wash, the combined filtrates were added to 50 ml of 2 *N* hydrochloric acid, saturated with 2,4-dinitrophenylhydrazine. The work-up gave 240 mg (90%) of 2-methylbutanal 2,4-dinitrophenylhydrazone, mp 112–115° (uncorrected), lit.[21] mp 132.5–133°.

*Anal.* Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.05. Found: C, 49.60; H, 5.53; N, 20.95.

**Cleavage of XI with Sodium Hypobromite to 2-Hydroxy-3-methylpentanoic Acid (XIV).**—To a sodium hypobromite solution [8.40 g (0.21 mole) of sodium hydroxide (70 ml of water) and 12.0 g (0.075 mole) of bromine] was added slowly 2.60 g (0.02 mole) of XI, the mixture was stirred in an ice bath for 45 min and then at room temperature for 3 hr. Bromoform was separated, and the aqueous phase was carefully acidified with 10 ml of concentrated sulfuric acid. After ether extraction, the ether solution in turn was extracted with several portions of saturated sodium bisulfite and dried over anhydrous magnesium sulfate. Work-up resulted in 1.60 g of a gummy mass of colorless crystals, but recrystallization from toluene–petroleum ether gave 0.72 g (47% yield) of product, mp 45–48°; sublimation of this material resulted in a pure substance melting sharply at 48°.

*Anal.* Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.67; H, 9.16.

(21) E. J. Badin and E. Pacsu, *J. Am. Chem. Soc.*, **67**, 1352 (1945). The difference in melting points may be due to *syn-anti* isomerism or crystalline modification of the same isomer.

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# Cortical Steroid Analogs. V. Synthesis of *gem*-Dialkyldihydroxyacetones and 3-Butyl-3,6-dihydroxy-1-aroyloxy-2-heptanone[1a]

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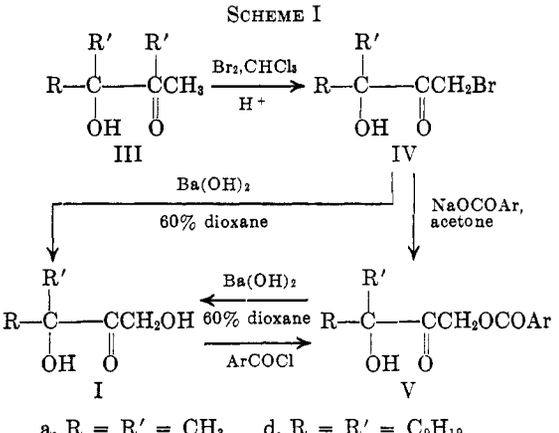
By utilization of the now available *gem*-dialkylacetylcarbinols (III), synthesis of three *gem*-dialkyldihydroxyacetones (I) has been accomplished. One of these (Id) possesses the corticosteroid carbon content of 21 carbon atoms. Thus, the general ease with which this synthetic scheme may be applied is established. In a different but related phase of research, a partial structure, simulating the C and D steroid rings and possessing a hydroxyl group corresponding to that of position 11 in cortisol, is reported. As the free dihydroxyacetone IIa itself resisted isolation, it was obtained as the aromatic ester derivative, *i.e.*, 3-butyl-3,6-dihydroxy-1-aroyloxy-2-heptanone (IIb and c). The over-all synthesis proceeds from ethyl 3-oxoenanthate (VI) through five steps to 3-butyl-3,6-dihydroxy-2-heptanone (XI). This key intermediate then intersects the previously employed scheme for conversion of acetylcarbinols III to dihydroxyacetones I, and its application finally gives IIb and c. None of these analogs showed significant corticoid activity.

Several excellent procedures have been developed for the elaboration of the dihydroxyacetone group common to the antiinflammatory corticosteroids.[2] In the preparation of *open-chain* analogs, there is a greater flexibility of approach in handling this synthetic problem, however, as we have previously demonstrated.[3,4] Contemporarily, the synthesis of the related *gem*-dimethyldihydroxyacetone (Ia) was recorded by a Russian group.[5] Now that a convenient method for the preparation of *gem*-dialkylacetylcarbinols (III) (Scheme I) is at hand, as described in the foregoing companion paper,[6] the synthesis of a series of *gem*-dialkyldihydroxyacetones corresponding to the parent Ia has become feasible. The strategic advantage of this approach is that *gem*-dialkyldihydroxyacetones (I) of high carbon content may be constructed by selection of an appropriate Grignard reagent of less than half as many carbon atoms.[6] Accordingly, we have conveniently synthesized the 21-carbon analog (Id), which has a carbon content identical with that of the corticosteroids.

