A 5-Aza Analog of $\Delta^{6a(10a)}$-Tetrahydrocannabinol

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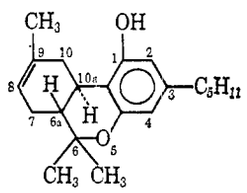
It has been shown that the active constituents of hashish (marijuana) are *l*-Δ^8-tetrahydrocannabinol **1**[1] and *l*-Δ^9-tetrahydrocannabinol **2**.[2] The early work of



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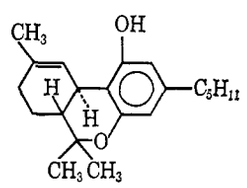

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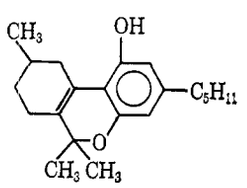
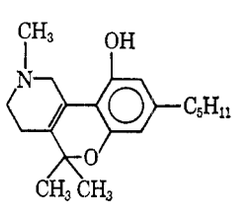
Adams and Todd and their collaborators[3] led to the synthesis of the physiologically active $\Delta^{6a(10a)}$-tetrahydrocannabinol isomer **3**.



3

Pars, *et al.*,[4] prepared the 9-aza analog **4** of the $\Delta^{6a(10)}$ isomer.

We now wish to report the synthesis of a 5-aza analog **5** of the $\Delta^{6a(10a)}$ isomer.



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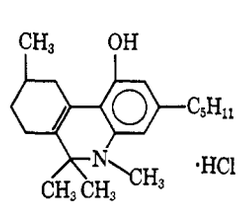
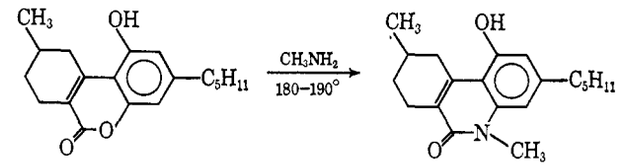


5

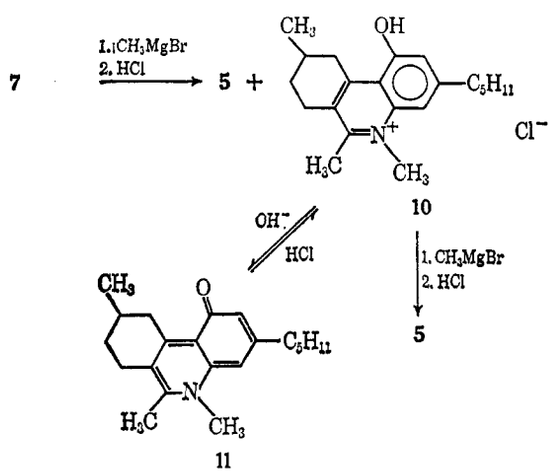
Although conversion of α- and β-pyrones into the corresponding 2- and 4-pyridones have been achieved by reaction with ammonia or aliphatic amines,[5] and similarly isoquinolines have been prepared from the corresponding isocoumarins,[6] no synthesis of tetrahydrophenanthridinones has been reported from a reaction of an aliphatic amine with the corresponding 6-dibenzopyrones. However, it has been found that heating the dibenzopyrone **6** with methylamine at 180–190° in a sealed tube for several days yielded the tetrahydrophenanthridin-6-one **7**.



6 7

The reaction probably proceeds through an initial formation of an amidoresorcinol **8** which then undergoes a Bucherer-type reaction to give the amino phenol **9**. Transaminating cyclization then yields **7**. A strong base is presumably required for this reaction, as it failed to take place with either ammonia or benzylamine. (See Scheme I.)

Treatment of **7** with an excess of methylmagnesium bromide yielded two products in about the same amounts, the tetrahydrophenanthridine as its hydrochloride **5** and the 6-methylphenanthridinium chloride **10**.



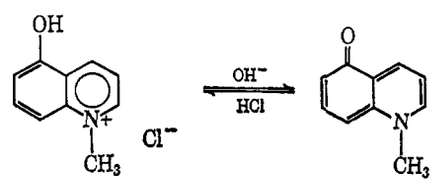
10

11

Further treatment of the quaternary salt **10** with methylmagnesium bromide yielded **5**.

