[CONTRIBUTION FROM THE SCHERING CORP. AND EMORY UNIVERSITY]

Wagner–Meerwein Rearrangements. III. Further Aspects of Acid-catalyzed Opening of Steroidal 16,17-Epoxides

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Hydrogen fluoride is found to catalyze the rearrangement of 16α,17α-epoxyprogesterone (I) to a compound tentatively designated as 18-nor-17β-methyl-17-iso-4,13-pregnadien-16α-ol-3,20-dione (II), and 16β,17β-epoxyprogesterone (III) to a compound tentatively designated as 18-nor-17β-methyl-17-iso-4,13-pregnadien-16β-ol-3,20-dione (IV). The microbiological saponification–oxidation–isomerization of 18-nor-17β-methyl-17-iso-5,12-pregnadiene-3β,16ξ-diol-20-one diacetate (VI)[3] by *Flavobacterium dehydrogenans* affords IV. The microbiological saponification–oxidation–isomerization of 18-nor-17β-methyl-17-iso-5,13-pregnadiene-3β,16ξ-diol-20-one diacetate (V) by the same organism yields II. The implications of these transformations are discussed.

A fluorine atom, appropriately placed in a suitable steroid hormone, has occasionally had remarkable effects on the biological activities of the derived product.[4] We have been interested in introducing fluorine into the D-ring and in this connection have studied the action of hydrogen fluoride on 16,17-oxidosteroids, in particular, 16α,17α-epoxyprogesterone (I) and 16β,17β-epoxy-17-isoprogesterone (III).

From the action of hydrogen fluoride in chloroform containing ethanol[4a] on I there was isolated a crystalline, fluorine-free solid (II) which was different from I, but possessed the same empirical formula. The infrared spectrum of II displayed conjugated carbonyl and side-chain carbonyl bands of I and, in addition, an hydroxyl band. The new hydroxyl group was converted into an acetate in pyridine solution upon treatment at room temperature with acetic anhydride from which it was inferred that the hydroxyl group was not tertiary. The nuclear magnetic resonance spectrum of II exhibited resonance frequencies, relative to chloroform, at 62 c.p.s. (*one* vinyl proton alpha to a carbonyl group), a broad triplet with center at 122 c.p.s. (*one* 16-proton), 129 c.p.s. (*one* 16-hydroxyl proton), 207 c.p.s. (*three* methyl ketone protons) and 244 c.p.s. (*six* quaternary methyl protons). The last resonance is a superposition of the 19-methyl with 3-keto Δ^4 in the A ring[5], and a migrated 18-methyl now located at 17- with a double bond at 13.[3] In view of our earlier experience with acid-catalyzed reaction involving oxygen functions at 17[3,6] we suspected that a Wagner–Meerwein rearrangement had occurred, and that the resulting product now contained a 17β-methyl group, a 16α-hydroxyl group and a 13-unsaturation as illustrated (II).

A parallel experiment starting from 16β,17β-epoxy-17-isoprogesterone[7] (III), and employing hydrogen fluoride under the same conditions, afforded a new, fluorine-free product (IV), different from II or III, but with the same empirical formula. The infrared spectrum of IV displayed an hydroxyl band, as well as conjugated and side-chain carbonyl bands derived from III. The new hydroxyl group was readily acylable with acetic anhydride in pyridine solution at room temperature and was therefore not tertiary. The nuclear magnetic resonance spectrum of IV showed resonance frequencies, relative to chloroform, at 62 c.p.s. (*one* vinyl proton alpha to a carbonyl group), 111 c.p.s. (center of triplet for *one* 16 proton), 156 c.p.s. (one 16-hydroxyl proton), 208 c.p.s. (*three* methyl ketone protons) and 245 c.p.s. (*six* quaternary methyl protons). The assignment of this last resonance is the same as discussed previously for II, thus showing that the 18-methyl group had migrated. Hence, we assigned to IV the illustrated structure which is consistent with the expected course for Wagner–Meerwein rearrangement III.

