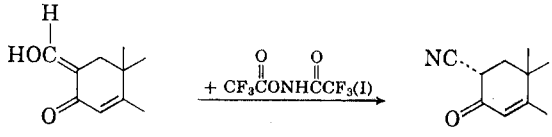
Communications TO THE EDITOR

Synthesis of Certain Steroidal α-Cyano Ketones

Sir:

We wish to report the synthesis of certain steroid hormones substituted at C-2 or C-16 with the cyano group. These compounds were prepared from the corresponding 2- or 16-hydroxymethylene steroid derivatives by application of the method of Pomeroy and Craig,[1] whereby an aldehyde is converted to a nitrile through reaction with *O,N*-bis-(trifluoroacetyl)hydroxylamine (I). Thus, treatment of 2-hydroxymethylenetestosterone[2] with two equivalents[3] of I for two hours in refluxing benzene containing pyridine afforded 70% 2α-cyanotestosterone trifluoroacetate [m.p. 212–217°; $(\alpha)_D$ + 83.3°; λ_{max} 242 mμ (ε 16,400)].[4] Hydrolysis gave *2α-cyanotestosterone (64%) [m.p. 155–156°; $(\alpha)_D$* +119°; λ_{max} 242 mμ (ε 15,600)].



In a similar manner, *2 α-cyanoprogesterone* [m.p. 193–195°; $(\alpha)_D$ + 212°; λ_{max} 242 mμ (ε 16,300)], *2α-cyanodeoxycorticosterone* [m.p. 183–184°; $(\alpha)_D$ + 208°; λ_{max} 242 mμ (ε 15,280)], *2α-cyanohydrocortisone* [m.p. 235–237°, $(\alpha)_D$ + 172° (*c* 0.26 in methanol); λ_{max} 243 mμ (ε 14,330)], *2α-cyanocortisone*[5] [m.p. 246–247°; $(\alpha)_D$ +194° (dioxane); λ_{max} 235 mμ (ε 18,500)], and *2α-cyano-9α-fluoro-11β,21-dihydroxy-16α, 17α-isopropylidenedioxy-4-pregnene-3,20-dione* [m.p. 293–296°; $(\alpha)_D$ +132° (acetone); λ_{max} 238 mμ (ε 17,300)] were prepared by the reaction of I with 2-hydroxymethylene-progesterone 20-ethylene ketal [m.p. 160–164°; $(\alpha)_D$ +42 4°], 2-hydroxymethylenedeoxycorticosterone 20-ethylene ketal [m.p. 191–192°; $[\alpha]_D$ +41.2°], 2-hydroxymethylenehydrocortisone 20-ethylene ketal [m.p. 233–236°; $(\alpha)_D$ +47.1°],[6] 2-hydroxymethylene - 17α,20;20,21 - bismethylenedioxy-4-pregnene-3,11-dione[5] [m.p. 206–209° $(\alpha)_D$ +9.2°] and 9α-fluoro-11β-hydroxy-2-hydroxymethylene-16 α,17 α-isopropylidenedioxy-21-(tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione [m.p. 125–128°; $(\alpha)_D$ +68.5°], respectively, followed by acid-catalyzed hydrolysis of the side-chain blocking groups. The requisite 2-hydroxymethylene derivatives were prepared in the usual manner[2] by formylation with sodium hydride and ethyl formate of progesterone 20-ethylene ketal,[7] deoxycorticosterone 20-ethylene ketal [m.p. 163–165°, prepared from the corresponding 21-acetate[8]], hydrocortisone 20-ethylene ketal,[9] 17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione[10] and 9α-fluoro-11β-hydroxy- 16α,17α - isopropylidenedioxy - 21 - (tetrahydropyran-2-yloxy)-4-pregnene-3,20-dione[11] respectively.

