terial eluted from the chromatogram with more polar solvents showed no biferrocenyl or other recognizable compounds.

Reaction of Iodoferrocene with *n*-Butyllithium.—To 0.31 g. (0.001 mole) of iodoferrocene[17] in 8 ml. of anhydrous tetrahydrofuran was added 32 ml. (0.051 mole) of *n*-butyllithium in hexane. The solution was heated at reflux for 7 hr. under nitrogen, cooled, and poured onto ice. The aqueous layer was drawn off and extracted with ether until the extracts were colorless. The ethereal extracts were combined, dried, concentrated to about 10 ml., and chromatographed on Merck acid-washed alumina. Elution with hexane gave 0.015 g. (8.2%) of ferrocene, and further elution with hexane–benzene and benzene–ether mixtures gave only oils. Vapor phase chromatography and thin layer chromatography on alumina G both failed to detect any butylferrocene or biferrocenyl.

2-Chloroferrocenecarboxylic Acid. A.—To 1.76 g. (0.008 mole) of chloroferrocene was added 10 ml. of butyllithium solution (0.014 mole), 10 ml. of ether, and 10 ml. of hexane. The solution was stirred at room temperature for 7 hr. and then poured into a Dry Ice–ether slush. Water was added and the aqueous layer was drawn off. The ethereal solution was extracted with 5% sodium bicarbonate and dried and the solvent was removed at reduced pressure to give a mixture of 7% ferrocene (0.028 g., 1.9% yield) and 93% chloroferrocene (0.362 g., 20.6% recovery); analysis was by gas chromatography.

The aqueous layer was acidified and extracted with ether. After drying, removal of the solvent *in vacuo* gave 1.66 g. of a yellow solid which decomposed rapidly in air when impure. Recrystallization from hexane gave 0.060 g. of material, m.p. 170–172° (evacuated capillary).

Anal. Calcd. for $C_{11}H_9ClFeO_2$: C, 49.95; H, 3.43; Cl, 13.40. Found: C, 49.81; H, 3.46; Cl, 13.51.

B.—When the reaction was carried out at reflux using 1.76 g. of chloroferrocene there was obtained, in addition to 3% ferrocene and 5% chloroferrocene, 0.71 g. (crude) of the chloro acid, identical in all respects with that prepared in part A, above.

Studies on Resin Acids. II.[1] Synthesis of Some Tricyclic Steroid Analogs

J. W. HUFFMAN AND P. G. ARAPAKOS[2]

Department of Chemistry and Geology, Clemson University, Clemson, South Carolina

Received December 15, 1964

1-Ketonordehydroabietane (II) has been converted to a variety of tricyclic steroid analogs. Condensation of II with ethyl formate and base, followed by oxidation gave the seco diacid IV. Cyclization of the diester of this acid gave *cis*-1a-methyl-3-oxo-7-isopropyl-1,1a,2,3a,4,5-hexahydronaphthalene (V) which was converted to the ethynylcarbinol VI with the lithium acetylide–ethylenediamine complex. This acetylenic alcohol was rearranged to a Δ^{16}-20-keto steroid analog (VII) and also converted to a 17-hydroxy-20-keto steroid analog (X). The stereochemistry of these compounds is discussed.

Although various tricyclic steroid analogs have been prepared in the past, these compounds have all been made by relatively laborious totally synthetic routes.[3] The resin acids and, more specifically, dehydroabietic acid (I) appear to present an attractive source of a tricyclic steroid nucleus, with the A-ring of the resin acid becoming the D-ring of the des-A steroid.[4]

