aqueous formaldehyde at room temperature. Crystals formed within 5 min. and the reaction was complete after 0.5 hr. The solid was removed by filtration and dried at 110°. Crystallization from ethanol gave 25.8 g. of material which melted at 157–158°. Infrared spectrum (C—O—C) 1125 cm.$^{-1}$, (C—N—C) 1190 and 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{26}O_2N_2$: C, 67.63; H, 9.83; N, 10.52; mol. wt., 266. Found: C, 67.62; H, 9.89; N, 10.43; mol. wt.: Rast, 265.1; perchloric acid titration,[10] 266.2.

The Reaction of the Oxazolidine with Phenylmagnesium Bromide.—Twenty milliliters of 3 *M* phenylmagnesium bromide in ether was added to 3.1 g. of the oxazolidine in 250 ml. of ether over a period of 10 min. The mixture was stirred for 30 min. Water (25 ml.) was added and after thorough mixing, the ether layer was removed. The residue was washed with ether and combined with the first ether layer. Evaporation of the ether and crystallization from ethanol gave a solid melting at 90–91° (3.0 g.). The melting point of N,N-dibenzyl-2-aminocyclohexanol is given as 89.5–91°.[11] Infrared spectrum (bonded OH) 3440 cm.$^{-1}$ (aromatic C=C) 1590 cm.$^{-1}$, 1480 cm.$^{-1}$ (monosubstituted benzene) 755 cm.$^{-1}$, 700 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{25}ON$: C, 81.45; H, 8.53; N, 4.74; mol. wt., 295. Found: C, 81.33; H, 8.40; N, 4.78; mol. wt.: perchloric acid titration, 296.

(10) R. Belcher and A. Godbert, "Semi-Micro Quantitative Organic Analysis" Longmans, Green and Co., New York, 1954, pp. 152–154.

(11) F. Winternitz and R. M. Thakkar, *Bull. soc. chim. France*, 646 (1952).

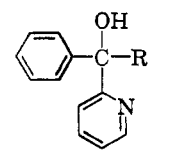
Communications TO THE EDITOR

Palladium-Catalyzed Hydrogenation of Pyridines

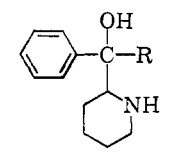
Sir:

Platinum[1,2] and nickel[3] in various forms have been used extensively in hydrogenation of pyridines (salts or bases, respectively), and currently the search for catalysts for the same purpose, less susceptible to inhibition by organic bases, is being extended to ruthenium[4] and rhodium.[5] General or practical use of palladium catalysts in hydrogenating pyridines, quinolines, and like compounds has not been made, the impression perhaps having been that palladium is more easily "poisoned" than platinum by such heterocyclic bases. We wish to report, in contrast to what may be a fairly well established misconception, that supported palladium *can* be employed, often more successfully than platinum oxide,[1c] in convenient low pressure hydrogenation of the acetate salts of many compounds incorporating the pyridine nucleus, to corresponding piperidines. What is more, the new technique is ideally adapted to *selective* reduction of the pyridine ring without any attack upon other, more or less nickel- or platinum-reducible, functional groups (appended oxyphenyl, cyclopropyl, aldehyde, acetal, ester, amide, and so forth) appropriately located in various molecules,[6] and has now facilitated the synthesis, in uniformly high yields, of a number of new compounds closely related to the profoundly useful central stimulants, pipradrol[2d,2e] and methylphenidate,[2j,2k] as well as novel piperidylalkyloxindoles,[2l,2m] dipiperidyl compounds, and many others.