In an attempt to relate the Wagner–Meerwein rearrangement products of another series to II and IV, V[3] and VI[3] were subjected to the action of *Flavobacterium dehydrogenans*,[8,9] a microörganism known to hydrolyze acetates, oxidize the 3β-hydroxyl group and isomerize the 5-double bond. Both V and VI afforded thereby acetate-free, ultraviolet-absorbing products. Careful chromatography of the respective reaction mixtures afforded, as the principal products, II from V and IV from VI.

That V gave II was consistent with the structures assigned in both series. Since the location of the acetate group at 16 in V has been proved,[3] the location of the hydroxyl group in II is assured. Since the conditions of hydrogen fluorine-catalyzed opening of the epoxide were exceedingly mild, we are prepared to assume that no inversion at 16 occurs during this reaction and hence that the hydroxyl group at 16 in II and Va is in the α-configuration.

A remarkable correlation in rotation has been observed for II and Va, which points to a common structural feature in the two series. From Table I it may be seen that II, Va and the 4,5-dihydro derivative of II display dramatic shifts in molecular rotation measured in chloroform with respect to rotations measured in dioxane. No such shifts are observed with the acetates of II and Va (V),

(1) Schering Corp.

(2) Emory University.

(3) H. L. Herzog, *et al.*, THIS JOURNAL, **81**, 6478 (1959).

(4) For example (a) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957); (b) J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *ibid.*, **78**, 4814 (1956); (c) A. Bowers and H. J. Ringold, *ibid.*, **80**, 4423 (1958).

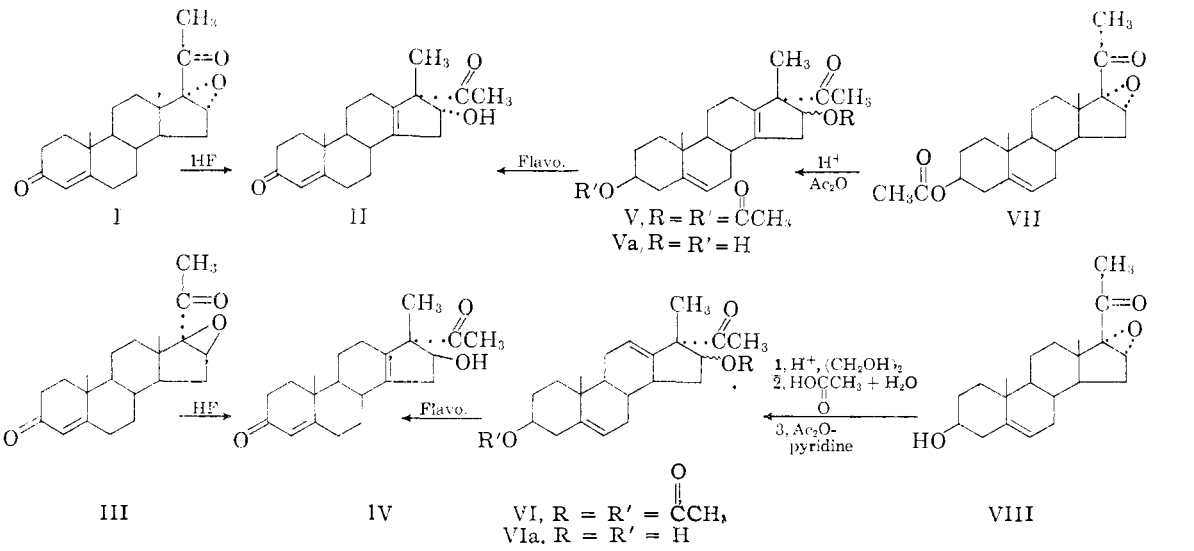
(5) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958).

(6) H. L. Herzog, *et al.*, *J. Org. Chem.*, **22**, 1413 (1957).

(7) G. Gansau, Doctorate thesis, Technische Universitat, Berlin-Charlottenburg, 1952.