SCHEME I




a, R = R′ = $CH_3$ d, R = R′ = $C_9H_{19}$
b, R = R′ = $C_2H_5$ e, R = $CH_3$; R′ = $C_6H_5$
c, R = R′ = $C_4H_9$

For purposes of comparison and development of synthetic procedures, the *gem*-diethyl analog Ib and the *gem*-dibutyl analog Ic were prepared in addition to Id. As in earlier work,[3,4] it was found that α-bromo-α′-hydroxy ketones (IV) frequently undergo decomposition on attempted distillation. It was, therefore, ordinarily expedient to employ the freshly prepared crude intermediate for the subsequent step. The crude α-bromo-α′-hydroxy ketone also was on occasion characterized as a crystalline salt resulting from reaction with 3-methylisoquinoline.[7] When the α-bromo-α′-hydroxy ketone was a solid, as in the case of the C-21 analog IVd, it was possible to obtain a pure inter-

(1) (a) Presented in part before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958. (b) In part from the Ph.D. Thesis of S. L. Razniak, Washington State University, June 1960.

(2) *Cf.* G. Rosenkranz and F. Sondheimer, "Progress in the Chemistry of Organic Natural Products," Vol. X, L. L. Zechmeister, Ed., Springer Verlag, Vienna, 1953, p 274.

(3) G. W. Stacy, R. A. Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, **79**, 3587 (1957).

(4) G. W. Stacy, R. A. Mikulec, C. R. Bresson, and L. D. Starr, *J. Org. Chem.*, **24**, 1099 (1959).

(5) I. N. Nazarov, M. S. Burmistrova, and A. A. Akhrem, *Zh. Obshch. Khim.*, **29**, 735 (1959); *Chem. Abstr.*, **54**, 1354 (1960).

(6) G. W. Stacy, I. L. Klundt, G. T. Davis, N. A. Nielsen, M. S. Power, D. L. Rector, and S. L. Razniak, *J. Org. Chem.*, **31**, 1753 (1966).

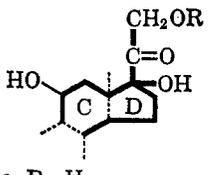
(7) R. S. Shelton, *J. Am. Chem. Soc.*, **68**, 753 (1946).

mediate by crystallization from petroleum ether (bp 35–60°).

Formation of the crystalline intermediate, *p*-nitrobenzoate V, proceeded more smoothly and in higher yield (70–76%) than had been our previous experience.[4] However, the final step leading to the desired *gem*-dialkyldihydroxyacetones (Ib–d) usually was wrought with difficulties. Previously, the methylphenyldihydroxyacetone (Ie) had been obtained in yields of 44–66% by saponification of the imtermediate *p*-nitrobenzoate Ve by aqueous–ethanolic barium hydroxide.[4] For the *gem*-diethyl analog Ib, this identical procedure failed, giving only a 5% yield of Ib. Yields of the *gem*-dibutyl analog Ic were also poor (37%). These unsatisfactory results were ascribed to the difficulty of separating ethyl *p*-nitrobenzoate from the product in question and the product's alkali sensitivity.[4] However, a satisfactory method utilizing 60% aqueous dioxane as the solvent medium was devised; this modification gave yields of Ib greater than 50%. More conveniently, Ib was obtained directly from the $\alpha$-bromo-$\alpha'$-hydroxy ketone IVb in aqueous dioxane in even higher yield (62%), thus bypassing the *p*-nitrobenzoate intermediate Vb. In the C-21 series, direct conversion of IVd to Id (mp 34–35°) by this procedure proceeded in 42% yield.

Returning to the *gem*-diethyl analog Ib, one can conclude that the structure is that of the expected dihydroxyacetone. The infrared spectrum of Ib showed absorption bands for the carbonyl and hydroxyl groups of a ketose. The possible isomeric aldose was ruled out by the absence of the characteristic C–H stretching frequency (2720 $cm^{-1}$) of the aldehyde function,[8] and the infrared spectra of samples of Ib obtained from either IVb or Vb were identical. Also, a sample of Ib, derived from the $\alpha$-bromo-$\alpha'$-hydroxy ketone IVb, reacted with *p*-nitrobenzoyl chloride to give the *p*-nitrobenzoate intermediate Vb. The same interconversion was demonstrated in the *gem*-dibutyl series (Ic $\rightleftarrows$ Vc).