When the yellow quaternary salt **10** was treated with alkali, a deep violet color was observed $\lambda_{max}^{CH_3OH/pH\ 11}$ 284 mμ (ϵ 35,000), 340 (3500), 470 (4900)].

The similar spectral data of the known quinolinium chloride[7] **12** [$\lambda_{max}^{EtOH/pH\ 8.5}$ 273 mμ (ϵ 33,000), 318 (1240), 332 (1150), 462 (3800)] led to the structural assignments **10** and **11**.



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(6) W. J. Gensler in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p 373 ff; H. E. Ungnade, D. V. Nightingale, and H. E. French, *J. Org. Chem.*, **10**, 533 (1945).

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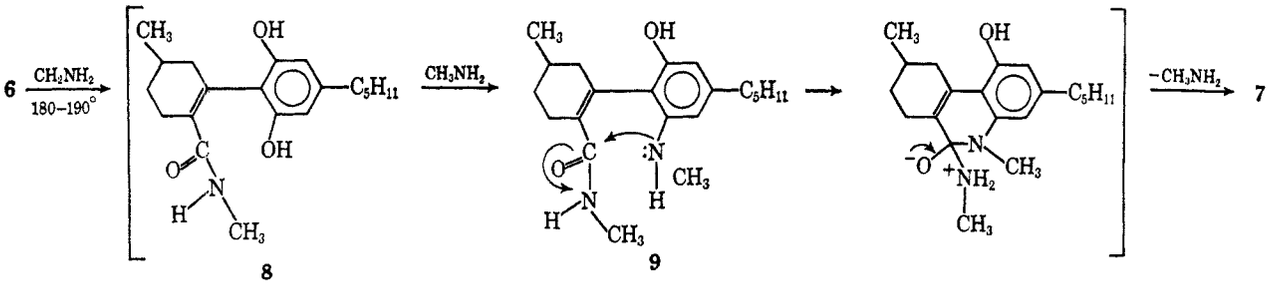
SCHEME I



Experimental Section

Melting points were determined on a Thomas–Hoover Unimelt and are uncorrected. Ultraviolet spectra were determined on a Beckman Model DK-2A ultraviolet spectrophotometer in methanol solution, unless otherwise stated. Ascending thin layer chromatography was performed on Eastman silica gel chromatogram sheets, K301R. Analyses were performed by Mr. Charles Pouchert of our analytical department.

7,8,9,10-Tetrahydro-1-hydroxy-5,9-dimethyl-3-*n*-pentylphenanthridin-6-one (7).—A mixture of 0.5 g (1.67 mmol) of 7,8,9,10-tetrahydro-1-hydroxy-3-*n*-pentyl-6-dibenzopyrone[3] (6) and 2.7 g (35 mmol) of 40% aqueous methylamine was heated in a Carius tube at 190 ± 5° for 42 hr. After cooling to room temperature, methylene chloride was added and the mixture was washed with 2 *N* hydrochloric acid. The organic layer was dried over magnesium sulfate and evaporated to dryness yielding 0.5 g (95.5% theory) of the product, mp 216–219°. Recrystallization from ethyl acetate yielded fine colorless needles, mp 219–220°.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.83; H, 8.45; N, 4.39.

7,8,9,10-Tetrahydro-1-hydroxy-5,6,6,9-tetramethyl-3-*n*-pentylphenanthridine Hydrochloride (5) and 7,8,9,10-Tetrahydro-1-hydroxy-5,6,9-trimethyl-3-*n*-pentylphenanthridinium Chloride (10).—To a refluxing solution of 1.8 g (5.74 mmol) of 7,8,9,10-tetrahydro-1-hydroxy-5,9-dimethyl-3-*n*-pentylphenanthridin-6-one (7) in 125 ml of dry benzene, 16.7 ml (50 mmol) of a 3 *N* solution of methylmagnesium bromide in ether was added over a 5-min period. After heating under reflux for 26 hr, addition of 50 ml of 2 *N* hydrochloric acid to the cooled (0°) reaction mixture resulted in the formation of a yellow-orange precipitate. The solid (shown by tlc with 1:1 methanol–ethyl acetate on silica to contain two components) was twice recrystallized from 5% aqueous methanol, yielding 0.72 g (34.6% theory) of **5** (the faster moving component on tlc) as colorless plates: mp 233–235° dec; $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 27,400), 293 (6000); $\lambda_{max}^{CH_3OH\text{-}HCl}$ 262 mμ (ε 12,100), 304 (8500); $\lambda_{max}^{CH_3OH/pH\ 11}$ 242.5 mμ (ε 25,600); ir absorption, 3.26 (OH), 4.01 (⁺NH), 6.11 (s, conjugated C=C), 6.35 μ (Ph).