(8) C. Arnaudi, *Zentr. Parasitenk*, **105**, 352 (1942).

(9) A. L. Nussbaum, *et al.*, THIS JOURNAL, **79**, 4814 (1957); see also South African Patent 3462/55.



I II V, Va VII

III IV VI, VIa VIII

or with any other Wagner–Meerwein rearrangement product of this general class whose rotation we have measured. It follows from our previous arguments then that a 16α-hydroxyl group is a necessary, but not sufficient, requirement for the observed effect. It is established that no irreversible, chemical change occurs in the chloroform solutions of II and Va, since the substances in question are recovered unchanged following measurement of rotation.

TABLE I

ROTATIONAL SHIFTS PROMOTED BY CHLOROFORM

Compound	M_D (chloroform)	M_D (dioxane)	ΔM_D
18-Nor-17β-methyl-17-iso-4,13-pregnadien-16α-ol-3,20-dione (II)	269	614	−355
Acetate of II	564	529	+ 35
18-Nor-17β-methyl-17-iso-4,13-pregnadien-16β-ol-3,20-dione (IV)	446	462	− 16
Acetate of IV	590	581	+ 9
18-Nor-17β-methyl-17-iso-5,13-pregnadiene-3β-16ξ-diol-20-one (Va)	−437	− 50	−387
3,16-Diacetate of Va (V)	− 75	− 39	− 36
18-Nor-17β-methyl-17-iso-5,12-pregnadiene-3β,16ξ-diol-20-one (VIa)	−307[a]	−224[a]	− 83
3,16-Diacetate of VIa (VI)	−121	− 57	− 64
20-Cycloethylene ketal of VIa	−637	−570	− 67
20-Cycloethylene ketal of VI	−465	−443	− 22
4,5-Dihydro derivative of II	122	460	−338
4,5-Dihydro derivative of IV	304	339	− 35

[a] Sample contained one-half mole of hexane of solvation; M_D calculated accordingly.

The transformation of VI into IV presents two complicating aspects not encountered in the transformation of V into II. The double bond migration from 12- to 13- was unexpected, but is not inconsistent with the previously established ability of the microörganism to promote other, double bond isomerization. On the other hand, the transformation of VIII into IV *via* VI requires that inversion occur at some point along the synthetic chain if the structure of IV is correct. We have already chosen to assume that the hydrogen fluoride opening of the α-epoxide proceeds without inversion at 16 and this assumption is now extended to the opening of the β-epoxide (III → IV). Within this framework then, isomerization at 16 occurs either during the ethylene glycol–*p*-toluenesulfonic acid treatment of VIII or during the microbiological transformation of VI into IV. While there is little basis for distinguishing between the latter two possibilities, we prefer to believe that the epimerization takes place during the ethylene glycol reaction, affording, ultimately, VI with a 16β-acetoxy substituent. We think that if V and VI had possessed the same substituent (16α-acetate) at 16 a common microbiological transformation product (II) would have formed.

Collins and Bonner[10] have described the Wagner–Meerwein rearrangement of the 1,2,2-triphenylethyl system and have concluded that an intermediate carbonium ion is probably involved in the cited rearrangement. In the transformation of III into IV the entering and leaving groups are both considered to be beta. This change seems more easily accommodated *via* a carbonium ion intermediate at 17 (even though benzylic resonance stabilization is absent here) than *via* a push–pull or bridged-ion mechanism, because of the steric requirements around the 17-carbon atom.

