(551 mg, 1 mmol) in 20 ml of dimethylformamide containing 1.1 ml of 2 *N* HCl over 100 mg of 10% palladium-on-charcoal catalyst, filtration through Celite, and removal of solvent under reduced pressure afforded a colorless solid which was treated with 3 ml of 1 *N* ethanolic HCl, and filtered. The filtrate was immediately treated with 5 ml of pyridine and cooled. The crude peptide hydrochloride separated as an amorphous solid which crystallized from water–methanol in two crops totaling 201 mg (88%): homogeneous on tlc (C,D); $[\alpha]^{25}D$ +69.1° (*c* 1.06, H_2O) [lit.[15] $[\alpha]^{20}D$ +69.5° (*c* 1.0, H_2O)].

Acknowledgments.—We are grateful to the National Institutes of Health for Predoctoral Fellowship 5 F01 GM 43911-03 granted to one of us (F. G.) by the General Medical Science Unit and to the Sloan Basic Research Fund (Grant No. 27609) for general support. We also wish to thank Mr. J. Farrington, Department of Chemistry, Boston College, for his assistance in the hydrogen fluoride reaction.

Registry No.—**4**, 21240-34-6; **5**, 40719-46-8; **7**, 40719-47-9; **8**, 40719-48-0; benzoin, 119-53-9; desyl chloride, 447-31-4; tetramethylammonium hydroxide, 75-59-2; 1,1,3,3-tetramethylguanidine, 80-70-6; 2-phenethylamine 4,5-diphenyl-4-oxazolin-2-one derivative, 37628-64-1; 2-phenethylamine, 64-04-0; Ox-L-Ala-Gly-OEt, 37628-68-5; glycine ethyl ester hydrochloride, 623-33-6; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 25952-53-8; Ox-L-Val-L-Val-OMe, 40719-51-5; Ox-L-Phe-Gly-OEt, 40719-52-6; Ox-L-Phe-L-Val-OMe, 40719-53-7; Ox-L-Ser-L-Ser-OMe, 40719-54-8; Ox-L-Ala-Gly-OEt hydrolysis derivative, 40719-55-9; L-valyl-L-valine, 3918-94-3; L-alanylglycine, 687-69-4; L-phenylalanylglycine, 721-90-4; L-phenylalanyl-L-valine, 3918-90-9; α-carbobenzoxy-L-lysine, 2212-75-1; dicyclohexylamine, 101-83-7; α-carbobenzoxy-ε-Ox-L-lysylglycine dicyclohexylammonium salt, 40719-56-0; ε-Ox-L-Lys-Gly-OEt·HBr, 40719-57-1; L-lysylglycine hydrochloride, 40719-58-2.

15-Oxa Steroids

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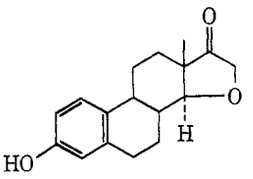
The preparation of the 15-oxa steroid **29** is described, using the half-ester 3β-acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic acid 17-methyl ester (**5b**) as starting material. Treatment of **5b** with lead tetraacetate affords the diacetate **9** which upon hydrolysis and reacetylation gave the acid **26**. Conversion to the diazo ketone **28** followed by treatment with boron trifluoride causes spontaneous ring closure to give 3β-hydroxy-15-oxa-5α-androstan-17-one (**29**). Its conversion to 15-oxaestrone (**1**) is described.

The steroid nucleus has over the past number of years undergone numerous structural modifications in an attempt to bring about an increase in biological activity as well as attempting to control or minimize undesirable side effects. One such modification is the insertion of an oxygen atom in place of a methylene group. This type of transformation has in several cases produced derivatives possessing interesting biological properties.[1] A review of the publications in this field reveals that the introduction of an oxygen atom into the steroid nucleus has produced synthetic modifications which can be generally classified into two main categories. The first of these is the formation of a lactone *via* an oxygen insertion α to a keto group.[2-4] This type of transformation would be expected to alter considerably the chemical nature of the original carbonyl function.

In the second category, the oxa steroid takes the form of a cyclic ether. In this class of compounds the heteroatom takes the place of a carbon atom in a position which is known to effect greatly the biological activity of the parent steroid, *e.g.*, C-11, C-17.[5,6]

The aim therefore of this present work was to prepare an oxa steroid in such a manner so as to (1) not compromise the functionality of the original carbonyl groups, and (2) replace a methylene for an oxygen atom while at the same time not affecting those positions which are known to be essential for biological activity. Such a compound is represented by structure **1**.



1

The starting material in our synthesis was 3β-hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic acid (**3**) which was obtained from the reaction of 3β-hydroxy-5α-androstan-17-one (**2**) with *o*-nitrobenzaldehyde.[7] Esterification and acetylation of **3** afforded **4b** which has been reported to give 3β-acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic acid 17-methyl ester (**5b**) when oxidized with chromium trioxide in acetic acid[3,8] (Scheme I).