The starting material chosen for these synthetic efforts was 1-ketonordehydroabietane (II), which has been prepared in several steps from dehydroabietic acid.[1,5] Although the over-all yield by the modified version of this sequence is 39%,[1] the procedure is laborious and a new two-step synthesis has been devised. Reaction of dehydroabietic acid with lead tetraacetate affords $\Delta^{1\text{-}exo}$-dehydroabietene, the olefin corresponding to II, in 80% yield.[6] Ozonization of the olefin and reduction of the ozonide with zinc dust affords the ketone in 65% yield[1]; however, the crude product from this procedure shows strong infrared absorption at 2.92 in addition to the carbonyl band at 5.86 μ.[7] Consequently, the ozonide was decomposed with potassium iodide and the liberated iodine was then reduced with thiosulfate giving the ketone in 90% yield (72% for two steps).[8]

Condensation of the ketone with ethyl formate and base to the formyl derivative III followed by oxidation to the seco diacid IV proceeded smoothly. By analogy with II[1] and the cyclopentanone obtained on cyclization of IV (*vide infra*), it is assumed the diacid has the *cis* stereochemistry indicated (see Scheme I).

The dimethyl ester of this diacid was cyclized to *cis*-1a-methyl-3-oxo-7-isopropyl-1,1a,2,3a,4,5-hexahydrocyclopenta[*a*]naphthalene (V), using the method of Johnson.[9] The rotatory dispersion curve[10] of this ketone shows a strongly positive Cotton effect, and by analogy with A-nor-3-ketocholanic acid[11] has a *cis* ring fusion. Attempted direct cyclization of the acid IV with acetic anhydride[12] failed and afforded a compound which, although apparently a ketone, was not the desired material and is still of unknown structure.

The cyclopentanaphthalene V was envisioned as being the precursor of a series of compounds possessing a pregnane side chain and may itself be considered to be an equilenin analog. Reaction of the ketone with

(1) Part I: J. W. Huffman and R. F. Stockel, *J. Org. Chem.*, **28**, 506 (1963).

(2) Abstracted from the thesis presented by P. G. Arapakos in partial fulfillment of the requirements for the Ph.D. degree.

(3) (a) L. J. Chinn, H. L. Dryden, and R. R. Burtner, *J. Org. Chem.*, **26**, 3910 (1961), and references cited therein; (b) N. A. Nelson, J. C. Wollensak, R. L. Foltz, J. B. Hester, J. I. Brauman, R. B. Garland, and G. H. Rasmusson, *J. Am. Chem. Soc.*, **82**, 2569 (1960).

(4) It should be noted that this approach suffers principally from the facts that this gives a steroid analog of unnatural configuration with the methyl group and hydrogen at the CD bridgeheads interchanged.

(5) (a) H. H. Zeiss and W. B. Martin, *J. Am. Chem. Soc.*, **75**, 5935 (1953); (b) A. Brossi, H. Gutman, and O. Jeger, *Helv. Chim. Acta*, **33**, 1730 (1950); (c) R. P. Jacobsen, *J. Am. Chem. Soc.*, **75**, 4709 (1953).

(6) N. A. Ayer, C. E. McDonald, and J. B. Stothers [*Can. J. Chem.*, **41**, 1113 (1963)] have carried out a similar reaction on a levopimaric acid derivative

(7) The presence of the band at 2.92 μ is apparently caused by partial reduction of the ketone by the zinc employed to reduce the ozonide.

(8) We would like to thank Dr. C. B. S. Rao of these laboratories for his assistance with the ozonizations.

