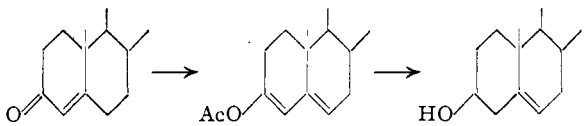
COMMUNICATIONS TO THE EDITOR

ON THE CONVERSION OF CHOLESTENONE TO CHOLESTEROL

Sir:

Turner[1] has recently reported the preparation of C^{14}-labeled cholestenone and discussed its possible use in the study of cancer. The desirability of a similarly labeled cholesterol for other biological studies has prompted us to investigate the transformation of cholestenone to cholesterol. Reich and Lardon[2] previously have devised a seven step process for such a conversion but the over-all yield was only 12%. It has now been found that cholesterol (III) can be obtained more directly and in better yield by the reduction of the enol acetate (II) of cholestenone with lithium aluminum hydride.



I II III

Cholestenone was converted to its enol acetate in 90% yield by the method of Westphal.[3] The product from the lithium aluminum hydride reduction of II at −15° was fractionated with digitonin. Each crude fraction was heated with dilute alcoholic hydrochloric acid in order to dehydrate the Δ^4-isomers present.[4] Marker and co-workers have reported[5] that *epi*-cholesterol also undergoes dehydration upon treatment with alcoholic hydrochloric acid. We found, however, that the mild conditions employed in this research did not affect *epi*-cholesterol to any appreciable extent (<5%).

The material obtained after dehydration of the reduction product was separated by chromatography using alumina. Cholesterol (m. p. 146–148°), $M^{24}D$ −154° ($CHCl_3$), was isolated from the β-fraction and *epi*-cholesterol (m. p. 137–138°), $M^{25}D$ −149° ($CHCl_3$), from the α-fraction. The yields based on the enol acetate of cholestenone were 34 and 15%, respectively. No depression of melting point upon admixture with authentic samples was noticed with either of the sterols. Further work is in progress with regard to other aspects of this transformation.

CHEMICAL LABORATORY
UNIVERSITY OF CALIFORNIA WILLIAM G. DAUBEN
BERKELEY 4, CALIF. JEROME F. EASTHAM

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(1) Turner, THIS JOURNAL, **72**, 579 (1950).
(2) Reich and Lardon, *Helv. Chim. Acta*, **29**, 671 (1946).
(3) Westphal, *Ber.*, **70**, 2128 (1937).
(4) Schoenheimer and Evans, *J. Biol. Chem.*, **114**, 567 (1936); McKennis and Gaffney, *ibid.*, **175**, 217 (1948).
(5) Marker, Kamm, Oakwood and Laucius, THIS JOURNAL, **58**, 1948 (1936).

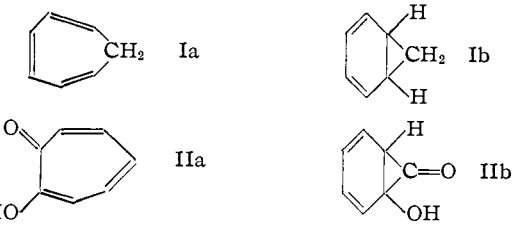
SYNTHESIS OF TROPOLONE

Sir:

Following Dewar's original and stimulating conception of tropolone (cycloheptatriene-2,4,6-ol-2-one-1) as a unit possessing resonance stabilization and unique chemical characteristics and constituting a part of colchicine and stipitatic acid,[1] much evidence of a degradative nature has been accumulated supporting the presence of a tropolone system in these molecules, in purpurogallin and the thujaplicins as well,[2] while syntheses have been limited to 3,4-benztropolone[3] and 4,5-benztropolone.[4] We wish to report the synthesis in two steps of tropolone itself.