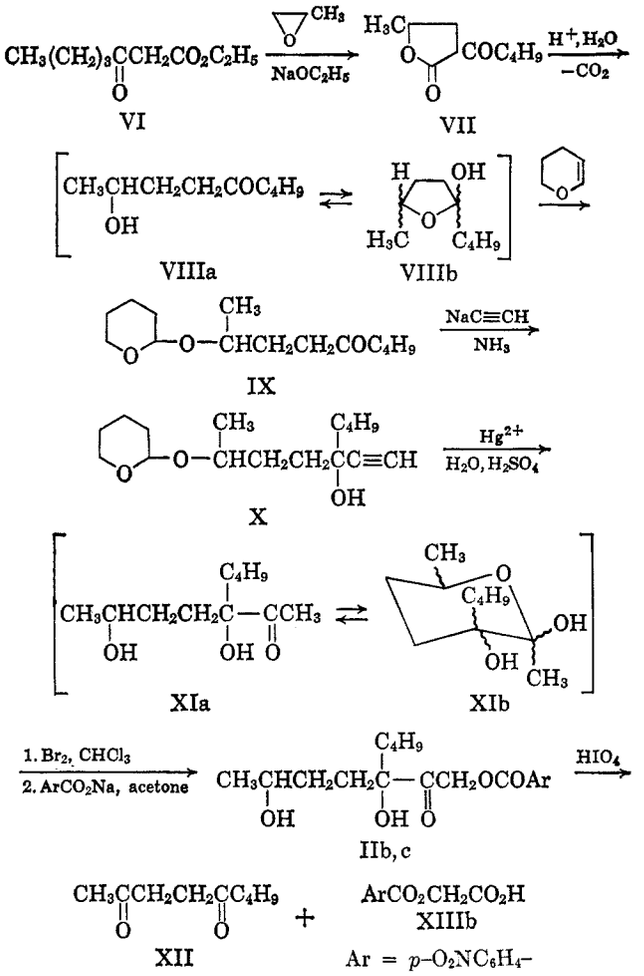
Another acylic analog of interest was that which might be viewed as a partial structure simulating the C and D rings of cortisol, including a simulated 11-oxygen function, namely, 3-butyl-1,3,6-trihydroxy-2-heptanone (IIa). The concept of partial structures, of course, has been employed widely in the design of prospective therapeutic agents and in the present context, particularly for a stilbesterol-type analog.[9]




IIa, R = H
b, R = $COC_6H_4NO_2$-*p*
c, R = $COC_6H_4OH$-*p*

The synthesis of IIa required the dihydroxy ketone intermediate XI in application of the above-described scheme for elaboration of the dihydroxyacetone moiety. Accordingly, the synthesis of XI was accomplished

SCHEME II




by a five-step route leading from ethyl 3-oxoenanthate (VI) (Scheme II).

The $\beta$-keto ester VI was converted to 2-hydroxy-5-nonanone (VIIIa) by way of the $\gamma$-valerolactone VII, which was obtained by reaction of VI with propylene oxide (two-step over-all yield, 75%), a method employed for a lower homolog by Adams and VanderWerf.[10] Possible tautomerization to the ring form VIIIb was of no unfavorable consequence in the reaction of VIII with dihydropyran[11] to form the tetrahydropyranyl ether IX in 58% yield. The appropriate *t*-hydroxy ketone function was then introduced at the carbonyl site of IX.[12] Ethynylation with sodium acetylide in liquid ammonia gave a 54% yield of the ethynylcarbinol X; the tetrahydropyranyl group was retained in the conversion. No attempt was made to maintain diastereomeric purity at this point or subsequently, nor was any attempt made to characterize diastereoisomers. Hydration of the ethynyl group[12] with simultaneous removal of the tetrahydropyranyl group proceeded smoothly to yield 3-butyl-3,6-dihydroxy-2-heptanone (XIa).

At this point, the synthesis interesected the regular route discussed earlier in this paper for the elaboration of the dihydroxyacetone structural element. Bromination of XI occurred normally to form the intermediate $\alpha$-bromodihydroxy ketone. The crude ketone was

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p 156.
(9) J. H. Burckhalter, P. H. Jackson, J. Sam, and H. R. Meyer, *J. Am. Chem. Soc.*, **76**, 4112 (1954).
(10) R. M. Adams and C. A. VanderWerf, *ibid.*, **72**, 4368 (1950).
(11) W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948).
(12) G. W. Stacy and R. A. Mikulec, *ibid.*, **76**, 524 (1954).

then employed in the final step to yield the aromatic ester derivatives (IIb and c) with sodium *p*-nitrobenzoate or *p*-hydroxybenzoate, respectively. Although possible detrimental influence of ring tautomerization of XIa to XIb in this series of reactions was not ascertained, it could be a factor in explaining the lower than average yields of the esters (IIb and c, 20–21%) compared with V. Since attempts to obtain the free trihydroxyacetone derivative IIa failed, possible biological activity for the *p*-hydroxybenzoate ester IIc was investigated. Structural evidence for these substances was furnished by the periodic acid oxidation of IIb to 2,5-nonanedione (XII) (2,4-dinitrophenylhydrazone) and O-*p*-nitrobenzoylglycolic acid (XIIIb).

**Biological Evaluation.**—Neither the *gem*-dialkyldihydroxyacetones (Ib–d) nor 3,6-dihydroxy-1-*p*-hydroxybenzoyloxy-2-heptanone (IIc) displayed significant corticoid activity by the antiinflammatory, thymolytic, or glycogen deposition assays in adrenalectomized rats.

## Experimental Section

All melting points are corrected. Boiling points at reduced pressures are uncorrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tenn., and Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England. The infrared spectra were determined on a Beckman IR-5 spectrophotometer with sodium chloride optics; the spectra of liquids were run as neat films.