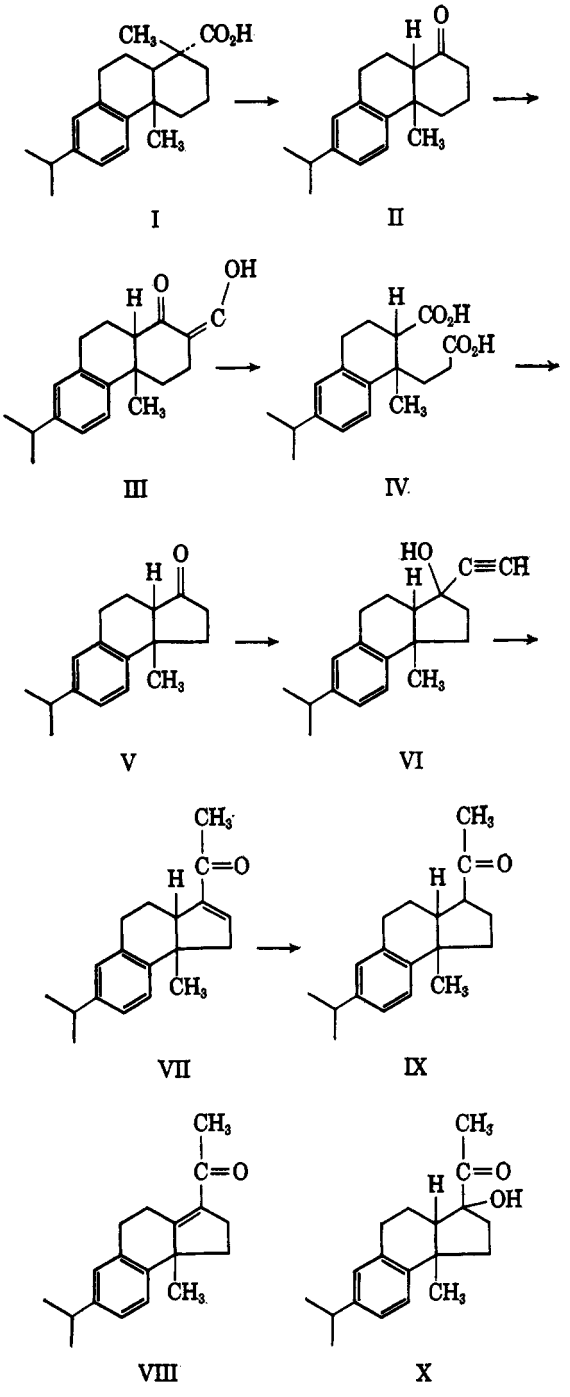
(9) (a) W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956); (b) W. S. Johnson, R. Pappo, and W. F. Johns, *ibid.*, **78**, 6339 (1956).

(10) We would like to thank Professor Werner Herz of Florida State University for carrying out this determination.

(11) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 97.

(12) (a) T. Rull and G. Ourisson, *Bull. soc. chim. France*, 1573 (1958); (b) J. F. Biellmann and G. Ourisson, *ibid.*, 341 (1962).

SCHEME I



either sodium acetylide in liquid ammonia[13] or acetylene and potassium *t*-amyloxide[14] gave the acetylenic alcohol VI, although in very poor yield. However, the reaction of the ketone with the commercially available lithium acetylide–ethylenediamine complex[15] proceeded smoothly to give VI in good yield.

Comparison of the Dreiding models of ketone V and 3-keto-14-methyl-A-norcholestanone,[16] indicates that the addition of reagents to the carbonyl group of V should be less stereospecific than in the case of the steroid derivative. Since the A-nor steroid apparently gives a mixture of alcohols on reaction with methylmagnesium iodide, it may be assumed that the acetylenic alcohol derived from V is a mixture of stereoisomers.[17]

Two methods of elaborating the side chain were explored. In the first, the acetylenic alcohol was subjected to boiling formic acid or, better, treatment with Dowex 53W-X12 resin in acetic acid,[18] affording the α,β-unsaturated ketone VII. Although it might be expected that the tetrasubstituted isomer of VII (VIII) should be formed, the compound obtained shows a vinyl proton in the n.m.r. at τ 3.42, and the ultraviolet spectrum shows a maximum at 240 mμ, the same place as that of Δ^{16}-20-keto steroids.[19] In addition, integration of the n.m.r. spectrum shows that this compound can contain a relatively small amount of isomer VII, since within experimental error the intensity of the peak from the vinyl proton is equivalent to a full proton.

