressed mixture melting points. The products in order of elution were:

10-Deoxyacetylandromedenol-5,6-acetonides (XV), 68 mg. (8%), crystallized from ethanol–water, had m.p. 152–154°, $\lambda^{C=O}_{CHCl_3}$ 5.79 μ, $\lambda^{C=O}_{CHCl_3}$ 6.00 μ (very weak), λ_{max} 203 mμ (ϵ 6490).

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.64; H, 9.23.

For gas chromatography[15] a column 9 ft. long maintained at 203° and a carrier-gas inlet pressure of 20 p.s.i. were used. A major component (71%) with a retention time of 14.8 min. and a minor component (29%) with a retention time of 16.8 min. were detected.

10-Deoxyacetylandromedol-5,6-acetonide (XI), 164 mg. (19%), crystallized from ethyl acetate–cyclohexane, had m.p. 194–196°, $[\alpha]^{27}D$ +14.0° (*c* 0.5, ethanol), $\lambda^{C=O}_{CHCl_3}$ 5.71 and 5.76 μ, no ultraviolet absorption down to 190 mμ.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.55; H, 9.16.

10-Deoxyacetylandromedenols (XVII), 102 mg. (13%), crystallized from ethyl acetate–cyclohexane, had m.p. 196–197°, $[\alpha]^{26}D$ +25° (*c* 0.4, ethanol), $\lambda^{C=O}_{CHCl_3}$ 5.81 μ, $\lambda^{C=C}_{CHCl_3}$ 6.02 μ, λ_{max} 203 mμ (ϵ 6670).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 69.81; H, 9.05. Found: C, 69.90; H, 9.02.

For gas chromatography[15] the same conditions were employed as given above for the corresponding acetonides (XV). In the present case (XVII), the minor component (26%) had the lower retention time, 12.6 min., and the major component (74%) had a retention time of 14.0 min.

Attempted Conversion of 10-Deoxyacetylandromedol-5,6-acetonide (XI) to 10-Deoxyacetylandromedol (VII).—The 10-deoxyacetonide (XI), 135 mg., was subjected to the same aqueous acetic acid treatment described above for the diene acetonides (XIV). Crystallization of the crude product from ethyl acetate gave 59 mg. of material, m.p. 264–268°, with an infrared spectrum identical with that of 10-deoxyandromedol (V). Thin layer chromatography of the mother liquor revealed the presence of approximately equal amounts of 10-deoxyacetylandromedol (VII), 10-deoxyandromedol (V), and 10-deoxyacetylandromedenols (XVII).

Ozonization of 10-Deoxyacetylandromedenols (XVII).—Under conditions described above for $\Delta^{10(18)}$-andromedenol (II), 125 mg. of XVII provided, after hydrogenolysis of the ozonides, silicic acid chromatography, and crystallization from ethyl acetate–cyclohexane, 36 mg. of **16-keto-17-nor-10-deoxyacetylandromedol (XXI)**, m.p. 202–204°, $[\alpha]^{24}D$ +18° (*c* 0.9, ethanol), $[\alpha]^{24}_{320}$ +490°, positive Cotton effect, $\lambda^{C=O}_{CHCl_3}$ 5.71 and 5.76 μ (sh).

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.14; H, 8.72.

A second peak was eluted from the column and crystallized from ethyl acetate to give 15 mg. of the 10-deoxy-15,16-seco compound (XIX), m.p. 218–221°, $\lambda^{C=O}_{KBr}$ 5.72 and 5.82 μ.

Anal. Calcd. for $C_{22}H_{34}O_7$: C, 64.37; H, 8.35. Found: C, 64.46; H, 8.42.