We have found that the chromium trioxide oxidation of **4b** produced an acid whose melting point of 152–158° differed sharply from the reported figure of 204°[3] but was in fact consistent with a second reported value of 158–160°.[8] As a means of verifying structure **4**, and the acid ester obtained from its oxidation with chromium trioxide, a reductive ozonization was carried out which produced the aldehyde **6** in high yield. The nmr confirmed both the secondary nature of the aldehydic group and the axial conformation of the C-14 proton: δ 9.72 (d, 1, J = 3.5 Hz, CHO), 2.58 (d of d, 1, J = 3.5, 11 Hz, C-14 H). Furthermore, chromium trioxide oxidation of the alde-

(1) (a) S. D. Levine, *J. Med. Chem.*, **8**, 537 (1965); (b) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962); (c) H. D. Lennon and F. J. Saunders, *Steroids*, **4** (1964).

(2) R. W. Kierstead and A. Farone, *J. Org. Chem.*, **32**, 704 (1967).

(3) A. K. Banerjee and M. Gut, *J. Org. Chem.*, **34**, 1614 (1969).

(4) C. C. Bolt, *Recl. Trav. Chim. Pays-Bas*, **70**, 940 (1957).

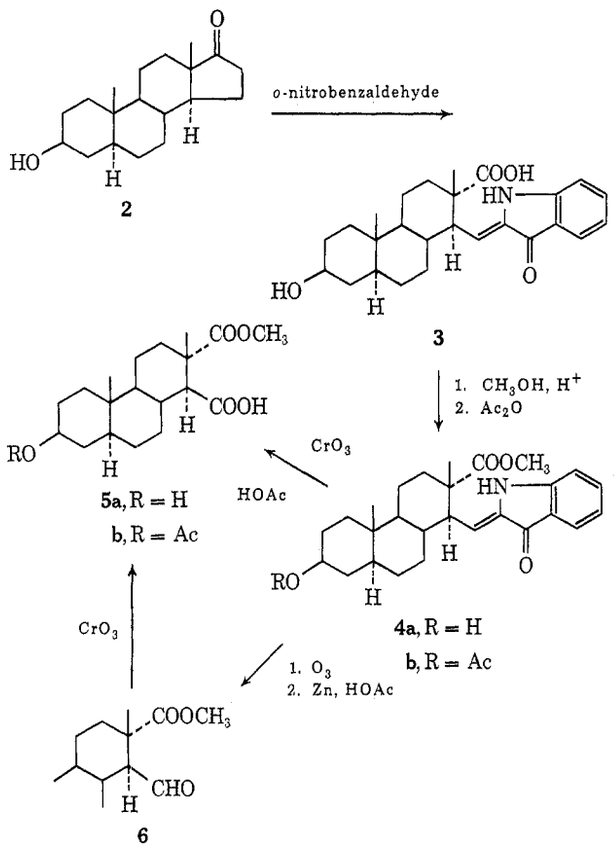
(5) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

(6) Ch. R. Engel and M. V. R. Chowdhury, *Tetrahedron Lett.*, 2107 (1968).

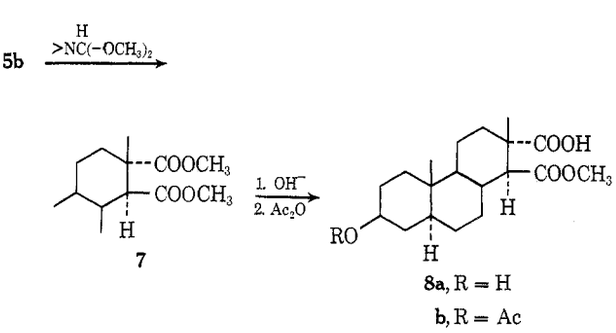
(7) A. Hassner, M. J. Haddadin, and P. Catsoulaces, *J. Org. Chem.*, **31**, 1363 (1966).

(8) M. Fetizon and N. Moreau, *Bull. Soc. Chim. Fr.*, 4385 (1969).

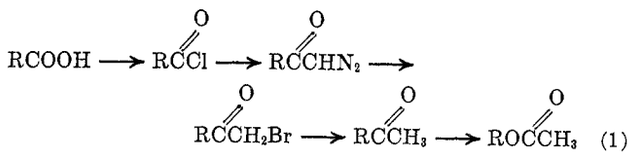
SCHEME I



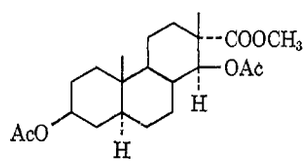
hyde **6** afforded the same acid ester **5b** (mp 160°)[8] which we had obtained directly from the oxidation of **4b**: δ 3.65 (s, 3, $COOCH_3$). Esterification of **5b** with the dimethyl acetal of dimethylformamide produced the dimethyl ester **7** which, after partial hydrolysis and reacetylation of the 3β-hydroxyl group, gave a monoester derivative with a melting point (204°) corresponding to that previously reported[3] for **5b**: δ 3.60 (s, 3, $=COOCH_3$). This material was found to be identical with a sample previously assigned structure **5b**.[9] The nmr spectrum of a mixture of the two acid esters showed two distinct methoxyl peaks: δ 3.59, 3.65. Since it would be generally safe to assume that the hydrolysis of a secondary ester should take place with greater facility than a tertiary ester, the



partial hydrolysis of **7** would have been expected to give rise to **5a** rather than the isomeric derivative **8a**.