In reductions of pyridines to corresponding piperidines described below as the more interesting, selected examples, a *ca.* 0.3–0.5 (by weight) ratio of 10% palladium–charcoal to compound, glacial



Ia. R = $CH(OEt)_2$
b. R = CHO
c. R = CH=NOH
d. R = CH_2NH_2
e. R = CH_2OH
f. R = CH_2–(1,3-dioxolan-2-yl)



IIa. R = $CH(OEt)_2$
b. R = CH_2NH_2
c. R = CH_2OH
d. R = $-CH_2$–(1,3-dioxolan-2-yl)

(1) (a) A. Skita and W. Brunner, *Ber.*, **49**, 1597 (1916); (b) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.* **45**, 2738 (1932); (c) T. S. Hamilton and R. Adams, *ibid.*, **50**, 2260 (1928).

(2) (a) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929); (b) K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4006 (1930); (c) R. R. Burtner and J. M. Brown, *ibid.*, **69**, 630 (1947); (d) C. H. Tilford, R. S. Shelton, and M. G. Van Campen, *ibid.*, **70**, 4001 (1948); (e) H. W. Werner and C. H. Tilford, U. S. Patent 2 624,739 (1953); (f) C. H. Tilford and M. G. Van Campen, *J. Am. Chem. Soc.*, **76**, 2431 (1954); (g) F. J. McCarthy, C. H. Tilford, and M. G. Van Campen, *ibid.*, **79**, 472 (1957); (h) E. L. Schumann, M. G. Van Campen, and R. C. Pogge, U. S. Patent 2,804,422 (1957); (i) N. Sperber, *et al.*, U. S. Patents 2,739,968 and 2,739,969 (1956); (j) L. Pannizzon, *Helv. Chim. Acta*, **27**, 1748 (1944); (k) K. Scholz and L. Pannizzon, *ibid.*, **37**, 1605 (1954). (l) H. Bader and W. Oroshnik, *J. Am. Chem. Soc.*, **79**, 5686 (1957); (m) A. P. Gray, *J. Org. Chem.*, **23**, 1453 (1958).

(3) H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Am. Chem. Soc.*, **56**, 2425 (1934); H. Adkins and H. R. Billica, *ibid.*, **70**, 695 (1948).

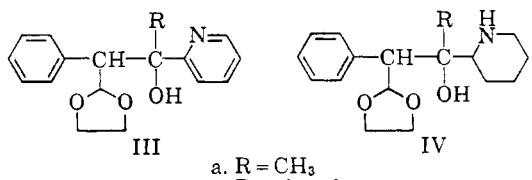
(4) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3805 (1961).

(5) M. Freifelder, R. M. Robinson, and G. R. Stone, *ibid.*, **27**, 284 (1962).

(6) The sole, presently evident disadvantage of the new method is that primary and secondary (but ordinarily *not tertiary*) alcohol and oxo groups on carbon atoms adjacent to aromatic rings are hydrogenolyzed under the conditions necessarily used to promote reduction of the heterocyclic moiety. However, this as well as other side reactions also may occur with other catalysts, especially rhodium [see E. Breitner, E. Roginski, and P. N. Rylander, *ibid.*, **24**, 1855 (1959); M. Freifelder, *J. Am. Chem. Soc.*, **82**, 2386 (1960)], ruthenium [E. Breitner, E. Roginski, and P. N. Rylander, *J. Chem. Soc.*, 2918 (1959)], and rhenium [H. S. Broadbent, *et al.*, *J. Org. Chem.*, **24**, 1847 (1959)].

acetic acid (except where otherwise noted) as solvent, and usually reaction temperatures and pressures of 70–80°[7] and 3–4 atm., respectively, were used.