Heterocyclic Spirans. VI.[1] 1-Aza-3-oxaspiro[4.5]dec-1-ene

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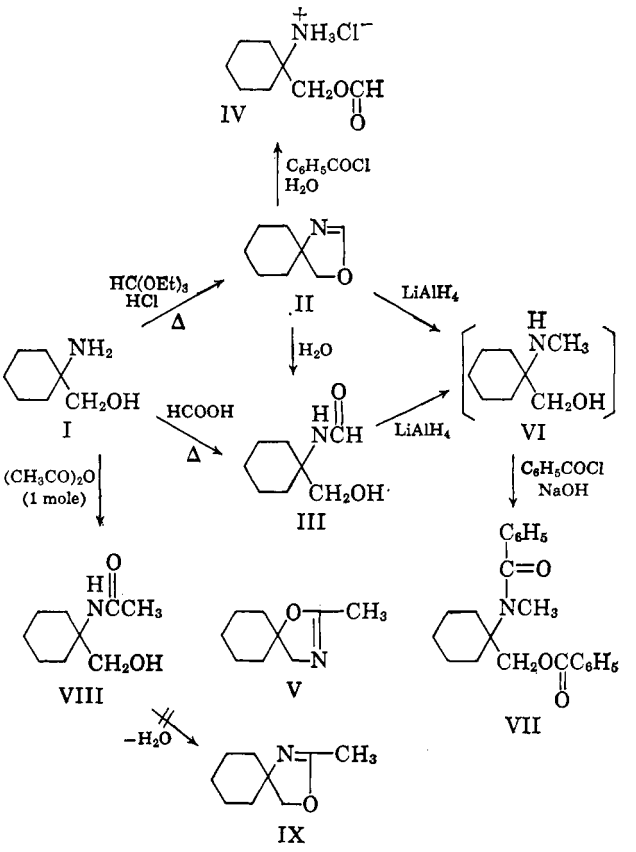
Spirooxazolidines have been prepared from the cyclic ethanolamine derivative, 1-aminocyclohexanemethanol (I), by condensation with aldehydes and cyclic ketones.[1b] Similarly, spiroimidazolones have been prepared by condensation of cyclic α-aminoamides, such as 1-aminocyclohexanecarboxamide, with triethyl orthoformate.[2] We now wish to report the synthesis of the parent unsubstituted spirooxazoline, 1-aza-3-oxaspiro[4.5]dec-1-ene (II), by acid-catalyzed condensation[3] of I with triethyl orthoformate. The spirooxazoline (II) was obtained as an oil, having a strong imine double-bond band at 1634 cm.$^{-1}$ in its infrared spectrum. The oil (II) is readily hydrolyzed, with ring opening, to the formamide III. The hydrolysis even takes place in the presence of moist air, as indicated by the gradual appearance of crystals of III in the oil. Hydrolysis of II with benzoyl chloride in moist ether gave, not the formamide III, but the formate ester hydrochloride (IV), in which protonation of the amino group has stabilized location of the formyl group on oxygen. A related spirooxazoline, 2-methyl-1-oxa-3-azaspiro[4.5]dec-2-ene[4] (V), is also reported to be hygroscopic and to undergo hydrolysis in moist air with ring opening.[4a]



Reduction of oxazoles[5a] and their intermediate reduction products, oxazolidines,[5b] with lithium aluminum hydride is reported to go all the way, with ring opening, to ethanolamine derivatives.[5c] Reduction of the spirooxazoline II with lithium aluminum hydride proceeded similarly, giving an oil (VI) having an amine odor. The oil was characterized through its crystalline dibenzoyl derivative (VII), which has no NH or OH absorption in its infrared spectrum, and was identical with a sample obtained by reduction of the formamide III with lithium aluminum hydride.

(1) Previous papers in this series on the synthesis of heterocyclic spiranes: (a) I: W. E. Noland, J. F. Kneller, and D. E. Rice, *J. Org. Chem.*, **22**, 695 (1957); (b) II: W. E. Noland and R. A. Johnson, *ibid.*, **25**, 1155 (1960); (c) III: W. E. Noland and R. J. Sundberg, *Tetrahedron Letters*, 295 (1962); (d) IV: W. E. Noland and R. J. Sundberg, *J. Org. Chem.*, **28**, 3150 (1963); (e) V: W. E. Noland, R. J. Sundberg, and M. L. Michaelson, *ibid.*, **28**, 3576 (1963).

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