These results were not expected, since it has been shown that the acid-catalyzed rearrangement of acetylenic carbinols to unsaturated ketones (Rupe reaction) probably proceeds in two discreet steps, namely dehydration to the vinylacetylene, followed by hydration.[20] It would therefore be expected that the rearrangement would afford the more stable of the pair of possible vinylacetylenes,[21] and consequently the more highly substituted α,β-unsaturated ketone, in our case VIII.[22] Another point worthy of note is that this unsaturated ketone would form neither a normal dinitrophenylhydrazone nor a semicarbazone. From models it appears that the carbonyl group is rather hindered, and addition is probably occurring at the β-position.[23]

Catalytic hydrogenation of the unsaturated compound proceeded normally to give the saturated ketone IX. Although hydrogenation might be expected to afford a mixture of stereoisomers, the subsequent chromatography on alumina would be expected to afford predominantly the more stable isomer, namely that where the acetyl group is *cis* to the angular methyl.[24] This dihydro compound also failed to give normal carbonyl derivatives.

The final compound in this series, the 17-hydroxypregnane analog X, was prepared by hydration of the acetylenic alcohol. Since the alcohol VI is probably a mixture of stereoisomers at C-3, and the Dowex-catalyzed hydration[25] should not disturb the configura-

(13) (a) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); (b) K. N. Campbell, B. K. Campbell, and L. T. Eby, *J. Am. Chem. Soc.*, **60**, 2882 (1938).

(14) (a) E. H. Stavely, *ibid.*, **61**, 79 (1939); (b) L. Velley, G. Muller, R. Jequier, and C. Plotka, *ibid.*, **80**, 2026 (1958).

(15) O. F. Beumel and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).

(16) D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

(17) From examination of the models it would appear that the isomer with the ethynyl group *cis* to the angular methyl group should predominate.

(18) M. J. Newman, *J. Am. Chem. Soc.*, **75**, 4740 (1953).

(19) L. Dorfman, *Chem. Rev.*, **53**, 76 (1953).

(20) G. F. Hennion, R. B. Davis, and D. E. Maloney, *J. Am. Chem. Soc.*, **71**, 2813 (1949).

(21) K. Suga and S. Watanabe [*Chiba Daikagu Kogakubu Kenkyu Hokoku*, **9**, 67 (1958); *Chem. Abstr.*, **54**, 5432 (1960)] have shown that the rearrangement of 3-methyl-1-butyn-3-ol affords 4-methyl-3-penten-2-one. An alternative mechanism for the Rupe reaction suggested by M. F. Ansell, J. W. Hancock, and W. J. Hickinbottom [*J. Chem. Soc.*, 911 (1956)] also predicts that one should obtain the most stable unsaturated ketone.

(22) Examination of models fails to show any significant differences in steric interactions between the vinylacetylenes corresponding to VII and VIII.

(23) Although solid materials were obtained from these reactions, they were not the expected derivatives and are of unknown structures.

(24) In the other isomer there are rather severe interactions between the side chain and the C-6 hydrogens (C-12 if one considers this a des-A steroid).

(25) G. Amiard, M. Legrand, J. Mathieu, R. Heymes, and T. Van Thuong, *Bull. soc. chim. France*, 2417 (1961).

tion of this center, it follows that the hydroxy ketone should also be a mixture of stereoisomers. The gross structure of this compound was proven by its periodate cleavage to the original cyclopentanone (V).

Experimental[26]

$\Delta^{1\text{-}exo}$-Dehydroabietane.—To a solution of 30 g. of dehydroabietic acid in 150 ml. of dry benzene and 12 ml. of dry pyridine under nitrogen was added 50 g. of lead tetraacetate. After 1 hr. of stirring at room temperature, the contents of the flask were stirred at reflux for 3 hr. The reaction mixture was filtered through Celite and washed several times with benzene. The filtrate and washings were combined and concentrated by means of a water aspirator and a steam bath. The resulting viscous bright yellow oil was dissolved in hexane and chromatographed over 1 lb. of Merck acid-washed alumina using hexane as eluent. After evaporation of the solvent there was obtained 20 g. (80%) of a clear, colorless oil. The infrared spectrum of this compound was identical with that of material prepared *via* the Cope reaction.[1]