In the preceding paper of this series[3] it was suggested that the nature of the group at 20 in 21-carbon-17-oxygenated steroids undergoing Wagner–Meerwein rearrangement, controls the site of the double bond whose introduction follows methyl migration. All examples in which the substrate for rearrangement bears a 20-carbonyl group (I, III and VII[3]) afford a product with a 13-unsaturation. All examples in which starting materials are saturated (bulkier?) at 20 (pregnane-3α,11β,17α,20β-tetrol-3,20-diacetate,[6] 5-pregnene-3β,17α,20β-triol-3,20-diacetate[6] and 16α,17α-oxido-5-pregnene-3β-ol-20-one 20 ketal[3]), or in which a

(10) C. J. Collins and W. H. Bonner, THIS JOURNAL, **77**, 92 (1955).

saturated (at 20) intermediate is postulated (VIII[3]) yield a product with a 12-unsaturation.[11]

We thank Drs. D. H. R. Barton and J. Meinwald for helpful discussions.

Experimental[12]

Reaction of Hydrogen Fluoride with 16α,17α-Oxidoprogesterone (I) to Give II.—A solution of 2.0 g. of I in 40 ml. of distilled chloroform and 2.0 ml. of absolute ethanol was cooled to 0°. Anhydrous hydrogen fluoride was passed into the solution with vigorous agitation for 30 minutes, the temperature being maintained at 0°. At the end of this time two layers had formed, the upper being red and the lower colorless, which is the end-point used for the addition of hydrogen fluoride. The reaction mixture was held at 0° with stirring, without further addition of hydrogen fluoride, for an additional 1.5 hours, and was then poured into excess dilute aqueous sodium bicarbonate-on-ice. The mixture was then extracted with ethylene dichloride, and the extracts were washed with water, dried and concentrated *in vacuo*. The resulting yellow resin was crystallized from ether–hexane affording thereby 0.74 g. of II, m.p. 135–138°. An additional crystallization from acetone–hexane raised the m.p. to 141–142°, $[\alpha]^{25}D$ +187° (dioxane), $[\alpha]^{25}D$ +82° (chloroform); λ_{max} 238 mμ (ε 18,500); λ^{max}_{nujol} 2.97 (OH), 5.89 (20-carbonyl), 6.02 (3-carbonyl), 6.19 μ (Δ^4).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H. 8.59. Found: C, 76.99; H, 8.58.

Acetylation of II with acetic anhydride in pyridine at room temperature overnight gave the **acetate**, which after crystallization from acetone–hexane melted at 149°, $[\alpha]^{25}D$ +152.4° (chloroform), $[\alpha]^{25}D$ +143° (dioxane); λ^{max}_{nujol} 5.78 (acetate carbonyl), 5.88 μ (20-carbonyl), 6.04 (3-carbonyl), 6.22 (Δ^4), 8.10 μ (COC).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56: H. 8.16. Found: C, 74.57; H, 8.21.

Preparation of 16β-Hydroxy-17α-bromoprogesterone.[13]—To a solution of 1.7 g. of 16-dehydroprogesterone in 80 ml. of tetrahydrofuran and 40 ml. of water, maintained at 0°, was added 1.2 g. of freshly crystallized N-bromoacetamide. After one hour at 0° the reaction mixture was allowed to warm to room temperature and stand for 18 hours. The reaction mixture was then diluted with 1 l. of water containing 1.2 g. of sodium sulfite which was in turn extracted with methylene chloride. The washed and dried methylene chloride extracts were concentrated and the residue was crystallized from ethyl acetate, affording 0.5 g. of 16β-hydroxy-17α-bromoprogesterone, m.p. 175–176°, $[\alpha]^{25}D$ +111.5° (dioxane), $\lambda^{ethanol}_{max}$ 241 mμ (ε 16,600).

Anal. Calcd. for $C_{21}H_{29}O_3Br$: Br, 19.52. Found: Br, 19.55.

Preparation of 16β,17β-Oxidoprogesterone (III).—A solution of 3.0 g. of 16β-hydroxy-17α-bromoprogesterone in 200 ml. of acetone was heated at reflux in the presence of 10 g. of potassium acetate for 17 hours. The reaction mixture was then cooled, the insolubles were removed by filtration and the filtrate was concentrated to an amorphous residue. The residue was triturated with water, dried and crystallized from hexane affording 1.8 g. of III, m.p. 143–145°. Another recrystallization from hexane gave III, m.p. 144–146°, $\lambda^{ethanol}_{max}$ 241 mμ (ε 16,200), $[\alpha]^{25}D$ +69.8° (chloroform), $[\alpha]^{25}D$ +64.8° (dioxane) [Gansau[7] gives m.p. 150–151°, $[\alpha]^{25}D$ +65.2° (chloroform), $\lambda^{methanol}_{max}$ 242.5 mμ (ε 16,520)].