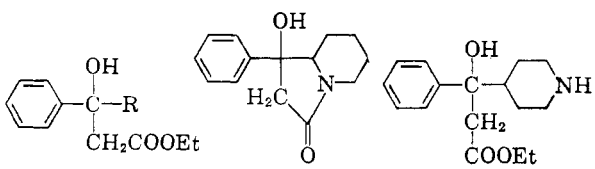
Compound Ia, from phenylglyoxal diethylacetal with 2-pyridyllithium, was reduced to IIa (·HCl, m.p. 180–181°; *Anal.* Found: C, 62.08; H, 8.58; N, 4.39). The corresponding aldehyde Ib (m.p. 149–150°; *Anal.* Found: C, 72.94; H, 5.30; N, 6.77, actually, like indole-3-aldehyde, a formamide-like substance: λ_{max}^{nujol} 6.22 and 6.25 μ), prepared by dilute acid hydrolysis of Ia (*no* rearrangement), was converted to oxime Ic (m.p. 133–135°; *Anal.* Found: C, 68.34; H, 5.32; N, 12.07), which was reduced, *via* Id, to IIb (·2HCl, m.p. from 130°; *Anal.* Found: C, 50.68; H, 8.20; N, 8.53) and similarly the diol Ie (m.p. 102–104°; *Anal.* Found: C, 72.44; H, 6.09; N, 6.79), prepared by borohydride reduction of Ib, was reduced to IIc (m.p. 130–132°; *Anal.* Found: C, 70.45; H, 8.71; N, 6.6). Compound If (m.p. 95–96°; *Anal.* Found: C, 70.97; H, 6.52; N, 5.13), from the ethyleneacetal of hydroxymethyleneacetophenone[8] with 2-pyridyllithium was reduced to IId (·HCl, m.p. 107° dec.; *Anal.* Found: C, 61.13; H, 7.85; N, 4.49), and from similar ethylenedioxymethylene-substituted phenyl acetone[8] and desoxybenzoin were synthesized, in the same manner, pyridyl (IIIa and b, respectively) and piperidyl (IVa and b, respectively) carbinols.



III IV

a. R = CH_3
b. R = phenyl

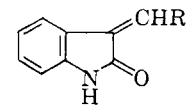
The lactam VI (m.p. 185.5–187°; *Anal.* Found: C, 72.59; H, 7.54; N, 6.13; λ_{max}^{Nujol} 3.14 and 5.96 μ) was formed upon palladium reduction at 25° of



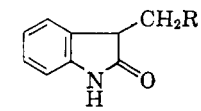
Va. R = 2-pyridyl
b. R = 4-pyridyl

VI VII

Va (m.p. 59–61°; *Anal.* Found: C, 70.85; H, 6.42; N, 5.10; λ_{max}^{Nujol} 2.90 and 5.88 μ), in turn obtained by Reformatsky reaction of 2-benzoylpyridine with ethyl bromoacetate; reduction of corresponding 4-benzoylpyridine Reformatsky product Vb (m.p. 82–84°; *Anal.* Found: C, 70.67; H, 6.32; N, 5.24) gave VII (·HOAc, m.p. 158–160°; *Anal.* Found: C, 64.06; H, 8.10; N, 4.17; λ_{max}^{Nujol} 2.91 and 5.88 μ). Reduction of compounds VIII was achieved in two well defined stages through the use of palladium–charcoal: VIIIa, b, and c (respective m.p. 208, 197, and 231°; correct and virtually identical *Anal.* figures in each case),



VIIIa. R = 2-pyridyl
b. R = 3-pyridyl
c. R = 4-pyridyl



IX. R = pyridyl, piperidyl

reduced in ethyl acetate solution at room temperature, gave IX, R = 2-, 3-, and 4-pyridyl (respective m.p. 130–132°, 139–141°, and 199–201°; *Anal.* Found, respectively: C, 74.80, 74.99, 74.99; H, 5.48, 5.45, 5.60; N, 12.45, 12.27, 12.49), which were further reduced in acetic acid [cases (b) and (c)] or merely in ethyl acetate at 75° [case (a); *ortho* group assistance] to IX R = 2-, 3- and 4-piperidyl (respective m.p. 140–142, 137–138, and ·HOAc, m.p. 223–226° *Anal.* Found, respectively: C, 73.05, 72.56, 65.90; H, 7.92, 7.81, 7.75; N, 11.76, 11.53, 9.49). The oxindoles VIII and IX showed expected (5.8–5.9 μ) infrared peaks, except IX, (R = 2-piperidyl) (5.99 μ; shifted by —C=O ··· HN).