1-Ketonordehydroabietane.—A stream of ozone was passed through a solution of 10 g. of $\Delta^{1\text{-}exo}$-dehydroabietene in 300 ml. of methylene chloride at −70° until the solution was saturated with ozone. The reaction mixture was allowed to warm to room temperature and 400 ml. of saturated aqueous potassium iodide solution and 10 ml. of glacial acetic acid were added. The mixture was shaken vigorously and allowed to stand at room temperature for 15 min. Saturated aqueous sodium thiosulfate solution was then added and the mixture was again shaken vigorously until the orange-brown color (iodine) disappeared. The aqueous layer was separated and the organic layer was washed several times with 300-ml. portions of distilled water. The organic layer was then dried, filtered, and concentrated giving 9.0 g. (90%) of ketone as a viscous oil after chromatography on acid-washed alumina using benzene as solvent and as eluent. The infrared spectrum showed a single carbonyl band at 5.86 μ. The 2,4-dinitrophenylhydrazone had m.p. 90–91°, from ethanol. A mixture melting point with the 2,4-dinitrophenylhydrazone of the material prepared by the earlier method showed no depression.

2-Hydroxymethylene-1-ketonordehydroabietane.[27]—To a suspension of 0.288 g. of sodium hydride in 45 ml. of dry ether 1.48 g. of freshly distilled ethyl formate and 16 drops of methanol were added. The solution was stirred under nitrogen for 10 min., following which the reaction flask was cooled in an ice bath. A solution of 1 g. of ketone in 20 ml. of dry ether was added dropwise over the period of 1 hr., and the solution was allowed to come to room temperature and stirred overnight under nitrogen. Ice water was added to decompose the excess sodium hydride, and after the vigorous evolution of hydrogen had ceased, the solution was poured into an excess of ice-cold 5% hydrochloric acid and the aqueous layer was drawn off. The ether was washed well with water and dried, and the solvent was removed under vacuum. The resulting yellow oil was dissolved in 5% sodium hydroxide and the solution was extracted several times with ether. Upon acidification with 5% hydrochloric acid, it was again extracted with ether. The ethereal solution was dried, filtered, and evaporated *in vacuo* giving the formyl compound as a pale yellow semisolid material in 65% yield (0.71 g.). Attempted purification led to extensive decomposition and the crude material was used for the next step.

***cis*-3-(Methyl-2-carboxy-6-isopropyl-1,2,3,4-tetrahydro-1-naphthyl)propanoic acid.**[27]—To a solution of 47 ml. of 10% sodium hydroxide in 35 ml. of ethanol was added 0.4 g. of the formyl derivative, then 15 ml. of 30% hydrogen peroxide was added and the solution was allowed to stand at room temperature for 20 min. An additional 47 ml. of 10% sodium hydroxide and 30 ml. of peroxide were added and the solution was allowed to stand at room temperature overnight. The reaction mixture was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried; the solvent was removed under vacuum to give a yellow semisolid material which was dissolved in 10% sodium hydroxide extracted with ether, acidified, and then once again extracted with ether. Upon removal of the ether a pale yellow solid was obtained in 75% yield. Recrystallization from aqueous methanol or ether–hexane gave the analytical sample, m.p. 194–195°, $[\alpha]^{25}D$ −92.7° (*c* 0.345, ethanol).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.94. Found: C, 71.17; H, 7.84.

The oily dimethyl ester was prepared by reaction of the acid with excess diazomethane. The compound showed the expected infrared absorption at 5.80 μ and had $[\alpha]^{25}D$ −107° (*c* 0.160, chloroform).

