A Steroidal Analog of a Tetrahydrocannabinol

R. K. RAZDAN, H. G. PARS, F. E. GRANCHELLI,

Organic and Medicinal Chemistry Laboratories, Arthur D. Little, Inc., Cambridge, Massachusetts 02140

AND L. S. HARRIS

Department of Pharmacology, University of North Carolina, Chapel Hill, North Carolina 27515

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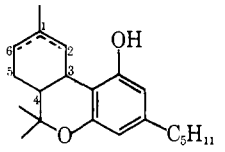
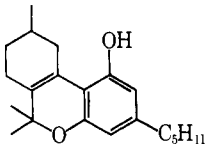
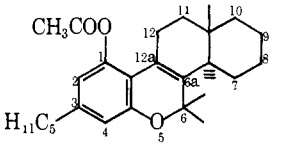
The recent interest in the active constituents of hashish, Δ^1- and Δ^6-3,4-*trans*-tetrahydrocannabinols (I),[1] prompts us to record our findings on related compounds.[2] Another tetrahydrocannabinol, II, with the double bond in the 3,4 position and in conjugation with the aromatic ring was synthesized by both Adams and Baker[3] and Todd, *et al.*,[4] and was shown to possess a



I



II

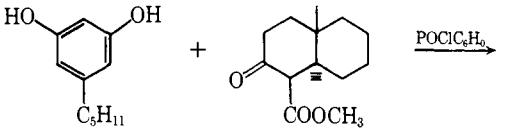


III

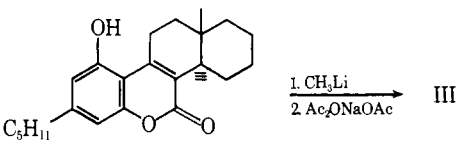
pharmacological profile similar to I, particularly in its effects on the central nervous system (CNS).

We now wish to report the synthesis and biological activity of a steroidal analog (III) of tetrahydrocannabinol II. This has been achieved by utilizing a different route from that used by Smith *et al.*,[5] to synthesize 6-oxa steroids. Recently Stork and his coworkers[6] have shown that alkylation and carbonation of ketones by trapping the enolates from the reduction of α,β-unsaturated ketones can give synthetically useful materials, *e.g.*, V. This suggested to us an entreé into oxa steroids of type III by utilizing the Pechmann condensation and thus allowing one to vary substituents in the aromatic ring, which is otherwise difficult. We had hoped that the steroidal analog III would retain the CNS activity possessed by tetrahydrocannabinols I and II.

Olivetol (IV) was condensed with 10-methyl-1-carbomethoxy-*trans*-2-decalone (V)[6] in the presence of



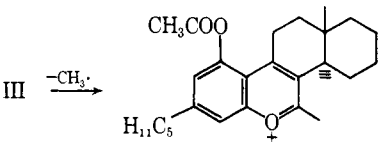
IV V



VI

$POCl_3$ to give the pyrone VI. After the intermediate VI had been treated with a large excess of methyllithium, the dark greenish blue residue obtained was acetylated to give a reddish brown gum. This gum was chromatographed on silicic acid and finally purified by preparative tlc to give III. The absence of vinyl proton in the nmr spectrum rules out the Δ^{12} isomer. The presence of a *gem*-dimethyl group as a singlet and the aromatic protons as two multiplets is in agreement with the assigned structure III. The structure was also confirmed by a mass spectrum which showed (*inter alia*) peaks at *m/e* 410, 395 ($M^+ - CH_3$), 368 ($M^+ - 42$), 367 ($M^+ - C_2H_3O$), 353 ($M^+ - C_4H_9$).

Similar to the fragmentation pattern of II,[7] the major peak is at *m/e* 395, which corresponds to the chromenyl ion VII, obtained by loss of one of the geminal methyl groups.



VII, *m/e* 395

The biological activity of III was determined by the technique of Irwin.[8] It was inactive at doses up to 10 mg/kg iv in polyethylene glycol 200 (PEG). At 20 mg/kg only minimal changes were observed which were not any different from solvent controls. Higher doses, 40 mg/kg, which necessitated a higher volume of PEG (0.1 ml/kg), produced lethalities in both drug and solvent control animals. Compound II in this test procedure is an active depressant at doses less than 1.0 mg/kg. In this connection it is interesting to note that Adams, *et al.*, reported that the natural tetrahydrocannabinol acetate is just as active as the free alcohol in the dog ataxia test.[9] From this we conclude that III has little or no effect on the CNS.

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(8) S. Irwin in "Pharmacologic Techniques in Drug Evaluation," J. H. Nadine and P. E. Siegler, Ed., Year Book Medical Publishers, Chicago, Ill., 1964.

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Experimental Section[10]

1-Hydroxy-10a-methyl-3-pentyl-6b,7,8,9,10,10a,11,12-octahydro-6H-benzo[*b*]naphtho[1,2-*d*]-6-pyrone (VI).—$POCl_3$ (3 ml) was added to a mixture of 4.5 g (0.025 mole) of olivetol (IV) and 5.6 g (0.025 mole) of 10-methyl-1-carbomethoxy-*trans*-2-decalone[6] (V) in C_6H_6, and the mixture was heated under reflux. After 5 hr the volatile material was removed *in vacuo* and the residue was crystallized from MeOH to give 4.5 g (51%) of colorless crystals of VI, mp 220–222°. Absorption bands of spectrum (uv, ir, nmr) were as expected.

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.82; H, 8.48.

