glass when cooled to −70°. The infrared spectrum (Fig. 1) revealed the absence of characteristic olefinic unsaturation noted with compound (V) (Fig. 2).

Anal. Calc'd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.65; H, 11.08.

Its *acetamino* derivative melted at 146.5–147.5° after crystallization from aqueous methanol.

Anal. Calc'd for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.59.

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Derivatives at C_{20} of 17(α)-Hydroxy 20-Ketosteroid 21-Acylates

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Received February 2, 1956

In 1954, H. Reich and B. K. Samuels[1] reported the isolation, in high yield, of the *20*-2,4-dinitrophenylhydrazone and the 20-semicarbazone of 21-acetoxypregnenolone. These results were of interest in view of reports[2–6] on the inertness of the 20-keto 21-acylate grouping towards carbonyl derivatization. Reich did not, however, describe the direct formation of derivatives, such as the semicarbazone, at position 20 in the presence of both 17(α)-hydroxyl and 21-acylates. This might be presumed a still more hindered case with respect to difficulty of formation of such derivatives.

We report here the formation of 20-semicarbazones and oximes of steroids in the presence of both 17(α)-hydroxyl and 21-acylate functions without loss of the 21 acyl group. The yields are generally good and real doubt is cast on the importance of "steric hindrance" in view of two factors. First, the 20-semicarbazones are obtained by careful buffering of the reaction mixture into the pH range described for the case of simpler unhindered ketones.[7] Second, in the case of cortisone, 3,20-disemicarbazones of several "hindered" esters were formed without undue difficulty. Models of such esters, in accord with the above observations, do not show extensive hindrance about the 20-carbonyl position.

(1) H. Reich and B. K. Samuels, *J. Org. Chem.*, **19**, 1041 (1954).

(2) O. Mancera, *J. Am. Chem. Soc.*, **72**, 5752 (1950).

(3) N. L. Wendler, Huang-Minlon, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3818 (1951).

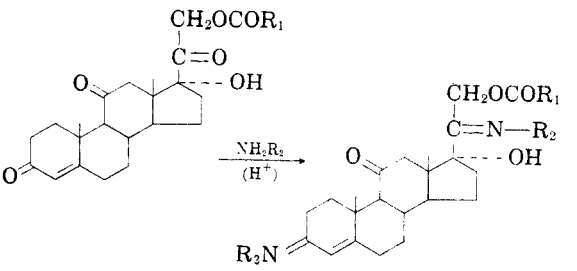
(4) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 556 (1951).

(5) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(6) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953).

(7) J. Conant and P. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932).

EXPERIMENTAL[8]



All derivatives were made by the following general methods:

Cortisone acetate 3,20-disemicarbazone (I). Cortisone acetate (10.0 g., 0.025 mole) was suspended in 268 cc. of methanol, and 8.6 cc. of water; the suspension was blanketed with nitrogen. To the mixture were added 13.6 g. (0.122 mole) of semicarbazide hydrochloride and 7.4 g. (0.084 mole) of sodium bicarbonate and the mixture was heated under reflux for 3½ hours. At the end of this time, the cortisone acetate had all dissolved; the temperature was reduced to 45° and heating at this temperature was continued for 21 hours. After one hour at 45°, crystallization of product took place. At the end of the 21-hour heating period, the suspension was cooled to room temperature and to it was added slowly 358 cc. of water. The resulting crystalline semicarbazone derivative (I) was cooled for 2 hours in an ice-bath, filtered, washed with water, and dried under a vacuum; wt., 12.9 g., m.p. >300°. Recrystallization was effected from pyridine-methanol.

Anal. Cf. Table I. Calc'd: Acetyl, 8.33. Found: Acetyl, 8.32.

Peaks were observed in the infrared spectrum at 5.81 μ and 7.97 μ which indicated acetoxyl. For the ultraviolet spectra, *Cf.* Table I.

Cortisone acetate 3,20-dioxime (II). A mixture of 5.0 g. (0.0124 mole) of cortisone acetate, 134 cc. of methanol, and 4.3 cc. of water was placed in a flask with stirring and the air was replaced by nitrogen. To the mixture was added 3.84 g. (0.0553 mole) of hydroxylamine hydrochloride and 5.48 g. (0.0653 mole) of sodium bicarbonate. After the reaction mixture had been heated as for the preparation of I (see above), it was concentrated *in vacuo* to 45 cc. and 50 cc. of water and 50 cc. of nearly saturated salt solution were added. The crystalline slurry was stirred for 3 hours at 0–5° and the solid was removed by filtration and washed with water. The dry wt. was 3.9 g.; m.p. soften, 150°, melted at 163–166°, dec. 188°.

After recrystallization from ethyl acetate and petroleum naphtha, the compound showed the same poorly defined melting point.

Anal. Cf. Table I.

For ultraviolet spectra, *Cf.* Table I; $[\alpha]_D^{20}$ +179.2° (*c*, 1, acetone).

3(α),17(α),21-Trihydroxypregnane-11,20-dione 20-semicarbazone 21-acetate (VIII). In 2710 cc. of methanol, 100 g. (0.246 mole) of 3(α),17(α),21-trihydroxypregnane-11,20-dione 21-acetate was dissolved. After replacing the air above the stirred solution by nitrogen, 62.3 g. (0.56 mole) of semicarbazide hydrochloride and 37.3 g. (0.45 mole) of sodium bicarbonate were added. The solution was heated under reflux for 3 hours and at 45° for an additional 20 hours; at the end of this time it was concentrated *in vacuo* to a volume of 1000 cc. The product began to crystallize at a volume of about 1500 cc. and, at the end of the concentration, crystallization was forced to completion by the addi-

(8) Analyses by R. N. Boos and associates; ultraviolet spectra by F. A. Bacher and associates. Melting points are uncorrected.

