Notes

A department for short papers of immediate interest.

The Interconversion of Nepetalic Acid and Isoiridomyrmecin (Iridolactone)

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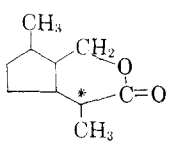
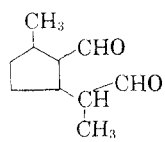
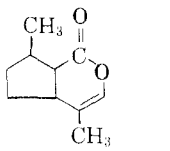
Three compounds that have been isolated from certain *Iridomyrmex* species of ants recently have been shown to bear a remarkable structural and configurational relationship to the nepetalic acids which result from the hydrolysis of nepetalactone (III), the principal constituent of the volatile oil of catnip.[1] Iridomyrmecin was isolated from a species of Argentine ants, *Iridomyrmex humilis* by Pavan[2] and shown by Fusco and collaborators[3] to have the structure I by its oxidation to one (V) of the four nepetalinic acids that have been obtained *via* the corresponding nepetalic acids IV, from nepetalactone (III).[4] The lactone I was epimerized at the asymmetric center* to isoiridomyrmecin (Ia)



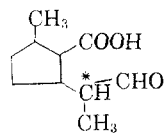
I, m.p. 60–61°
Ia, m.p. 58–59°



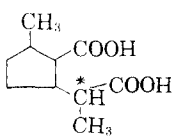
II



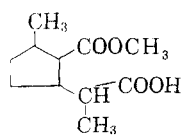
III



IV



V, m.p. 117°
Va, m.p. 85°



VI

by treatment with potassium methoxide. This epimer was converted[5] by oxidation to the nepetalinic acid Va, which had been shown[4] to be an epimer of V at the asymmetric center*.

Iridodial, a dialdehyde isolated from *I. detectus* and *I. conifer*, has been converted by Cavill and coworkers[6] to iridolactone, which previously had been obtained from *I. nitidus*. This lactone was shown to have the structure Ia by oxidation to Va and by comparison with an authentic sample of isoiridomyrmecin (Ia). On the basis of these relationships iridodial was assigned[6] structure II.

One pure nepetalic acid (IV), m.p. 72°, has been obtained from the mixture of two epimeric acids resulting from the hydrolysis of nepetalactone (III). The oxidation of this acid yielded Va and the oxidation of its methyl ester gave the monomethyl ester (VI) of Va.[4] It has now been found that the reduction of VI with a limited amount of lithium aluminum hydride converts VI to a lactone which is identical with isoiridomyrmecin (Ia). Thus the interconversions of compounds isolated from the *Iridomyrmex* species of ants and those obtained from the catnip plant, *Nepeta cataria*, are completed.

EXPERIMENTAL

Isoiridomyrmecin (Ia). To a cooled (−30°) solution of 1.78 g. (0.0084 mole) of methyl nepetalinate (VI),[4] neut. equiv. 212 (calc'd 214), in 30 ml. of tetrahydrofuran, freshly distilled from lithium aluminum hydride, was added over a period of 30 minutes a solution containing 0.0063 mole of lithium aluminum hydride in 17.5 ml. tetrahydrofuran.[7] After stirring for an hour, a few drops of ethyl acetate were added to decompose any excess of the hydride. The solvent was distilled under reduced pressure until foaming was encountered near the end of the distillation; then portions of benzene were added and the distillation continued under reduced pressure to entrain the tetrahydrofuran. When the dry residue was treated with 25 ml. of 20% hydrochloric acid, a distinct odor of lactone was detected. The acidified reaction mixture was thoroughly extracted with ether and with chloroform, and the combined extracts were dried over magnesium sulfate, filtered, and the solvent was distilled at atmospheric pressure. The resulting crude oil, which weighed 1.28 g. (71% yield) crystallized on standing overnight. The crude product was purified by pressing between sheets of filter paper to remove adherent oil and then was sublimed twice at 55° (0.1 mm.) to give isoirido-

(1) S. M. McElvain, R. D. Bright, and P. R. Johnson, *J. Am. Chem. Soc.*, **63**, 1558 (1941).
(2) M. Pavan, *Chimica e industria* (*Milan*), **37**, 714 (1955).
(3) R. Fusco, R. Trave, and A. Vercellone, *Chimica e industria* (*Milan*), **37**, 251, 958 (1955).
(4) S. M. McElvain and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **77**, 1599 (1955).
(5) Private communication from Professor Fusco.
(6) G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Chemistry & Industry*, 465 (1956).
(7) (a) H. Felkin, *Bull. soc. chim. France*, 347 (1951); (b) *Cf.* also E. L. Eliel, A. W. Burgstahler, D. E. Rivard, and L. Haefele, *J. Am. Chem. Soc.*, **77**, 5092 (1955) for selective reduction of monomethyl phthalates to phthalides.

myrmecin (Ia), m.p. 58–59°, which contained 71.42% C and 9.67% H (calc'd 71.39 and 9.59). The infrared spectrum of Ia was found to be identical with that of authentic isoiridomyrmecin and there was no depression in melting point on admixture of Ia from the two sources.