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H. 8.77. Found: C, 76.54; H, 8.50.

Reaction of Hydrogen Fluoride with 16β,17β-Oxido-17-iso-progesterone (III) to Give IV.—Two grams of III was treated as described for the conversion of I into II, except that the temperature was maintained at −5 to −10°. The same cherry-red phase separated as noted previously. The product was crystallized from ether affording 0.6 g. of IV, m.p. 132°. Additional crystallization from ether raised the m.p. to 134–136°, $\lambda^{ethanol}_{max}$ 238 mμ (ε 17,300), $[\alpha]^{25}D$ +136° (chloroform), $[\alpha]^{25}D$ +140.8° (dioxane); λ^{max}_{Nujol} 2.92 (OH), 5.90 (20-carbonyl), 6.00 (3-carbonyl), 6.16 μ (Δ^4).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.77. Found: C, 76.89; H, 8.50.

Acetylation of IV with acetic anhydride in pyridine solution at room temperature overnight afforded the acetate; after crystallization from acetone–hexane, m.p. 169–171°, $\lambda^{ethanol}_{max}$ 238 mμ (ε 17,200), $[\alpha]^{25}D$ +156.9° (dioxane), $[\alpha]^{25}D$ +159.4° (chloroform); λ^{max}_{Nujol} 5.76 (acetate carbonyl), 5.86 (20-carbonyl), 5.97 (3-carbonyl), 6.19 (Δ^4), 8.06 μ (COC).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.87; H, 8.24.

The *p*-toluenesulfonate of IV (prepared at 0° in pyridine solution), after crystallization from ether–hexane and from methanol, melted at 175–178°; $\lambda^{ethanol}_{max}$ 228 mμ (ε 25,400), inflection 245 mμ; $[\alpha]D$ 63.8° (dioxane).

Anal. Calcd. for $C_{28}H_{34}O_5S$: C, 69.68; H, 7.10; S, 6.64. Found: C, 69.78; H, 7.18; S, 6.49.

Microbiological Transformation of VI into IV and a 4,5-Dihydro Derivative of IV.—*Flavobacterium dehydrogenans* was grown in a 1% Difco yeast buffered solution (10 g. of Difco yeast, 4.68 g. of disodium hydrogen phosphate, 4.48 g. of potassium dihydrogen phosphate) with shaking and illumination for 20 hours. To the culture was then added 0.500 g. of VI in 20 ml. of methanol and the transformation was allowed to proceed with shaking and illumination for 12 hours. The steroidal products were separated by extraction with chloroform, the extracts were concentrated, taken up in a minimum volume of methylene chloride and chromatographed on 20 g. of Florisil prepared with hexane. Elution with hexane and mixtures of ether and hexane removed oily contaminants and elution with ether afforded a series of crystalline fractions. These were pooled and recrystallized from acetone–hexane yielding 0.138 g. of IV, m.p. 123–126° (with a transition at 108°). Additional recrystallization from ether raised the m.p. to 128–129°. The infrared spectrum of IV so obtained was identical with that prepared from III.