**1-Bromo-3-ethyl-3-hydroxy-2-pentanone (IVb).**—To a solution of 6.51 g (0.05 mole) of IIIb[6] in 150 ml of chloroform, to which several drops of glacial acetic acid had been added as catalyst, was added about 5 drops of a solution of 8.07 g (0.051 mole) of bromine in 90 ml of chloroform. The mixture was stirred and warmed, the bromine color disappearing within a few minutes. The bromine solution was then added at such a rate that a light brown color was maintained in the reaction mixture. The addition required 1.25 hr, and, after it had been completed, the reaction mixture was stirred an additional 15 min at room temperature. The mixture was washed with 5% sodium hydroxide solution and finally with saturated sodium chloride solution. It was then dried over anhydrous sodium sulfate, to which 0.2 g of magnesium oxide had been added as a stabilizer. The chloroform was removed *in vacuo* to yield a light yellow residue of the $\alpha$-bromo-$\alpha'$-hydroxy ketone IVb, which was used directly for the preparation of Vb.

For identification, 0.42 g (0.002 mole) of crude IVb was mixed with 0.56 g (0.004 mole) of 3-methylisoquinoline.[7] On standing at room temperature for 3 hr, the reaction mixture solidified. The crystals were then washed with anhydrous ether, and the ether-insoluble material was recrystallized from ethanol–ether (1:1) to give tan N-(3-hydroxy-3-ethyl-2-pentanone)-3-methylisoquinolinium bromide, mp 195–196°.

*Anal.* Calcd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.30; Br, 22.68. Found: C, 57.89; H, 6.36; Br, 22.47.

**1-Bromo-3-hydroxy-3-nonyl-2-dodecanone (IVd).**—To a solution of 5.0 g (0.015 mole) of impure IIId[13] in 100 ml of chloroform, to which 2 drops of glacial acetic acid had been added as catalyst, was added dropwise 2.5 g (0.016 mole) of bromine in 100 ml of chloroform. After the usual procedure as described above, 5.0 g of a residue was obtained, which soon solidified at 25°. Several recrystallizations from petroleum ether (bp 35–60°) gave 3.0 g (48%), mp 38–39°.

*Anal.* Calcd for $C_{21}H_{41}BrO_2$: C, 62.20; H, 10.19; Br, 19.71. Found: C, 62.45; H, 10.35; Br, 19.84.

**3-Ethyl-3-hydroxy-1-(*p*-nitrobenzoxy)-2-pentanone (Vb).**—A mixture of 42.6 g (0.25 mole) of *p*-nitrobenzoic acid and 25.0 g (0.25 mole) of potassium bicarbonate in 700 ml of acetone was stirred and heated under reflux for 0.5 hr, during which time a precipitate of potassium *p*-nitrobenzoate separated. A solution of freshly prepared IVb [from 6.51 g (0.05 mole) of IIIb and 8.07 g (0.05 mole) of bromine] in 100 ml of acetone was added dropwise over a 20-min period, and the mixture was stirred under reflux for 24 hr. The reaction mixture was filtered, and the residue was washed with acetone. The acetone was removed leaving a semisolid, to which was added 20 ml of a 5% sodium bicarbonate solution. The solid which then separated was collected by filtration and was recrystallized from carbon tetrachloride: yield 103.0 g (70%) of light tan product, mp 147–148°.

*Anal.* Calcd for $C_{14}H_{17}NO_6$: C, 56.93; H, 5.83; N, 4.74. Found: C, 57.21; H, 5.88; N, 4.54.

**3-Butyl-3-hydroxy-1-(*p*-nitrobenzoxy)-2-heptanone (Vc).**—An acetone solution of freshly prepared IVc [from a solution of 18.6 g (0.10 mole) of IIIc and 16.8 g (0.10 mole) of bromine in chloroform] was added to potassium *p*-nitrobenzoate [from a mixture of 87.7 g (0.52 mole) of *p*-nitrobenzoic acid and 50.1 g (0.50 mole) of potassium bicarbonate in 1.5 l. of acetone].

The reaction mixture was filtered, and the resulting filter cake, consisting of excess potassium *p*-nitrobenzoate, was washed with acetone. To reduce the volume of the acetone filtrate, it was distilled until bumping occurred. To this concentrated volume was added 375 ml of 5% sodium bicarbonate solution. An oil separated and was taken up in 1:3 carbon tetrachloride–petroleum ether (bp 30–75°) from which white platelets crystallized to yield 26.6 g (76%), mp 60.5–61.5°. Recrystallization gave mp 61.5–62°.

*Anal.* Calcd for $C_{18}H_{25}NO_6$: C, 61.53; H, 7.17; N, 3.98. Found: C, 61.34; H, 7.23; N, 4.15.

**3-Hydroxy-3-nonyl-1-(*p*-nitrobenzoxy)-2-dodecanone (Vd).**—To potassium-*p*-nitrobenzoate, prepared from a mixture of 4.71 g (0.022 mole) of *p*-nitrobenzoic acid and 2.22 g (0.022 mole) of potassium bicarbonate in 150 ml of acetone, was added a solution of 1.8 g (0.0044 mole) of IVd in 50 ml of acetone. After the usual reaction process and work-up, a residue was obtained, which upon crystallization from petroleum ether afforded 1.6 g (72%) of a colorless, crystalline product, mp 65–66°.