The introduction of the 2-cyano group (λ_{max} 4.43–4.45 μ) results in a hypsochromic shift of the 3-carbonyl band (to 5.90–5.95 μ) in the infrared and does not affect the location of the maximum of the Δ^4-3-keto chromophore in the ultraviolet. The differences in molecular rotation between the 2-cyano compounds and the respective parent compounds are in the range of +15 to +81. These values are in general agreement with the effect on molecular rotation caused by substitution of halogen,[12] hydroxy,[13] acetoxy,[13] and methyl[14] groups at the 2 α-position.[15] In view of the foregoing, it is concluded that the various 2-cyano steroids are most probably in the α (equatorial) configuration.

(1) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959).

(2) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954).

(3) In general it was found that, under these conditions, I will effect trifluoroacetylation of accessible hydroxy groups such as the 17β-hydroxy group in testosterone or the 21-hydroxy group in hydrocortisone 20-ethylene ketal, but will not attack the 11β- or the 17α-hydroxy groups of the latter compound.

(4) M.p., corrected; $[\alpha]_D$ in chloroform unless stated otherwise, *c* approx. 0.5 to 1.5; infrared spectra in potassium bromide disks and ultraviolet spectra in methanol. Combustion analysis values for all new compounds were satisfactory.

(5) Prepared from 2α-cyanocortisone BMD. Recently J. A. Zderic et al. [Chem. & Ind., 1625 (1960)] reported the preparation of 2α-cyanocortisone BMD from 2-hydroxymethylenecortisone BMD *via* alkaline treatment of the BMD derivative of 4-pregnene-[2,3-d]isoxazole-17α,21-diol-11,20-dione [(BMD = 17α, 20; 20, 21 (bismethylenedioxy)].

(6) Australian Patent Specifications No. 23,672, May 12, 1956, assigned to Merck and Co., Inc.

(7) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

(8) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959).

(9) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960).

(10) R. E. Beyler, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960).

(11) L. J. Leeson and J. Weidenheimer, *J. Pharm. Sci.*, **50**, 86 (1961).

(12) B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956).

(13) G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 145 (1955).

(14) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

(15) The cyano group at C-6 has an effect on molecular rotation similar to that caused by the above groups [see A. Bowers, E. Denot, M. B. Sánchez, L. M. Sánchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5233 (1959)].

By the same general method, 16-hydroxymethylene-3-ethylenedioxy-5-androsten-17-one [m.p. 203–206°; $(\alpha)_D$ +26.8°], prepared from 3-ethylenedioxy-5-androsten-17-one,[16] gave the corresponding 16 ξ-cyano derivative [m.p. 240–242°; $(\alpha)_D$ +4.3° (±21°, *c* 0.23)] which was converted to 16ξ-cyanotestosterone [m.p. 218–219°; $(\alpha)_D$ +88.5°; λ_{max} 240 mμ (ε 16,170)] by lithium borohydride reduction and acid-catalyzed removal of the ring-A blocking group. 16-Hydroxymethyleneestrone 3-methyl ether[17] and I yielded 16ξ-cyanosterone 3-methyl ether [m.p. 138–148°; $(\alpha)_D$ +189°] which on subsequent reduction with lithium borohydride afforded 16ξ-cyanoestradiol 3-methyl ether [m.p. 197–200°; $(\alpha)_D$ +54°].

The results of the as yet incomplete biological evaluation of these compounds will be reported in a forthcoming paper. No outstanding endocrinological activities have been discovered thus far.

ORGANIC CHEMICAL RESEARCH SECTION
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID CO.
PEARL RIVER, N. Y.