A benzene solution of diazomethane is irradiated[5] to give nitrogen and I, C_7H_8, b. p. 114.5° after fractionation in an 80-plate column. While I has the same infrared spectrum as Kohler's "cycloheptatriene,"[6] its chemistry which we are presently investigating is formulated equally well as cycloheptatriene (Ia) or norcaradiene (Ib).

$$C_6H_6 + CH_2N_2 \xrightarrow[365\ \mu]{h\nu} C_7H_8\ (I) \xrightarrow{KMnO_4} C_7H_6O_2 \quad (II)$$



The oxidation of I with 4% aqueous potassium permanganate produces a small amount of material extractable at *p*H 4 with chloroform. Shaking the concentrated extract with aqueous cupric acetate and evaporating to dryness affords a green, crystalline, chloroform-soluble copper complex (1% yield), m. p. 320° with dec., from which hydrogen sulfide liberates II. II is recrystallized from hexane as colorless needles, m. p. 48°. (*Anal.* Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.95; neut. equiv., 122.1. Found: C, 68.86; H, 4.96; neut. equiv., 122.8). II sublimes easily, is soluble in water and most organic solvents, is colored deep green by ferric chloride, and is an acid of *pK* 6.7 forming a yellow anion. The ultraviolet absorption spectrum has maxima in

(1) Dewar, *Nature*, **155**, 50, 141, 479 (1945).
(2) Reviewed by Loudon, *Ann. Rep. on Progress Chem. (Chem. Soc. London)*, **45**, 187 (1948).
(3) Cook and Somerville, *Nature*, **163**, 410 (1949).
(4) Tarbell, Scott and Kemp, THIS JOURNAL, **72**, 379 (1950).
(5) Meerwein, Rathjen and Werner, *Ber.*, **75**, 1610 (1942), who discovered the photochemical reaction of diazomethane with ether and isopropyl alcohol, imply that benzene gives toluene.
(6) Kohler, Tishler, Potter and Thompson, THIS JOURNAL, **61**, 1057 (1939).

mμ (log ε) at 235 (4.26), 327 (3.78), 368 (3.59) and 392 (3.11) and minima at 273 (3.25), 363 (3.57) and 387 (3.30). II absorbs four molar equivalents of hydrogen in ethanol with platinum oxide giving an oil oxidized with permanganate to pimelic acid, m. p. 99–102° (m. p. 100–102° in admixture with authentic material, m. p. 101–102°). These facts are consistent with the assignment of tropolone (IIa) as the structural hypothesis for II but do not completely exclude IIb.

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HICKRILL CHEMICAL RESEARCH FOUNDATION
KATONAH, NEW YORK
W. VON E. DOERING
LAWRENCE H. KNOX

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THE ACTION OF METHANOLIC POTASSIUM HYDROXIDE ON A Δ^{16}-20-KETOSTEROID: ISOLATION OF 3β-ACETOXY-16-METHOXY-Δ^5-PREGNEN-20-ONE

Sir:

The reaction recently described by Marker[1] for the introduction of a 17-hydroxyl group could have great significance in the synthesis of adrenal cortical hormones. Since no evidence was offered for the presence of a 17-hydroxyl group other than failure to acetylate the newly introduced oxygen function, and since the reaction postulated was improbable, we have investigated the problem and have arrived at a completely different conclusion.

3β-Acetoxy-$\Delta^{5,16}$-pregnadien-20-one was refluxed with a solution of potassium hydroxide in methanol. As evidenced by the ultraviolet absorption spectrum, $E^{1\%}_{1\,cm.}$ = 121 at 2390 Å., approximately half the product no longer contained the α,β-unsaturated carbonyl group of the initial compound. Acetylation followed by chromatography resulted in the separation of 3β-acetoxy-$\Delta^{5,16}$-pregnadien-20-one and a compound, m. p. 158.5–159.5°; $[\alpha]^{25}D$ −28.5° (chloroform), which showed no absorption in the ultraviolet above 2250 Å. The possibility that the compound was a 3β-acetoxy-17-hydroxy-Δ^5-pregnen-20-one was readily eliminated by comparison of the physical constants with the known epimers (17α-[2] m. p. 234–235°; $[\alpha]D$ −41.8° [dioxane]; 17β-[3] m. p. 187–188°; $[\alpha]D$ −61.3° (chloroform)). A D-homosteroid was similarly discarded as a possible interpretation. The most important evidence against these structures was provided by infrared spectrometry[4] which revealed that no free hydroxyl group was present in the product.