Anal. Calcd for $C_{22}H_{34}ClNO$: C, 72.59; H, 9.42; Cl, 9.74; N, 3.85. Found: C, 72.61; H, 9.45; Cl, 9.79; N, 3.96.

Evaporation of the mother liquor to dryness gave a solid which upon recrystallization from ethyl acetate gave 0.55 g (38.4% theory) of **10** as a yellow solid: mp 138–145° after charring at 125°; $\lambda_{max}^{CH_3OH}$ 267 mμ (ε 43,500), 289 (7500); $\lambda_{max}^{CH_3OH\text{-}HCl}$ 267 mμ (ε 54,100); $\lambda_{max}^{CH_3OH/pH\ 11}$ 284 mμ (ε 35,000), 340 (3500), 470 (4900); ir absorption, 2.97 (OH), 6.18 (C=C), 6.40 μ (Ph).

Anal. Calcd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69; Cl, 10.19; N, 4.02. Found: C, 72.59; H, 8.68; Cl, 10.20; N, 4.09.

7,8,9,10-Tetrahydro-1-hydroxy-5,6,6,9-tetramethyl-3-*n*-pentylphenanthridine Hydrochloride (5) from 7,8,9,10-Tetrahydro-1-hydroxy-5,6,9-trimethyl-3-*n*-pentylphenanthridinium Chloride (10).—A solution of methylmagnesium bromide (16.7 ml, 3 *N*, 50 mmol) in ether was added to a refluxing solution of 1.7 g (4.9 mmol) of **10** in 125 ml of dry benzene over a 5-min period. After heating under reflux for 24 hr, the cooled (0°) reaction mixture was decomposed with 50 ml of 2 *N* hydrochloric acid; the yellow precipitate which separated was taken up in methylene chloride and washed with 2 *N* hydrochloric acid. A white solid, insoluble in either phase, was filtered, yielding 0.7 g (39.3% theory) of **5**. The methylene chloride solution was dried and the solvent evaporated, yielding 0.9 g of the starting material.

Registry No.—**5**, 16666-72-1; **7**, 16666-73-2; **10**, 16666-74-3.

A Novel Synthesis of 2,3-Seco-A-nor-5α-cholestane-2,3-diol[1a]

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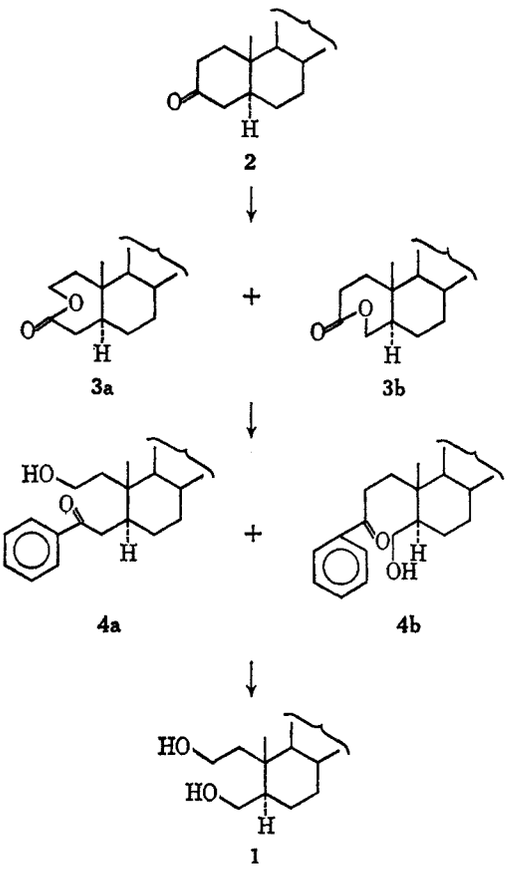
In connection with other work in these laboratories, it became necessary to prepare 2,3-seco-A-nor-5α-cholestane-2,3-diol [**1** (Scheme I)]. Seconordiols, useful intermediates in the synthesis of thia[2,3] and oxa[4]

SCHEME I



(1) (a) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67. (b) National Defense Education Act Fellow, 1967–1968.

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