***cis*-1a-Methyl-3-*exo*-7-isopropyl-1,1a,2,3a,4,5-hexahydrocyclopenta[*a*]naphthalene.**—To dry alcohol-free potassium *t*-butoxide, prepared from 2.0 g. of potassium, a solution of 0.20 g. of methyl 6-isopropyl-1-methyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene-1-propionate in 80 ml. of dry benzene was added under a nitrogen atmosphere, and the reaction mixture was heated at reflux with stirring for 5 hr. and then left at room temperature for 10 hr. Glacial acetic acid (5 ml.) was added, followed by 20 ml. of water. The mixture was shaken thoroughly, the aqueous layer was removed, and the organic layer was washed with water, dilute aqueous sodium bicarbonate, and finally with saturated sodium chloride solution. The benzene extract was dried, filtered, and concentrated to give the crude, oily β-keto ester. To this crude keto ester, 10 ml. of glacial acetic acid, 5 ml. of concentrated hydrochloric acid, and 1 ml. of water were added and the mixture was heated at reflux under a nitrogen atmosphere for 1.5 hr. The acetic and hydrochloric acids were removed at reduced pressure and the residue was treated with 32 ml. of 2.5% methanolic sodium hydroxide solution containing 3 ml. of water and heated at reflux under a nitrogen atmosphere for 2 hr. The methanol was removed under reduced pressure and 80 ml. of water was added to the residue. The aqueous mixture was extracted thoroughly with ether, the ether layer was dried, and the solvent was removed *in vacuo*. The resulting yellow-brown oil was dissolved in hexane and chromatographed on Merck acid-washed alumina. Elution with benzene gave 0.1 g. (70%) of pale yellow oil, which after being dissolved in a small amount of hexane and standing overnight at 0° gave a white crystalline solid, m.p. 58–59°. This compound showed carbonyl absorption at 5.76 μ; α_{600} +256°; α_{589} +282°; α_{321} +3584°; α_{315} 3865°; α_{275} −2893°; α_{245} −2176°.

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.08; H, 8.89.

The 2,4-dinitrophenylhydrazone was formed in the usual manner; m.p. 193–194° from ethanol, λ_{max} 366 mμ (log ϵ 4.40).

Anal. Calcd. for $C_{23}H_{26}N_4O_4$: C, 65.30; H, 6.20; N, 13.26. Found: C, 65.43; H, 6.19; N, 13.35.

***cis*-1a-Methyl-3-hydroxy-3-ethynyl-7-isopropyl-1,1a,2,3a,4,5-hexahydrocyclopenta[*a*]naphthalene.**—To 30 ml. of anhydrous dioxane saturated with acetylene, was added with stirring 3 g. of lithium acetylide–ethylenediamine complex, followed by a solution of 0.5 g. of the five-membered ketone in 10 ml. of anhydrous dioxane over a period of 0.5 hr. During the addition and for 40 min. thereafter, a stream of acetylene was bubbled through the reaction mixture. After allowing the mixture to stand for 24 hr. under a nitrogen atmosphere with constant stirring, an aqueous solution of ammonium chloride was added slowly. The layers were separated and the aqueous layer was extracted several times with ether until the ether extracts were clear. The organic phases were concentrated under vacuum and the resulting yellow-brown oil was dissolved in hexane and chromatographed over neutral alumina. Elution first with 400 ml. of benzene afforded a trace of unreacted five-membered ketone and the first 50 ml. of methanol gave the desired ethynylcarbinol. Evaporation of the methanol under vacuum gave 0.47 g. (85%) of pale yellow oil showing strong infrared absorption at 2.85 and 3.00 and weak absorption at 4.71 μ. This compound resisted purification by the usual methods and was used directly in the succeeding steps.