When an incubation with 1.0 g. of VI was carried out exactly as before except that the time of exposure of steroid was 26 hours, extraction and chromatography afforded in the 50% ether-in-hexane and 100% ether fractions a total of 0.208 g. of solid, m.p. 163–166°. Recrystallization from ether–hexane gave 0.168 g., m.p. 167–169°. Paper chromatography in the toluene–propylene glycol system revealed that one ultraviolet-absorbing and two non-ultraviolet-absorbing products (phosphomolybdic acid reagent) were present. Rechromatography of 0.104 g. of the mixture on 15 g. of Florisil and elution with 25% ether-in-hexane and 50% ether-in-hexane afforded a series of crystalline fractions which were not ultraviolet-absorbing and were homogeneous in the toluene–propylene glycol system. These were combined and recrystallized from ether–hexane to give 0.049 g., m.p. 172–173, $[\alpha]^{25}D$ +93° (chloroform), $[\alpha]^{25}D$ +104° (dioxane); λ^{max}_{Nujol} 2.95 (OH), 5.88, 5.92 μ (3- and 20-carbonyl).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.47; H, 9.20.

The configuration at 5 has not been assigned. In other respects we assume the structure derives from IV.

Microbiological Transformation of V into II and the 4,5-Dihydro Derivative of II.—From 0.500 g. of V, in a 12-hour fermentation as described for VI, followed by chromatography on Florisil and elution with ether, there was isolated 0.127 g. of needles, m.p. 122–125°. Rechromatography on 15 g. of Florisil afforded, in the 50% ether-in-hexane fractions, crystalline material, m.p. 133–138°. Recrystallization from acetone–hexane gave 35 mg. of II, m.p. 138–140°, the infrared spectrum of which matched that of II prepared from I.

When an incubation with 1.04 g. of V was carried out exactly as before except that the time of incubation of the steroid was extended to 24 hours, extraction and chromatography afforded 394 mg. of oily solid (25% and 50% ether-in-hexane fractions). Two recrystallizations from ether–hexane gave 0.230 g., m.p. 151–153°. Paper chromatogra-

(11) The n.m.r. spectrum of the rearrangement product from 5-pregnene-3β,17α,20β-triol-3,20-diacetate[8] has now been measured and is consistent with the previously assigned structure, 18-nor-17β-methyl-17-iso-5,12-pregnadiene-3β,20-diol diacetate.

(12) All m.p.'s are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of Schering Corp. We are indebted to Mr. Richard Wayne for the interpretation of the infrared spectra.

(13) By the method of B. Löken, *et al.*, THIS JOURNAL, **78**, 1738 (1956).

phy in toluene–propylene glycol showed trace amounts of II and a large amount of a non-ultraviolet-absorbing product (phosphomolybdic acid spray reagent). Rechromatography of 0.104 g. of the recrystallized solid on 15 g. of Florisil gave, in the 50% ether-in-hexane fractions, 0.033 g., m.p. 151.5–153° (transition at 146°) which was homogeneous, $[\alpha]^{25}D$ +144.9° (dioxane), $[\alpha]^{25}D$ +37.4° (chloroform); λ_{Nujol}^{max} 2.92 (OH), 5.88, 5.92 μ (3- and 20-carbonyl).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.44; H, 8.55.

The configuration at 5 has not been assigned. In other respects we assume that the structure derives from II.

Nuclear Magnetic Resonance Spectra.—The nuclear magnetic resonance spectra were determined using a Varian Associate model 4300 V high resolution spectrometer with super stabilizer and spinning sample. The resonance frequencies are reported in c.p.s. at 40 mc. relative to chloroform and were determined *via* the procedure given by Shoolery and Rogers.[5] Vinyl proton areas were measured relative to the area of the quaternary methyl protons. In all cases deuteriochloroform was used as solvent and the reference was chloroform added to the sample in a capillary tube.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. V. The Reaction of Cholestane-3-one with Diazomethane[1]

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The reaction of cholestane-3-one with diazomethane afforded A-homocholestane-4-one as the major product. This seven-membered ring ketone was shown to be identical with the ketone obtained from the Tiffeneau ring enlargement of 3-hydroxy-3-aminomethylcholestane. A-Homocholestane-3-one and A-bishomocholestanone were isolated as minor products from the diazomethane ring enlargement reaction. A-Homocholestane-3-one was synthesized by an unambiguous method involving bis-homologation of 2,3-secocholestane-2,3-dioic acid *via* the Arndt–Eistert sequence and pyrolysis of the thorium salt of the resulting diacid. A-Homocholestane-4-one was converted to the 3-hydroxymethylene derivative, thus illustrating the position of substitution in base-catalyzed reactions of this system.