Detailed accounts of this and other related work, together with pertinent pharmacological findings, will be published in the near future. I wish to acknowledge the patient support given this project by Dr. E. Schlittler, the microanalytical and spectrophotometric collaboration of Mr. L. Dorfman and his group, the technical assistance of Miss Barbara N. Weaver, and pharmacological evaluation of the compounds by Dr. A. J. Plummer, W. Barrett, and L. B. Witkin, and their respective staffs: *inter alia*, compounds Ia, Ie, and Id and its derivatives are central stimulants, and compounds VIII and IX exhibit strong cholinergic effects.

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RECEIVED APRIL 6, 1962

(7) The moderately elevated temperature is the key to success of this procedure since no reduction whatever of the pyridine ring in non-*ortho*-group-assisted compounds is observed at room temperature. On the other hand, once initiated by steady application of sufficient heat, the hydrogen uptake always proceeds smoothly to completion.

(8) G. N. Walker, *J. Org. Chem.*, **23**, 34 (1958).

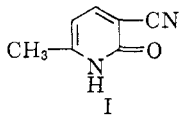
Formation of the Dianion of 6-Methyl-3-cyano-2(1)-pyridone. Condensations at the 6-Methyl Position[1]

Sir:

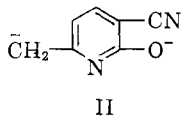
We wish to report that one of the 6-methyl hydrogen atoms of 6-methyl-3-cyano-2(1)-pyridone

(1) Supported by the National Science Foundation (NSF-G14527).

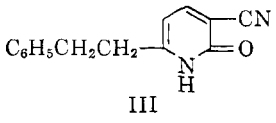
(I) can be replaced by an alkyl group and certain other groups through dianion II, which is prepared by means of two molecular equivalents of potassium amide in liquid ammonia. Thus treatment of II in this medium with a molecular equivalent of benzyl chloride afforded an excellent yield of 6-(2-phenylethyl)-3-cyano-2(1)-pyridone (III), m.p. 200.5–202.5° (reported m.p. 198°),[2] infrared λ_{max}^{KBr} 4.48 μ (CN), 6.02 μ (amide), ultraviolet λ_{max}^{EtOH} (log ϵ) 237 mμ (3.88), 337 mμ (4.12). The structure of III was established by independent synthesis involving cyclization of IV with cyanoacetamide.[2] IV was prepared both by the recently reported[3] terminal benzylation of the dicarbanion of formylacetone and by the formylation of 4-phenyl-2-butanone in basic media.[2] The dicarbanion method[3] readily afforded the pure product; whereas, the other method[2] apparently produced some of the isomer 2-benzyl-1,3-butanedione. This is not surprising since the related formylation of 2-butanone has been shown to produce a mixture of the two possible isomers.[4]