*Anal.* Calcd for $C_{28}H_{45}NO_5$: C, 68.40; H, 9.24; N, 2.85. Found: C, 68.46; H, 9.63; N, 2.91.

**1,3-Dihydroxy-3-ethyl-2-pentanone (Ib). A. From Vb in Aqueous Ethanol as Solvent.**—To 14.8 g (0.05 mole) of Vb, dissolved in 600 ml of 95% ethanol and cooled in an ice bath, was added with stirring over a 2-hr period an ice-cold solution of 8.69 g (0.026 mole) of barium hydroxide octahydrate in 300 ml of boiled distilled water. The reaction mixture was allowed to stand at room temperature overnight and then worked up as previously reported.[4] Only 0.36 g (5%) of Ia was obtained: bp 75° (1 mm); $n^{25}D$ 1.4553; $d^{25}_4$ 1.0620; $\nu_{max}$ ($cm^{-1}$) 3430(s) (O–H), 1350(m), 1150(w) (*t*-OH), 1710(s) (C=O).

*Anal.* Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.66; H, 9.56.

**B. From Vb in Aqueous Dioxane.**—To 14.8 g (0.05 mole) of Vb dissolved in 450 ml of purified dioxane was added with stirring over a 2-hr period a solution of 8.69 g (0.026 mole) of barium hydroxide octahydrate in 300 ml of boiled distilled water. The reaction mixture was allowed to stir at room temperature overnight. Sodium chloride was added until the reaction mixture separated into two phases. The organic phase was separated and dried over anhydrous sodium sulfate. The dioxane was removed *in vacuo*, and the residual liquid was filtered to remove solid material and fractionally distilled through a 15-cm Vigreux column to yield 3.84 g (53%) of Ib: bp 75° (1 mm), $n^{25}D$ 1.4550, infrared spectrum identical with that of A above.

**C. From 1-Bromo-3-ethyl-3-hydroxy-2-pentanone (IVb) in Aqueous Dioxane.**—Crude IVb [from 13.0 g (0.10 mole) of IIIb and 16.1 g (0.10 mole) of bromine] was dissolved in 900 ml of dioxane. A solution of 15.9 g (1.01 equiv) of barium hydroxide octahydrate in 600 ml of boiled distilled water was then added dropwise (3 hr). The solution was stirred overnight, and then sodium chloride was added until the reaction mixture separated into two phases. The organic phase was separated and dried over anhydrous sodium sulfate, and the dioxane was removed *in vacuo*. Fractional distillation of the residual liquid through a 15-cm Vigreux column gave 9.06 g (62% yield) of Ib: bp 57–61° (0.20–0.60 mm), $n^{25}D$ 1.4567, infrared spectrum identical with that of A above.

The *gem*-diethyldihydroxyacetone (Ib) from any of the above sources could be reconverted to the *p*-nitrobenzoate Vb. A 730-mg sample (5.0 mmole) of Ib and 930 mg (5.0 mmole) of *p*-nitrobenzoyl chloride were dissolved in 20 ml of pyridine. The re-

(13) 3-Hydroxy-3-nonyl-2-dodecanone (IIId) was prepared in 60% yield by the general procedure:[6] bp 183–184° (1 mm), $n^{25}D$ 1.4510. Although difficulty was experienced in analytically purifying IIId, the impure intermediate was satisfactory for conversion to IVd. *Anal.* Calcd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97. Found: C, 77.77; H, 12.66.

action mixture was heated for 1.5 hr; 50 ml of water was added and the mixture was cooled in an ice bath. The precipitate was filtered and washed with 5% sodium bicarbonate solution to give 780 mg (53%) of a light tan powder: mp 147–148°, infrared spectrum identical with authentic Vb.

**3-Butyl-1,3-dihydroxy-2-heptanone (Ic).**—To 10.5 g (0.03 mole) of Vc in 1 l. of 95% ethanol (ice bath), was added with stirring 255 ml of an ice-cold solution of 5.20 g of barium hydroxide octahydrate (4 hr). After work-up and separation of 1.50 g of ethyl *p*-nitrobenzoate, mp 56–57°, the filtrate was distilled through a 5-cm Vigreux column to yield 2.23 g (37%) of the didroxyacetone Ic as a light yellow liquid: bp 98–103° (0.6 mm); $n^{25}D$ 1.4596; $\nu_{max}$ ($cm^{-1}$) 3430(s) (O–H), 1350(m), 1150(w) (*t*-OH), 1710(s) (C=O).

*Anal.* Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.45; H, 10.50.