6b,7,8,9,10,10a,11,12-Octahydro-3-pentyl-6,6,10a-trimethyl-6H-benzo[*b*]naphtho[1,2-*d*]pyran-1-ol Acetate (III).—A mixture of 2.36 g (0.0066 mole) of pyrone VI and 60 ml of MeLi (2.4 *M* in hexane) was refluxed for 48 hr. After decomposition of the mixture with dilute H_2SO_4, the organic layer was separated. It was washed, dried, and evaporated to leave a residue which was heated under reflux for 1 hr in dry heptane to which a few drops of 48% HBr had been added. After cooling, the heptane solution was washed ($NaHCO_3$, H_2O) and then dried and evaporated. The dark greenish blue residue thus obtained was heated under reflux in excess Ac_2O containing 1 g of NaOAc. After 1.5 hr the volatile material was removed *in vacuo*, water was added, and the mixture was extracted (C_6H_6). The organic layer was washed, dried, and evaporated to leave a reddish brown gum. This gum was chromatographed on silicic acid (100 mesh) with C_6H_6 and finally purified by preparative tlc (C_6H_6) to give 90 mg of III as a brownish gum: *m/e* 410, 395 ($M^+ - CH_3$), 368 ($M^+ - 42$), 367 ($M^+ - C_2H_3O$), 353 ($M^+ - C_4H_9$). Absorption bands of spectra (uv, ir, nmr) were as expected.

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.69; H, 9.41.

Acknowledgment.—We wish to thank Dr. P. L. Levins for his assistance in the interpretation of spectra and Arthur D. Little, Inc., for supporting this work.

(10) All melting points are uncorrected; mass spectrum was determined with a CEC 21-110B instrument (direct introduction probe at 110°).

Spirans. XIV. Azatrispirans[1]

LEONARD M. RICE AND KENNETH R. SCOTT

College of Pharmacy, Howard University, Washington, D. C. 20001

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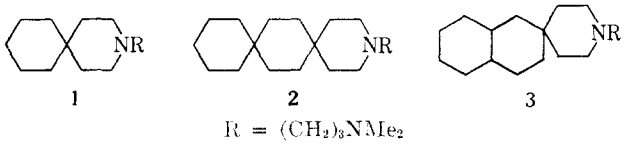
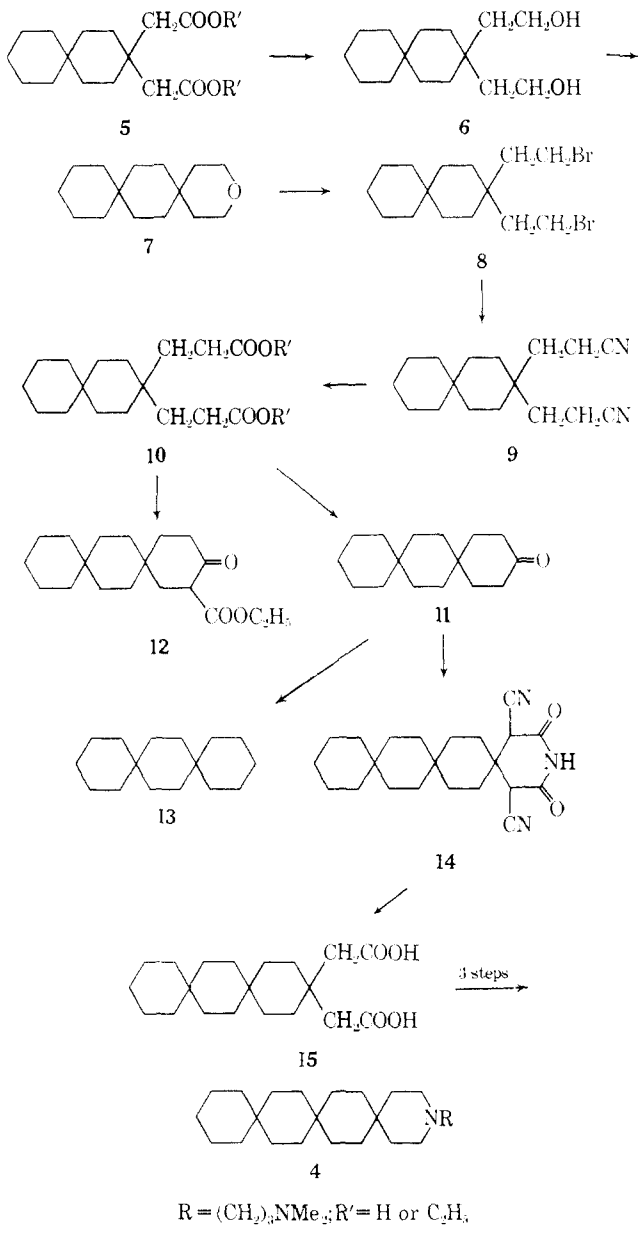
In previous papers[2,3] we described the synthesis of azaspiro (**1**) and azadispiro compounds (**2**). These compounds were of interest to us as a part of a broad program concerning the structure–activity relationships of spiro compounds on tissue culture cells. It was also of interest to study the effect, on the testes, of some of these compounds which may be related to structure **3** that had shown a profound effect on the testes of experimental animals.[4] This paper is concerned with the extension of the synthesis of the dispiro compounds (**2**) to the corresponding trispiro compounds (**4**).



1 2 3

R = $(CH_2)_3NMe_2$

CHART I



R = $(CH_2)_3NMe_2$; R' = H or C_2H_5

In the preparation of dispiro[5.2.5.2]hexadecan-3-one (**11**), considerable difficulty was experienced. For example, spiro[5.5]undecane-3,3-dipropionic ester (**10**, R = C_2H_5) was cyclized by means of potassium *t*-

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