I



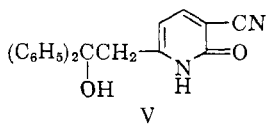
II



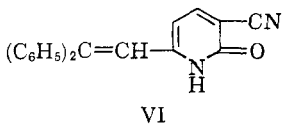
III

$C_6H_5CH_2CH_2COCH_2CHO$

Similarly dianion II was condensed with benzophenone to give presumably V, m.p. 215–216°, infrared λ_{max}^{KBr} 2.94 μ (OH), 4.47 μ (CN), 6.04 μ (amide), ultraviolet λ_{max}^{EtOH} (log ϵ) 235 mμ shoulder (4.04), 338 mμ (4.17), in high yield. *Anal.* Calcd. for $C_{20}H_{16}N_2O_2$; C, 76.06; H, 5.07; N, 8.81. Found: C, 76.00; H, 5.12; N, 8.94. The structural assignment of V was based in part on the facile dehydration effected on treatment with a catalytic amount of sulfuric acid in acetic anhydride. A nearly quantitative yield was obtained of the bright yellow unsaturated pyridone (presumably VI), m.p. 242.5–244°, infrared λ_{max}^{KBr} 4.48 μ (CN), 6.00 μ (amide), ultraviolet λ_{max}^{EtOH} (log ϵ) 246 mμ (4.32), 388 mμ (4.28). *Anal.* Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73; N, 9.39. Found: C, 80.46; H, 4.93; N, 9.48.



V



VI

These and other types of carbon-carbon condensations involving dianion II are being further investigated. Since I is readily available through cyclization of formylacetone with cyanoacetamide,[5] these reactions should furnish a useful method for the preparation of the 6-derivatives of I, certain of which appear not readily prepared by other means. Condensation at the 6-methyl group of I is to be contrasted with the earlier N- and O-alkylation of 2(1)-pyridones.[6]

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CHARLES R. HAUSER

RECEIVED MAY 11, 1962

(2) S. N. Joshi, R. Kaushal, and S. S. Deshapande, *J. Ind. Chem. Soc.*, **18**, 479 (1941).

(3) T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **84**, 1750 (1962).

(4) R. P. Mariella and E. Godard, *J. Org. Chem.*, **22**, 567 (1957).

(5) R. P. Mariella, *Org. Syn.*, **32**, 32 (1952).

(6) See H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. 1, Wiley, New York, 1950, pp. 534–537.

The Stereochemistry of Acetylandromedol[1]

Sir:

The structure of acetylandromedol (I) has recently been determined.[2-4] Evidence is presented here which establishes its stereochemistry as that shown in formula IA.

Like similar nor-ketones from gibberellic acid, (−)-kaurene, garryfoline, and steviol,[5] compound IV [m.p. 202–204°; $\lambda_{CHCl_3}^{C=O}$ 5.71, 5.76 (sh.); C, 66.14; H, 8.72] shows a positive Cotton effect ($[\alpha]^{24}D$ +18, $[\alpha]_{320}^{24}$ +490 in ethanol).[6] Therefore, the absolute stereochemistry of the C—D ring fusion in I is the same as in these other natural products, namely, with the C-15, C-16 bridge β.[7] A *cis* relationship between the 6-hydroxyl and C-15 is demonstrated by the spontaneous formation of the hemiacetal V (m.p. 218–221°; $\lambda_{KBr}^{C=O}$ 5.72, 5.82; C, 64.46; H, 8.42) instead of the free aldehyde in addition to IV on ozonization of III. The *cis* relationship of the 5- and 6-hydroxyls has already been shown in several ways.[1] The 1-hydrogen must also be *cis* to these groups; otherwise, the A–B ring fusion would be *trans*, and the formation of the previously described[1b] ether VI, in which two five-membered rings are fused, would be highly energetically disfavored.[8] The 14-acetoxyl

(1) For previous work see (a) H. B. Wood Jr., V. L. Stromberg, J. C. Keresztesy, and E. C. Horning, *J. Am. Chem. Soc.*, **76**, 5689 (1954) and (b) W. H. Tallent, Mary L. Riethof, and E. C. Horning, *ibid.*, **79**, 4548 (1957).

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

(3) J. Iwasa, Z. Kumazawa, and M. Nakajima, *Agr. Biol. Chem.* (Japan), **25**, 782, 793 (1961).

(4) H. Kakisawa, M. Kurono, S. Takahashi, and Y. Hirata, *Tetrahedron Letters*, 59 (1961).

(5) C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, and L. H. Briggs, *J. Am. Chem. Soc.*, **83**, 3720 (1961).

(6) The author wishes to thank Mrs. Katherine L. Warren of the National Heart Institute for determining the optical rotatory dispersion curve.