As in the previous case, this material could be reconverted to the intermediate *p*-nitrobenzoate Vc. A solution of 202 mg (1.0 mmole) of Ic in 1.5 ml of pyridine was added to 186 mg (1.0 mmole) of *p*-nitrobenzoyl chloride. Crystallization from 1:3 carbon tetrachloride–petroleum ether (bp 30–75°) gave 100 mg (29%) of colorless crystals: mp 61.5–62°, infrared spectrum identical with previously prepared Vc.

**1,3-Dihydroxy-3-nonyl-2-dodecanone (Id).**—A solution of 4.0 g (0.0082 mole) of IVd in 300 ml of purified dioxane and 1.61 g of barium hydroxide octahydrate in 150 ml of boiled distilled water was stirred for 14 hr and filtered to remove the precipitate. The filtrate was concentrated below 30°, and the residual liquid was extracted with 300 ml of petroleum ether and dried over anhydrous sodium sulfate. After the solvent had been removed, 2.5 g of residue was obtained which, after several recrystallizations from petroleum ether, gave 1.2 g (42%) of colorless crystals, mp 34–35°.

*Anal.* Calcd for $C_{21}H_{42}O_3$: C, 73.63; H, 12.36. Found: C, 73.71; H, 12.32.

**Ethyl 3-Oxoenanthate (VI).**—This β-keto ester was prepared essentially by the procedure of Anderson, *et al.*,[14] except that sodium hydride instead of sodium ethoxide was employed in the preparation of sodio ethylacetoacetate. To a mixture of 38.4 g (1.6 moles) of sodium hydride in 2.5 l. of absolute ether and 208 g (1.7 moles) of ethyl acetoacetate was added dropwise 160 g (1.33 moles) of freshly distilled *n*-valeryl chloride (4 hr) at 7–10°. After a work-up, distillation through a 15-cm Vigreux column (glass helices) gave 165.0 g (79%) of VI, bp 75–77° (0.1 mm).[15]

**β-Valeryl-γ-valerolactone (VII).**—A procedure similar to that of Adams and VanderWerf was employed.[10] To 250 ml of absolute ethanol, cooled in an ice bath, was added 13.1 g (0.57 g-atom) of sodium. The flask was then cooled to 0° and 98.0 g (0.57 mole) of VI was added rapidly. To the resultant solid mass, 64.1 g (1.1 moles) of propylene oxide, previously chilled in a Dry Ice chest, was added dropwise with stirring over a period of 30 min. The solid gradually dissolved as the solution was stirred for 12 hr at room temperature; it was then concentrated at below 50° to remove some of the ethanol. The residual syrup was shaken with 75 ml of chilled 50% aqueous acetic acid. The excess of acetic acid was neutralized with 5% sodium bicarbonate solution, and the organic phase was extracted with ether, which in turn was washed with water and dried over anhydrous sodium sulfate. The ether was removed, and the resulting residue was fractionally distilled through a 15-cm column (glass helices) to yield 54.0 g of recovered ester and 36.5 g of VII, representing a 33% yield or 78% considering recovered β-keto ester: bp 90–92° (0.1 mm); $n^{25}D$ 1.4614; $\nu_{max}$ ($cm^{-1}$) 1725(s) (C=O), 1772(s) (γ-lactone C=O).

*Anal.* Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.41; H, 9.12.

**2-Hydroxy-5-nonanone (VIIIa).**—A mixture of 64.0 g (0.35 mole) of VII, 40 ml of 10 *N* HCl, and 200 ml of water was warmed to 70° on a steam bath for 4 hr[10] and then allowed to cool while carbon dioxide evolved for the next 3 hr. The supernatant oil was separated, and the aqueous phase was extracted with ether. The combined extracts were washed with 5% sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. After the solvent had been removed, the residue was distilled under reduced pressure to give 54.0 g (98%) of VIII: bp 30–40° (0.03 mm); $n^{25}D$ 1.4370; $\nu_{max}$ ($cm^{-1}$) 3425(s) (O–H), 1725(s) (C=O).

*Anal.* Calcd for $C_9H_{18}O_2$: C, 69.18; H, 11.45. Found: C, 69.20; H, 11.72.

A **3,5-dinitrobenzoate** from 1.3 g (9.0 mmoles) of VIII and 2.1 g (9.0 mmoles) of 3,5-dinitrobenzoyl chloride in 30 ml of benzene and 4 ml of of anhydrous pyridine (heated for 2 hr) gave after recrystallization from methanol–chloroform, a colorless crystalline solid, mp 49–50°.[16]

*Anal.* Calcd for $C_{16}H_{20}N_2O_7$: C, 54.53; H, 5.73; N, 7.96. Found: C, 54.72; H, 5.69; N, 7.82.

**2-Tetrahydropyranoxy-5-nonanone (IX).**—A solution of 15.8 g (0.10 mole) of VIII was mixed with 15.0 g (0.18 mole) of dihydropyran containing 5 drops of hydrochloric acid, and the mixture was allowed to stand for 4 hr with occasional shaking.[11] It was then taken up in 600 ml of ether, and the solution was washed with 50 ml of 5% sodium hydroxide solution and then water and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was distilled under reduced pressure to give 14.1 g (58%) of IX: bp 100–103° (0.075 mm); $n^{25}D$ 1.4530; $\nu_{max}$ ($cm^{-1}$) 1725(s) (C=O), 1080(m), 1130(m) (alkyl ether), 820(m), 875(m), 1250(m) (cyclic ether).