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Synthesis of 11β-Acetoxytestosterone Acetate

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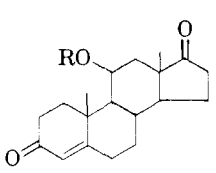
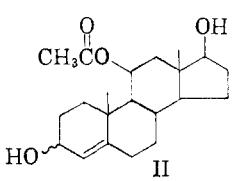
The disappearance of the androgenic and anabolic properties of testosterone upon 11β-hydroxylation[1] led us to examine the effect of esterification of this group. In the case of progesterone, for example, 17α-hydroxylation results in physiological deactivation, whereas the corresponding esters retain activity.[2]

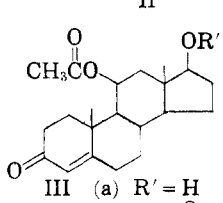
Attempts to prepare 11β-acetoxytestosterone acetate directly from the parent compound[3] were unsuccessful and an indirect route was chosen. Acetylation of 11β-hydroxy-Δ⁴-androstene-3,17-dione[4] (Ia) with special care to reverse the formation of enol acetates, gave the corresponding acetate (Ib). An attempt to perform a selective reduction at C-17 by the method of Norymberski and Woods[5]



I (a) R = H
(b) R = —OCCH₃



II



III (a) R′ = H
(b) R′ = OCCH₃

failed, as did an attempted reduction with yeast.[6] Reduction with sodium borohydride gave instead the triol acetate II, which crystallized as the hemihydrate. Subsequent oxidation of the allylic hydroxyl group with MnO_2[7] gave the desired 11β-acetoxytestosterone (IIIa), which was isolated as the diacetate (IIIb).

In the *levator ani* and seminal vesicle response of castrated rats, compounds Ib, II, and IIIb were essentially inactive.

EXPERIMENTAL[8]

11β-Acetoxy-Δ⁴-androstene-3,17-dione (Ib). 11β-Hydroxy-Δ⁴-androstene-3,17-dione (Ia) (2.00 g.) was suspended in a mixture of 20 ml. of glacial acetic acid and 9 ml. of acetic anhydride, and 200 mg. of *p*-toluenesulfonic acid was added. The resulting suspension was allowed to stand overnight. When almost all of the suspended material had dissolved, the small amount of solid remaining was removed by filtration and the solution was poured slowly onto a slurry of ice. Enough sodium carbonate solution was then added slowly with stirring to adjust to a *p*H of 8 (1.5 hr.) and the oily suspension was stirred for an hour longer. Extraction with ether, followed by washing of the extract with water, drying, and concentration under vacuum, gave a crude solid which was chromatographed on alkaline alumina. The material was placed on the column in benzene and eluted over a broad region (benzene-ether to ether–methylene chloride), combined and crystallized from methylene chloride–ether. There was obtained 1.01 g. of Ib, m.p. 193–194°; $[\alpha]_D$ +179° (diox.); λ_{max}^{MeOH} at 239 mμ (ε = 16,000); IR peaks at 5.78, 6.00, and 6.20μ.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22%; H, 8.19%; Found: C, 73.26%; H, 8.10%.

11β-Acetoxy-Δ⁴-androstene-3ξ,17β-diol (II). The acetate Ib (1.00 g.) was dissolved in 2 l. of methanol and cooled to 0°. Sodium borohydride (171 mg.) was added, and the solution was allowed to stand 1 hr. at ice temperature. Excess reagent was destroyed with acetic acid and the solution was evaporated to dryness *in vacuo*. The residue was distributed between water and chloroform, and the organic phase was again evaporated to dryness. This latter residue was then chromatographed on neutral alumina (Woelm) by the gradient elution technique, using benzene and 50% benzene–ethyl acetate solutions as the nonpolar and polar eluants, respectively. From the less polar eluates, 403 mg. of II were isolated and crystallized from moist ether,[9] m.p. 107–112°; no selective absorption in the ultraviolet; $[\alpha]_D^{25}$ +70.5°; IR bands at 2.91, 3.01, 3.20, 5.78, 6.02, and 8.00μ.

Anal. Calcd. for $C_{21}H_{32}O_4 \cdot {}^1/_2H_2O$: C, 70.55%; H, 9.34%; Found: C, 70.27%; H, 9.18%.

From the more polar eluates, a second material was isolated and crystallized from ether to give 30 mg., having m.p. 168–172°. It was not further investigated.

11β-Acetoxylestosterone acetate (IIIb). The triol monoacetate II (600 mg.) was ground to a fine powder, largely

(1) S. C. Lyster, G. H. Lund, and R. O. Stafford, *Endocrinol.*, **58**, 781 (1956).
(2) K. Junkmann, *Arch. exptl. Pathol. Pharmakol.*, **223**, 244 (1954).
(3) M. E. Herr, J. A. Hogg, and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956).
(4) T. Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937).
(5) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 1955, 3426.
(6) See, for instance, H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 266 (1953).
(7) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).
(8) All melting points were taken on a Kofler Block. Rotations were carried out in a 1-dm. tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.
(9) A few droplets of water actually had to be added to the ether to induce crystallization.