TABLE I

C_{20} OXIMES AND SEMICARBAZONES OF 17(α)HYDROXYL-21-STEROID ACYLATES

Compound	R_1	R_2	Molecular Formula	Nitrogen Calc'd	Nitrogen Found	M.P., °C.	Ultraviolet Peaks (in methanol)[a] λ, mμ.	E
I	$-CH_3$[c]	$-NHCONH_2$	$C_{25}H_{36}N_6O_5$	16.27	15.97	>300°	268	34,800
II	$-CH_3$	$-OH$	$C_{23}H_{32}N_2O_6$	6.48	6.33	188° dec.	241	20,100
III	$-C_6H_5$[b]	$-NHCONH_2$	$C_{30}H_{38}N_6O_6$	14.52	14.50	212–220° dec.	230	27,900
							267.5	29,900
IV	$-C(CH_3)_3$[b]	$-NHCONH_2$	$C_{28}H_{42}N_6O_6$	15.04	14.75	>300°	242	22,100
							267.5	30,700
V	$-(CH_2)_{10}CH_3$[b]	$-NHCONH_2$	$C_{35}H_{56}N_6O_6 \cdot 2CH_3OH$	11.68	11.62	228–230° dec.	245	27,200
							268	37,000
VI	$-CH_2C_6H_5$[b]	$-NHCONH_2$	$C_{31}H_{40}N_6O_6$	14.18	13.94	225° dec.	242	24,750
							268	34,600
VII	$-C_6H_4(o\text{-}CH_3)$[b]	$-NHCONH_2$	$C_{31}H_{40}N_6O_6$	14.18	14.04	225° dec.	236	32,400
							268	38,700
VIII	3(α),17(α),21-trihydroxy-pregnane-11,-20-dione 20-semicarbazone 21-acetate	$-NHCONH_2$	$C_{24}H_{37}N_3O_6$	9.07	9.07	245° dec.	242.5	12,950

[a] The semicarbazones were first dissolved in ethylene glycol (15–20 mg./cc.), then diluted to 100 cc. with methanol. [b] The parent esters of these compounds were prepared by Drs. E. F. Rogers and J. Conbere of these laboratories (unpublished work). [c] Recently this compound was reported by Eugene P. Oliveto, Richard Rausser, Herbert Q. Smith, Corrine Gerold, Lois Weber, Elliot Shapiro, David Gould, and E. B. Herschberg, *Abstracts of Papers, First Regional Meeting, Delaware Valley, American Chemical Society,* p. 43, February 16, 1956. The substance was prepared by essentially the same method as we have used; it subsequently was converted to hydrocortisone.

tion of 3000 cc. of water. After stirring the cooled mixture for 3 hours, the product was filtered, washed with water, and dried; wt. 107.9 g., m.p. 247° dec.

Anal. Cf. Table I.

For ultraviolet spectra, *cf.* Table I.

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A Novel Synthesis of Cyclohexenones by Intramolecular Acylation

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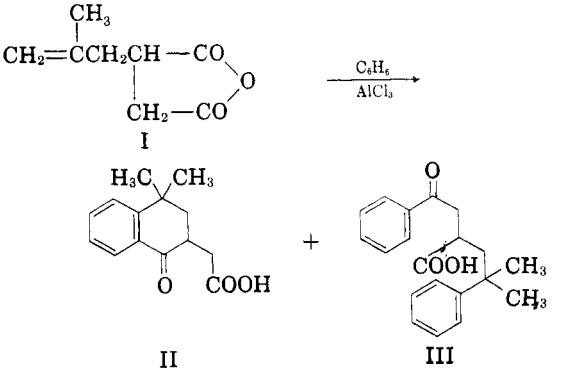
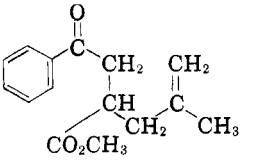
Received February 2, 1956

In a recent communication[1] we reported the synthesis of benzo[*c*]phenanthrene derivatives through a series of reactions that involved the tetraloneacetic acid (II) and the keto acid (III) as important intermediates. These acids were prepared in fair yield by the Friedel-Crafts' condensation between β-methallylsuccinic anhydride (I) and benzene. In the separation of these two acids (by distillation of their methyl esters) there was always obtained a substantial amount of a lower-boiling fraction whose identity at the time was not established. The infrared spectrum of this particular fraction (maxima at 5.77, 5.98, and 6.13 μ) led us to believe that the principal constituent was the monoacylated ester (IV), but an unequivocal synthesis of IV established their non-identity.





IV

The lack of absorption in the neighborhood of 6.25 μ indicated that this fraction was *not* aromatic in nature[2] and the ultraviolet absorption spectrum (λ_{max} 237 mμ, log ε 4.15 and 282 mμ, log ε 2.19) was characteristic of an α,β-unsaturated carbonyl

(1) Phillips and Johnson, *J. Am. Chem. Soc.*, **77**, 5977 (1955).

(2) Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen and Co. Ltd., London, 1954, p. 60.