***cis*-1a-Methyl-3-acetyl-7-isopropyl-1,1a,3a,4,5-tetrahydrocyclopenta[*a*]naphthalene. A.**—A stirred mixture of 0.5 g. of the acetylenic alcohol, 10 ml. of glacial acetic acid, 1 ml. of distilled water, and 3 g. of Dowex 50W-X12 (200–400 mesh)

(26) Melting points were determined on a Fisher-Johns block and are uncorrected. Infrared spectra were determined as potassium bromide pellets or liquid films using a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were carried out in ethanol or chloroform on a Perkin-Elmer Model 4000A spectrophotometer. Rotational values were determined in ethanol or chloroform using a Rudolph Model 70 polarimeter. The n.m.r. spectra were carried out in carbon tetrachloride solution, with tetramethylsilane as an internal standard, using a Varian A-60 spectrometer.

(27) This preparation was initially carried out by Dr. R. F. Stockel.

was heated at reflux under a nitrogen atmosphere for 24 hr. After cooling, the resin was filtered off and washed with ether until the filtrates were clear. The filtrates and washings were combined and neutralized with 40% aqueous sodium hydroxide solution and then washed with water. The ethereal solution was dried and the solvent was removed to give 0.42 g. (85%) of pale yellow mobile oil which showed strong infrared absorption at 6.02 and 6.2 and very weak absorption at 2.85 and 3.00 μ. After chromatography on Merck alumina, using a mixture of 30% benzene–70% hexane as eluent, a clear colorless oil was obtained: $[\alpha]^{22}D$ −14.3° (*c* 0.0388, $CHCl_3$), λ_{max} 240 mμ (log ϵ 4.01).

Anal. Calcd. for $C_{18}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.83; H, 8.86.

B.—A mixture of 0.5 g. of the ethynylcarbinol and 8 ml. of 98% formic acid was heated under reflux for 2.5 hr. The dark brown solution was cooled to room temperature, neutralized with saturated aqueous sodium bicarbonate solution, and extracted with ether. The ether extracts were washed several times with water, dried, concentrated, and chromatographed on Bio-Rad AG-7 neutral alumina with benzene as eluent. Upon removing the benzene under vacuum, there was obtained 0.38 g. (75%) of a pale yellow oil showing strong infrared absorption at 6.02 and 6.2 μ, identical with that obtained in method A.

***cis*-1a-Methyl-3-acetyl-7-isopropyl-1,1a,2,3,3a,4,5-hexahydrocyclopenta[*a*]naphthalene.**—To a well-stirred mixture of prereduced 10% palladium on carbon in ethyl acetate, 200 mg. of the above α,β-unsaturated ketone in 8 ml. of ethyl acetate was added. After 2.5 hr., 27.0 ml. of hydrogen at atmospheric pressure and room temperature was absorbed. The mixture was filtered, and upon evaporation of solvent 150 mg. of an almost colorless oil was obtained. This material showed strong infrared absorption at 5.86 μ. The compound was chromatographed on Merck alumina using benzene as solvent and as eluent: $[\alpha]^{22}D$ −5.04° (*c* 0.0250, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.16; H, 9.69.

***cis*-1a-Methyl-3-acetyl-3-hydroxy-7-isopropyl-1,1a,2,3,3a,4,5-hexahydrocyclopenta[*a*]naphthalene.**—A mixture of 0.5 g. of the ethynylcarbinol, 1 g. of Dowex 50W-X12, 1 g. of Dowex 50W-X12 which had been preactivated with mercuric acetate, and 40 ml. of aqueous ethyl ether was stirred for 50 hr. at room temperature. The resin was filtered off and washed with ethyl ether until the filtrate was clear. The filtrate and washings were combined, dried, and concentrated to give 0.49 g. (92%) of a pale yellow viscous oil. This oil showed strong infrared absorption at 2.81 and 5.90 and weak absorption at 3.00 μ. Chromatography on Florosil and elution with benzene gave a colorless oil. The analytical sample was a colorless oil prepared by rechromatography of the once-chromatographed material: $[\alpha]^{23}D$ −4.6° (*c* 0.0860, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.61; H, 9.20.