The elementary analysis conformed to the molecular formula $C_{24}H_{36}O_4$. *Anal.* Calcd.: C, 74.29; H, 9.34. Found: C, 74.53; H, 9.18. The additional carbon atom was shown to be in a methoxyl group by Zeisel determination (calcd. 7.99; found 8.59). When an ethanol solution of potassium hydroxide was used for the reaction a different product, the corresponding ethoxy compound, was obtained, m. p. 143–144.5°, $[\alpha]D$ −30.6° (chloroform). These results clearly prove that the reaction led to the formation of an ether rather than an alcohol. An examination of Marker's analytical data shows that there is equally good agreement for a methoxy derivative.

The addition of alcohol to an α,β-unsaturated 20-ketosteroid is entirely analogous to the base-catalyzed addition of alcohols to methyl acrylate or acrylonitrile to yield β-alkoxy propionic acid derivatives.[5] The product formed from 3β-acetoxy-$\Delta^{5,16}$-pregnadien-20-one upon treatment with methanolic potassium hydroxide is therefore 3β-hydroxy-16-methoxy-Δ^5-pregnen-20-one. The reaction is reversible, and an equilibrium mixture containing 69% of the 16-methoxy compound spectrophotometrically is reached from either compound at 23° in 3% methanolic potassium hydroxide in about two hours.

(1) Marker, THIS JOURNAL, **71**, 4149 (1949).
(2) Hegner and Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).
(3) Shoppee and Prins, *ibid.*, **26**, 201 (1943).
(4) We wish to express our appreciation to Dr. Konrad Dobriner of this Institute, who determined and interpreted the infrared spectra for us.
(5) Koelsch, THIS JOURNAL, **65**, 437 (1943).

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
NEW YORK, N. Y.
DAVID K. FUKUSHIMA
T. F. GALLAGHER

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A NEW ROUTE TO 11-KETOSTEROIDS

Sir:

Whereas 3-hydroxyl groups usually resist attack by N-bromosuccinimide in aqueous acetone,[1] methyl 3α-hydroxy-9α,11α-oxidocholanate (I, from the 9,11-ethylene,[2,3] m. p. 135.4–136.4°, $[\alpha]^{25}D$ +22° Chf.[4] *Anal.* $C_{25}H_{40}O_4$: C, 74.21, H, 9.97. Found: C, 74.51; H, 10.09) is oxidized to the 3-ketone (II, m. p. 129–130°, $[\alpha]^{25}D$ +4° Di.[4] *Anal.* $C_{25}H_{38}O_4$: C, 74.52; H, 9.52. Found: C, 74.34; H, 9.38. Semicarbazone, m. p. 209–210°; Wolff–Kishner reduction to 9α,11α-oxidocholanic acid, m. p. 158–159°, $[\alpha]^{22}D$ +17° Di.[5] *Anal.* $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.93; H, 10.42). Chromic acid oxidation of I or II gives the hemiketal III, m. p. 119–120° (variable), $[\alpha]^{23}D$ +102° Chf., λ^{Chf}_{Max} 2.85, 5.78, 5.85μ. *Anal.* $C_{25}H_{38}O_5$: C, 71.66; H, 9.16. Found: C, 71.89; H, 9.20. Acetate (BF_3–Ac_2O), m. p. 148.6–149.8°, $[\alpha]^{24}D$ +100.3° Chf. *Anal.* $C_{27}H_{40}O_6$: C, 70.38; H, 8.77. Found: C, 70.27; H, 8.76. Methyl ether (CH_3OH–HBr), m. p. 124.8–125.5°, $[\alpha]^{18}D$ +92.3°

(1) Fieser and Rajagopalan, THIS JOURNAL, **71**, 3935, 3938 (1949).
(2) Seebeck and Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).
(3) Mattox, Turner, Engel, McKenzie, McGuckin and Kendall, *J. Biol. Chem.*, **164**, 569 (1946).
(4) Chf. = chloroform; Di. = dioxane; An. = acetone.
(5) Alther and Reichstein, *Helv. Chim. Acta*, **26**, 492 (1943), give $[\alpha]D$ +18.8° An. for the methyl ester.