(7) In rigid cyclopentanones the first-order determinant of the Cotton effect is the nature of the skewing of the ring itself with substituents having only second-order effects. See among others (a) R. Henderson and R. Hodges, *Tetrahedron*, **11**, 226 (1960) and (b) W. Klyne, *ibid.*, **13**, 29 (1961).

(8) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436 (1935).

and C-7 are *cis* with respect to ring D, permitting the known γ-lactone formation between a free hydroxyl at C-14 and a carboxyl derived from C-6.[2-4] The stereochemistry at C-9 and C-10 is deduced from n.m.r.[9] evidence that the 10-hydroxyl is spatially near the 14-hydrogen. When the 10-hydroxyl is absent, the magnetic resonance of this proton is shifted upfield, *e.g.*, from 329 c.p.s. in I to 317 c.p.s. in 10-deoxyacetylandromedol, II (m.p. 191–193°; C, 66.71; H, 8.99; $[\alpha]^{26}D$ +22.5, *c* 1.0 in ethanol), from 255 c.p.s. in andromedol to 234 c.p.s. in 10-deoxyandromedol (m.p. 268–270°; $[\alpha]^{24}D$ +7.9, *c* 1.0 in ethanol; reported[3] m.p. 260–261° and $[\alpha]^{14}D$ +7), and from 351 c.p.s. in acetylandromedol 5,6-acetonide, VII (transition point 119–120°; m.p. 178–180°; C, 66.37; H, 8.84; $[\alpha]^{26}D$ −9.5, *c* 1.0 in ethanol) to 310 c.p.s. in its 10-deoxy analog, VIII (m.p. 194–196; C, 68.55; H, 9.16; $[\alpha]^{27}D$ +14.0, *c* 0.5 in ethanol). Confirmation of the C-9 configuration is provided by a 2-acetylbicyclo[3.2.1]octane obtained as a degradation product in which the C- and D-rings of the andromedol skeleton remain intact and C-10 and C-18 appear as a labile and presumably axial acetyl group isomerized in alkali to the equatorial conformation.[3] Finally, assignment of configuration at C-16 is based on infrared evidence for interaction between the 16-hydroxyl and the acetate carbonyl group. The spectra of II, VII, and VIII show doublet peaks at 5.71 and 5.76 which are replaced by single peaks near 5.80 μ in the absence of the 16-hydroxyl as in the mixture III and 10,16-dideoxyacetylandromedol (m.p. 176–177°; C, 69.56; H, 9.58; $[\alpha]^{26}D$ +20.0, *c* 0.7 in ethanol). In every case the shape and position of both carbonyl and hydroxyl bands are independent of concentration. At present, there is insufficient evidence for assignment of configuration at C-3.

Regarding the preparation and structures of the key compounds used in this study, VI was obtained by treatment of I with aqueous mineral acid. The 6–10 ether structure, supported by a shift of the 18-methyl n.m.r. band from 80 c.p.s. in I to 75 c.p.s. in VI, is the only one accounting for the evidence[1b] showing 5- or 6-hydroxyl involvement that would not be extremely strained if not indeed impossible. There is only mechanistic evidence concerning the, for present purposes, noncritical stereochemistry of the ether linkage. Other reactions, such as in the dehydration and hydrogenation sequence giving II from I, point to the 10-hydroxyl as the first one affected under acidic conditions. This suggests a concerted mechanism of backside attack at C-10 by the 6-hydroxyl as the protonated tertiary hydroxyl leaves to give a β-ether linkage as indicated for VI.