*Anal.* Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.82. Found: C, 69.66; H, 11.02.

**3-Butyl-3-hydroxy-6-tetrahydropyranoxy-1-heptyne (X).**—To 1 l. of liquid ammonia containing 0.2 g of ferric nitrate nonahydrate was added 8.56 g (0.35 g-atom) of sodium in small pieces over a period of 5 min.[12] With the volume of the reaction mixture being maintained at its original level with additional liquid ammonia, purified acetylene was introduced over a period of 4.5 hr. Then 60.5 g (0.25 mole) of IX was added dropwise (1 hr). The flow of acetylene was somewhat decreased, and vigorous stirring was continued for 7 hr. Introduction of acetylene was terminated, and the mixture was stirred for an additional 8 hr. After the ammonia had evaporated, 200 g of ice slurry was added to the residue, and to this resulting mixture was added portionwise a solution of 13.4 g of ammonium chloride in 100 ml of water, after which the mixture was stirred until the solid was dissolved. The organic phase was taken up in ether and the aqueous phase was extracted. The ether extracts were washed with water and dried over anhydrous sodium sulfate. After solvent removal, the residue was distilled through a spinning-band column under reduced pressure. Following a forerun of 20.0 g of unreacted IX, 36.0 g (54%, 80% considering recovered IX) of X was obtained: bp 100–110° (0.06 mm); $n^{25}D$ 1.4695; $d^{25}_4$ 0.9986; $\nu_{max}$ ($cm^{-1}$) 3400(s) (O–H), 3250(s), 2100(w) C≡C, 1380(s), 1200(m) (*t*-OH).

*Anal.* Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.41; H, 10.72.

A **3,5-dinitrobenzoate** was prepared by refluxing equimolar quantities of X and 3,5-dinitrobenzoyl chloride in a mixture of anhydrous pyridine, benzene, and petroleum ether for 7 hr. Recrystallization of the product from 95% ethanol afforded white plates, mp 100–101°.

*Anal.* Calcd for $C_{23}H_{30}N_2O_8$: C, 59.71; H, 6.55; N, 6.06. Found: C, 59.40; H, 6.50; N, 6.00.

**3-Butyl-3,6-dihydroxy-2-heptanone (XIa).**—To a solution of 1.7 g of mercuric oxide in 32 ml of water and 1.44 ml of concentrated sulfuric acid, which was stirred and heated to 65°, was added dropwise (1 hr) 36 g (0.13 mole) of X.[12] The mixture was stirred at this temperature for 20 min and then allowed to cool to room temperature. The organic phase was taken up with ether, and the aqueous phase was extracted. The ether extracts were washed with 5% sodium bicarbonate solution and then water and dried over anhydrous sodium sulfate. After solvent removal, the residue was distilled through a 5-cm column (helices) to yield 22.0 g (81%) of XIa: bp 95–97° (0.05 mm); $n^{25}D$ 1.4640; $d^{25}_4$ 1.0112; $\nu_{max}$ ($cm^{-1}$) 3450(s) (O–H), 1380(m), 1160(m) (*t*-OH), 1725(s) (C=O).

*Anal.* Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.92. Found: C, 65.54; H, 10.82.

A **2,4-dinitrophenylhydrazone** was prepared in the usual way. Several recrystallizations from 95% ethanol afforded yellow needles, mp 115–116°.

*Anal.* Calcd for $C_{17}H_{26}N_4O_5$: C, 53.39; H, 6.82; N, 14.65. Found: C, 53.40; H, 6.72; N, 14.85.

(14) G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Robbin, Jr., *J. Am. Chem. Soc.*, **67**, 2197 (1945).

(15) A. Wahl and M. Doll, *Bull. Soc. Chim. France*, **13**, 265 (1913).

(16) Although the structure was not established, it may well relate to the ring tautomer VIIIb rather than VIIIa.

**3-Butyl-3,6-dihydroxy-1-(*p*-nitrobenzoxy)-2-heptanone (IIb).**—To 0.1 mole of potassium *p*-nitrobenzoate in 400 ml of dry acetone (see Vb), was added 50 ml of an acetone solution of the crude α-bromo-α′-hydroxy ketone, prepared from 4.04 g (0.02 mole) of XIa and 4.00 g (0.025 mole) of bromine. The resulting mixture was heated under reflux for 20 hr with stirring and then allowed to stand for an additional 20 hr at room temperature. After work-up and solvent removal, the residue was crystallized from benzene–petroleum ether (bp 60–110°) (1:1), which afforded 1.5 g (20%) of colorless crystals of IIb: mp 109–110°; $\nu_{max}$ ($cm^{-1}$) 3450(s) (O–H), 1350(m), 1130(m), (*t*-OH), 1725(s) (C=O), 1530 (s) ($NO_2$).