In continuation of our work on the modification of steroidal A-rings[3] we wish to describe methods for the elaboration of A-homosteroids having an oxygen substituent at the 3- or 4-position. The studies, performed on cholestane derivatives, are of such a nature as to be applicable to the preparation of A-homosteroidal hormones.

The one-step ring expansion of a cyclic ketone with diazomethane offers an attractive route to homologous ketones provided the desired product can be separated from unchanged starting material and other products. Under the proper reaction conditions, the predominant product from a six-membered ring ketone will be the seven-membered ring homolog.[4] In the case of an unsymmetrically substituted cyclohexanone (*e.g.*, cholestane-3-one), two seven-membered ring ketones are theoretically possible. However, in similar rearrangement reactions carried out in the D-homosteroid series, it has been shown[5] that a preponderance of one isomer is usually formed. An A-homocholestanone has been synthesized (previously by a Tiffeneau ring-enlargement reaction), but the position taken by the keto group was not determined.[6]

In our work, the first method investigated for the preparation of A-homocholestanones involved the direct ring expansion of cholestane-3-one (I) with diazomethane. The ketone I was treated with a large excess of diazomethane generated *in situ* from N-methylnitrosourea. The product was a mixture from which the seven- and eight-membered ring ketones II–IV were isolated by chromatography. The infrared spectra of the ketones differed in the fingerprint region and this provided a means of telling which fractions collected in the chromatogram represented sufficiently pure material to be combined. A-Homocholestane-3-one (III) exhibits two bands of very weak intensity at 1333 and 1315 cm.$^{-1}$. A-Homocholestane-4-one (II), on the other hand, shows one absorption band at 1333 cm.$^{-1}$. A-Bishomocholestanone (IV) possesses a single band at 1320 cm.$^{-1}$. After chromatography the yields of crude ketones showing these spectral characteristics were II, 40–50%; III, 10%; and IV, 5%. Recrystallization of these compounds to constant melting points gave 27% of II, 0.5–1% of III and 2% of IV.

It was expected that the Tiffeneau ring enlargenent of cholestane-3-one should give as the main ketonic material a substance identical with the major ketone isolated from the diazomethane reaction, because of the similarity of the reaction mechanisms involved. Cholestane-3-one cyanohydrin acetate (V)[6] was reduced with lithium aluminum hydride and the product isolated as the oxazolidine derivative VI. Hydrolysis and deamination of VI with nitrous acid gave a ketone which was purified through its semicarbazone derivative and chromatography. The ketone was shown to be identical with II by a mixed melting point determination and comparison of their infrared spectra. This synthesis also established that compound II from the diazomethane ring enlargement of I is a seven-membered ring ketone.[7]

(1) Abstracted from the thesis submitted by Robert N. Schut to the Massachusetts Institute of Technology, 1958, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Public Health Service Research Fellow of the National Cancer Institute, 1955–1958.

(3) N. A. Nelson and R. N. Schut, THIS JOURNAL, **80**, 6630 (1958).

(4) C. D. Gutsche and H. H. Peter, *ibid.*, **77**, 5871 (1955).

(5) See, for example, N. L. Wendler, D. Taub and H. L. Slates, *ibid.*, **77**, 3559 (1955), and R. O. Clinton, R. G. Christiansen, H. C. Neumann and S. C. Laskowski, *ibid.*, **79**, 6475 (1957).

(6) M. W. Goldberg and H. Kirchensteiner, *Helv. Chim. Acta*, **26**, 288 (1943).

(7) An elemental analysis, within experimental error, does not allow one to distinguish between seven-, eight- or nine-membered ring ketones of this homologous series.