The structure of II was proved by conversion

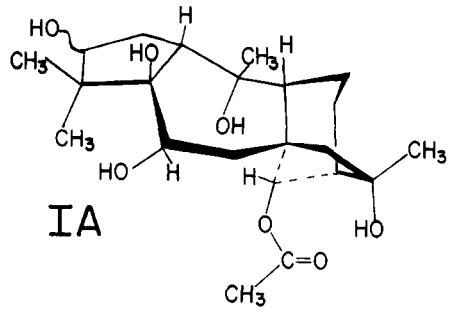

Figure 1

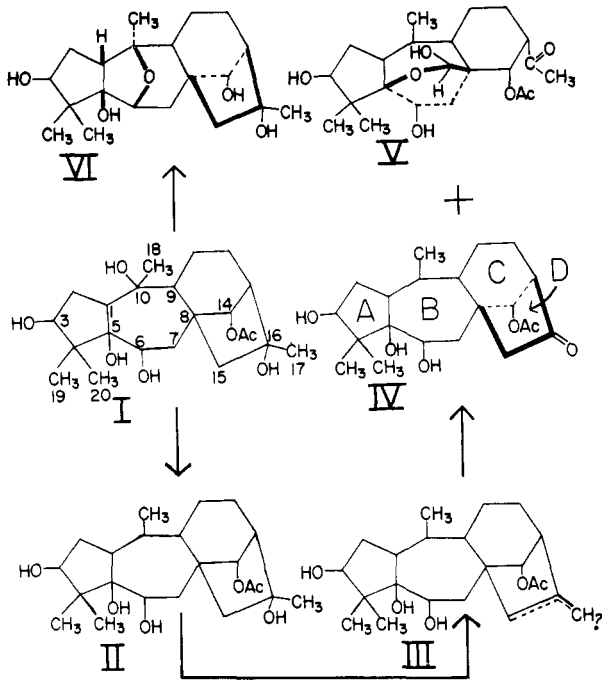

Fig. 2.—Scheme I

via treatment with lithium aluminum hydride to 10-deoxyandromedol, also prepared by catalytic hydrogenation of $\Delta^{10(18)}$-andromedenol (grayanotoxin-II[3]). The mixture of Δ^{15} and Δ^{16} olefins, III (C, 69.90; H, 9.02; $\lambda^{C=C}_{CHCl_3}$ 6.02) prepared from II by copper sulfate–acetone dehydration[1a] exhibited a constant melting point at 196–197°. Nevertheless, gas chromatography demonstrated that it contained two components in the ratio of 4:1,[10] and the relative yields of ozonization products IV and V showed the isomer with the exocyclic double bond to be the major one. The hemiacetal structure ascribed to V is based on the presence of only two sharp carbonyl bands in its infrared spectrum, absence of an aldehyde hydrogen band from its n.m.r. spectrum, and presence of the latter of a band at 295 c.p.s. attributable, according to model compound studies, to the hydrogen on the carbon hearing both ether and hydroxyl oxygens, *i.e.*, C-15. Since they are

(9) Mr. A. J. Damascus of this laboratory determined the nuclear magnetic resonance spectra using a Varian A-60 spectrometer and tetramethylsilane as an internal standard. Tetradeuteromethanol was used as solvent for compounds insoluble in deuterochloroform.

(10) The gas chromatograph was graciously run by Dr. R. J. Highet of the National Heart Institute.

known[1] to be *cis*, the same stereochemical conclusions are reached regardless of which of the *vic*-hydroxyls is involved in hemiacetal formation. Actually, participation of the 5- instead of the 6-hydroxyl was predicted from Dreiding models and confirmed by n.m.r. bands for V at 61 and 71 c.p.s. attributable to the *gem*-methyl groups and nearly unchanged from frequencies of 58 and 70 c.p.s. found for I. These bands are shifted upfield in derivatives in which the oxygen atom attached to C-6 is removed from the vicinity, *e.g.*, by cleavage with periodate. They are similarly shifted when its proximity to the methyls is destroyed as in VI (57 and 59 c.p.s.) and the acetonides VII (51 and 64 c.p.s.) and VIII (48 and 62 c.p.s.) and as would be the case in a hemiacetal formed with 6-hydroxyl involvement.

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