*Anal.* Calcd. for $C_{18}H_{25}NO_7$: C, 58.83; H, 6.87; N, 3.82. Found: C, 58.67; H, 7.01; N, 4.10.

A sample of 200 mg (0.54 mmole) of IIb in 30 ml of methanol was stirred with 1.5 ml of 0.54 *M* periodic acid solution for 12 hr. The solution was diluted with 30 ml of water, and the methanol was evaporated *in vacuo*. The residue was extracted with ether, and the ethereal extract was shaken vigorously with sodium bicarbonate solution and separated. The organic phase was washed with water and dried over anhydrous sodium sulfate. After solvent removal, the residue was taken up in 20 ml of ethanol and treated with 2,4-dinitrophenylhydrazine. The resulting crystalline precipitate was recrystallized from ethanol, affording 2,5-nonanedione (XII) as the 2,4-dinitrophenylhydrazone, mp 184–186° (lit.[17] mp 186°).

(17) K. Alder and C. H. Schmidt, *Ber.*, **76**, 187, 193 (1943).

The sodium bicarbonate extract was acidified with hydrochloric acid and extracted with ether, and the extract washed with water, and dried. After evaporation of the solvent, O-*p*-nitrobenzoylglycolic acid (XIIIb), mp 146–147°, was obtained which, on admixture with an authentic sample, showed no depression, mp 146–174°.[4]

**3-Butyl-3,6-dihydroxy-1-(*p*-hydroxybenzoxy)-2-heptanone (IIc).**—To a refluxing solution of potassium *p*-hydroxybenzoate [from 10.0 g (0.10 mole) of potassium bicarbonate and 13.8 g (0.10 mole) of *p*-hydroxybenzoic acid in 400 ml of dry acetone] was added dropwise the crude α-bromo-α′-hydroxy ketone intermediate [from 4.04 g (0.02 mole) of XIa and 4.0 g (0.025 mole) of bromine in 50 ml of dry acetone]. After continued heating for 20 hr and the usual work-up, the crude product was crystallized from benzene–petroleum ether (1:1) to give 1.43 g (21%) of colorless crystals IIc, mp 117–118°.

*Anal.* Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.75. Found: C, 63.95; H, 7.90.

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# Steroids. CCLXXXVII.[1] A Synthetic Route to 19-Substituted 10α-Steroids

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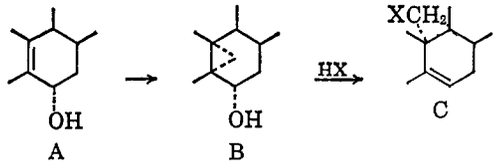
Simmons–Smith methylenations of estr-5(10)-en-6-ols have been studied. 3β-(Tetrahydropyran-2-yl)oxy-5α,19-cyclo-10α-androsta-6α,17β-diol (VIa) undergoes ring opening with ethanolic hydrochloric acid–lithium chloride to furnish 19-chloro-10α-androst-5-ene-3β,17β-diol (VII).

General acceptance of fertility control through the estrogen–progestagen oral contraceptive pill approach provided added impetus to the search for progestational agents of increased potency. Among the more remarkable findings was the observation by Dutch workers that certain 9β,10α- (retro) steroids display progestational activity.[4] Some results of our broad program aimed at developing new synthetic routes to steroids of abnormal configuration have already been disclosed.[5,6] This present communication describes a novel approach to 19-disubstituted 10α-androstanes which is considerably shorter than that previously described by Sondheimer and his colleagues.[7,8] The method chosen involves a stereospecifically controlled Simmons–Smith methylenation[9] of a $\Delta^{5(10)}$-steroid, a reaction used earlier in the synthesis of 10α-androstanes.[6] A study of molecular models[10] suggested no steric difficulties would be encountered in the realization of the sequence A → B → C.




3β,19-Dihydroxyandrost-5-en-17-one (Ia)[11] was oxidized with lead tetraacetate to afford 6β-acetoxy-3β-hydroxyestr-5(10)-en-17-one (IIa), the β configuration at C-6 becoming apparent from subsequent experiments (*vide infra*).[12] The acetate group in the derived 3β-(tetrahydropyran-2-yl) ether IIIa was hydrolyzed to afford the corresponding allylic alcohol IIIb. (See Chart I.) Simmons–Smith methylenation under normal conditions of ether reflux[9] converted this allylic alcohol IIIb into the cyclopropane IV. β-Face ad-

(1) Steroids. CCLXXXVI: J. A. Edwards, M. C. Calzada, L. Cuellar, and A. Bowers, submitted for publication.

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(6) R. Ginsig and A. D. Cross, *J. Am. Chem. Soc.*, **87**, 4629 (1965).

(7) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron Letters*, 38 (1960).

(8) M. Torigoe and J. Fishman [*ibid.*, 1251 (1963)] reported syntheses of 19-substituted 3-desoxy-10α-steroids.

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