Oxidation of *cis*-1a-Methyl-3-acetyl-7-isopropyl-1,1a,2,3,3a,4,5-hexahydrocyclopenta[*a*]naphthalene.—In 4 ml. of 95% ethanol, 15 mg. of the hydroxy ketone and 30 mg. of periodic acid were stirred overnight at room temperature. Dilute aqueous sodium bicarbonate was added to the reaction mixture which was extracted several times with ether. After washing well with water, drying, and concentrating the ether extracts, 9 mg. of yellow oil was obtained. The infrared absorption spectrum of this material was identical with that of original five-membered ketone.

Acknowledgment.—This work was supported by Grant GM-07817 from the Division of General Medical Sciences of the National Institutes of Health. The authors would like to thank the Hercules Powder Company for generous gifts of dehydroabietonitrile.

1,8-Naphthyridines. I. Derivatives of 2- and 4-Methyl-1,8-naphthyridines

ELLIS V. BROWN

Department of Chemistry, University of Kentucky, Lexington, Kentucky

Received December 17, 1964

2-Methyl-1,8-naphthyridine has been prepared by a series of reactions starting with 2-methyl-5-hydroxy-1,8-naphthyridine-6-carboxylic acid and compared with the known 4-methyl-1,8-naphthyridine. The compound previously thought to be 2-methyl-4-hydroxy-7-amino-1,8-naphthyridine has been shown to be 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine by conversion to 4-methyl-1,8-naphthyridine. A new ring closure has furnished 2-methyl-7-amino-1,8-naphthyridine and, in addition, 2-amino-5-methyl-1,8-naphthyridine and 2-methyl-5-amino-1,8-naphthyridine have been prepared by other means.

Our interest in naphthyridines arose from their gross similarity to quinolines and our desire to prepare azo compounds in this series to compare with the quinoline azo compounds which have such interesting variations in carcinogenic activity.[1,2] In the course of syntheses leading to the requisite amines, a number of interesting naphthyridines have been prepared (Scheme I).

In our first series we used as the starting material 2-methyl-5-hydroxy-6-carbethoxy-1,8-naphthyridine which was prepared by Lappin from 6-methyl-2-aminopyridine (I) and ethyl ethoxymethylenemalonate.[3] The same author also hydrolyzed the ester to the corresponding acid II. We have decarboxylated the acid in mineral oil at 300° to obtain 2-methyl-5-hydroxy-1,8-naphthyridine (III). Refluxing with $POCl_3$ gave the chloro compound IV. The chloro group could either be replaced by amino, hydrazino, or hydrogen. In the latter case, the new 2-methyl-1,8-naphthyridine (V) was produced. The hydrazine could also be converted to 2-methyl-1,8-naphthyridine by oxidation with copper sulfate.

For comparison, the known 4-methyl-1,8-naphthyridine was prepared. The usual starting material for this synthesis is 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine (XI) which has been prepared by heating ethyl acetoacetate and 2,6-diaminopyridine[4] to 145–150°. We have found that about the same yield of a nearly white product can be obtained by heating the reactants at 90–100° in phosphoric acid. This result was somewhat surprising because Hauser[5a] had claimed that these reactants in the presence of a few drops of concentrated HCl standing 30 days at room temperature produced an 8% yield of 2-methyl-4-hydroxy-7-amino-1,8-naphthyridine. We next heated the reactants at 80–90° for 1 hr. in the presence of concentrated

(1) E. V. Brown, R. M. Novack, and A. A. Hamdan, *J. Org. Chem.*, **26**, 2831 (1961).

(2) E. V. Brown, R. M. Novack, and A. A. Hamdan, *J. Natl. Cancer Inst.*, **26**, 1461 (1961).

(3) G. R. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

(4) O. Seide, *Ber.*, **59**, 2465 (1926).

(5) (a) C. R. Hauser and M. J. Weiss, *J. Org. Chem.*, **14**, 453 (1949); (b) S. Carboni, A. DaSettimo, and G. Pirisino, *Ann. Chim.* (Rome), [7] **54**, 677 (1964).