HENRY M. KISSMAN
ARLENE SMALL HOFFMAN
MARTIN J. WEISS

Received March 13, 1961

(16) H. J. Dauben, Jr., B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

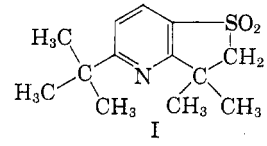
(17) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

Reactivity of 2,6-Di-*t*-butylpyridine Toward Sulfur Trioxide at Elevated Temperature

Sir:

It has been known for several years that 2,6-di-*t*-butylpyridine can be sulfonated with sulfur trioxide at low temperature.[1] In an extensive investigation of the reactivity of 2,6-dialkylpyridines one of us (v. d. Pl.), together with den Hertog, has shown that during this reaction the sulfonic acid group entered the 3-position,[2–4] as in the sulfonation of pyridine below 300°. Since sulfonation of pyridine above 300° leads to the formation of pyridine-4-sulfonic acid and 4-hydroxypyridine, together with the 3-sulfonic acid,[5] we also studied the behaviour of 2,6-di-*t*-butylpyridine toward sulfur trioxide at elevated temperatures.

When 2,6-di-*t*-butylpyridine was heated with sulfur trioxide at 240–250° for fifteen hours in a sealed tube, neither 2,6-di-*t*-butylpyridine-4-sulfonic acid nor 2,6-di-*t*-butylpyridone-4 was formed. Instead, together with unchanged 2,6-di-*t*-butylpyridine (30–35%) and the 3-sulfonic acid (30–35%), a compound was isolated (15–20%) melting at 140–141°. It was insoluble in water but easily soluble in ether and ethanol. From elemental analysis and molecular weight determination its composition was established as $C_{13}H_{19}NO_2S$. *Anal.* Calcd. for $C_{13}H_{19}NO_2S$: C, 61.62; H, 7.56; N, 5.53; S, 12.66; mol. wt. 253. Found: C, 61.9; H, 7.4; N, 5.5; S, 12.1; mol. wt. (according to Rast) 245. Taking into account its composition, mode of formation and the fact that the compound could not be hydrolyzed in an alkaline medium, it was considered to be best represented by structure I,[4] 2,3-dihydro-3,3-dimethyl-5-*t*-butylthieno[3,2-*b*]pyridine 1-dioxide.



I

We now wish to report that this conclusion was correct. The infrared spectrum of I in chloroform shows two strong bands at 1134 cm.$^{-1}$ and 1316 cm.$^{-1}$, both indicating the presence of a sulfone group in the molecule.[6] That no rearrangement of the *t*-butyl group occurred during heating of the 2,6-di-*t*-butylpyridine with sulfur trioxide was established by considering the NMR spectrum of I (internal reference tetramethylsilane, solvent tetrachloromethane, 60 mc., magnetic field approximately 14,100 gauss). In this spectrum two peaks were observed with τ-values,[7] 2.38 and 2.88, both peaks being characterized by doublet structures with coupling constants J = 8 c.p.s. The τ-values agree with those given for the β- and γ-protons of the pyridine nucleus.[8] The coupling constants, J = 8 c.p.s. also affirm the presence of both β- and γ-protons in the pyridine nucleus, being in good agreement with $J_{\beta\gamma}$ = 7.35 c.p.s. given for 2,3-substituted pyridines.[9] These data exclude the possibility of an α-proton being present in the pyridine nucleus. Further, the NMR spectrum shows peaks at τ-values 6.74, 8.45, and 8.63, attributed, respectively, to the proton resonance peaks of the methylene-, the two methyl groups, and the *t*-butyl group. The intensity ratio of these three peaks, 2:6.1:9, supports these assignments. The paramagnetic shift of the protons of the methylene group is due to the deshielding by the adjacent electron-withdrawing sulfone group.

(1) H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, **75**, 3865 (1953).

(2) H. C. van der Plas and H. J. den Hertog, *Chem. Weekblad.* **53**, 560 (1957).

(3) H. C. van der Plas and H. J. den Hertog, *Tetrahedron Letters*, No. 1, 13 (1960).

(4) H. C. van der Plas, Thesis, Amsterdam, 1960.

(5) H. J. den Hertog, H. C. van der Plas, and D. J. Buurman, *Rec. Trav. Chim.*, **77**, 963 (1958).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1958, page 360.

(7) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(8) L. H. Jackman. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York 1959, page 64.

(9) H. J. Bernstein, J. A. Pople, and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).