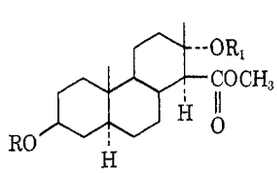


Using a multistep sequence of reactions (1), the degradation of the acid ester (mp 204°) has previously been carried out and reported to give a diacetate represented by formula **9**.[10]



9

This procedure was repeated using the acid ester which we had obtained from the partial hydrolysis of dimethyl ester **7**, and the physical properties of the product obtained were found to be identical with those of a sample previously assigned structure **9**.[9] Inspection of the nmr, however, reveals a broad multiplet at δ 4.8 (1, C-3 H) and a doublet at 2.85 (1, J = 10 Hz, C-14 H). Although the coupling constant is consistent with a C-14 axial hydrogen, the observed chemical shift presumably due to the presence of an acetoxy group at C-14 is much further upfield than one would have anticipated. The nmr would, however, be consistent with the isomeric diacetoxy compound **10a**.



10a, R = R_1 = $COCH_3$
b, R = $COCH_3$; R_1 = H
c, R = R_1 = H

Since the conversion to the diacetate was a multistep process, we attempted to degrade the same acid chloride to the acetate by a carboxy-inversion reaction.[11] It has been found that mixed peroxides derived from *m*-chloroperbenzoic acid rearrange to the mixed carbonate which can then be hydrolyzed to the alcohol.

Using this procedure we were able to obtain (after acetylation) a 55% yield of a monoalcohol whose nmr reveals a broad multiplet at δ 4.66 (1, C-3 H) and a doublet at 2.2 (1, J = 11 Hz, C-14 H). This result would indicate that the structure of the monoalcohol is in fact **10b** and is therefore derived from the acid chloride **11** *via* the peranhydride **12** and the mixed carbonate **13** (Scheme II).

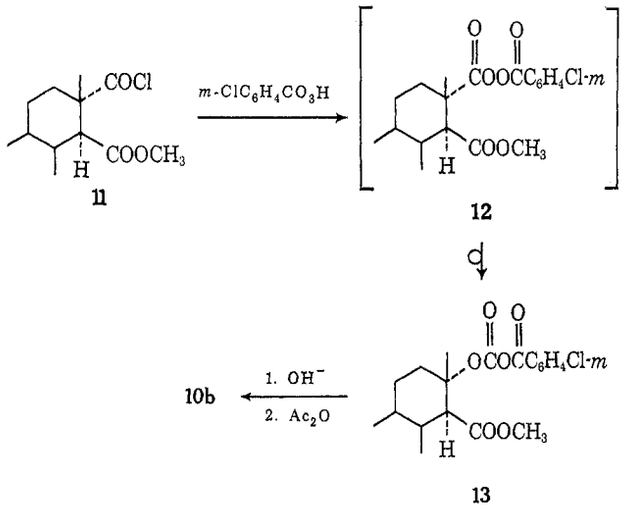
In addition a by-product was obtained which had an observed *m/e* 334 molecular ion peak and an nmr spectrum which reveals a broad multiplet at δ 4.68 and two broad singlets at 4.43 and 4.74. From this data

(9) Kindly supplied by Dr. M. Gut, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

(10) A. K. Banerjee and M. Gut, *Tetrahedron Lett.*, 51 (1969).

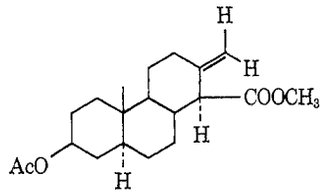
(11) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965).

SCHEME II



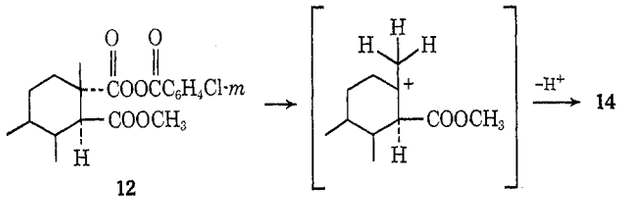
11 12 13

we are able to deduce the structure of this compound to be **14**.



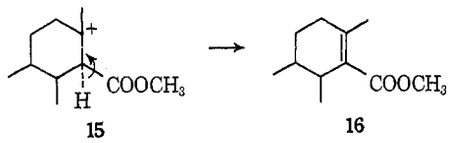
14

Since the carboxy-inversion reaction is depicted as proceeding through a carbonium-ion-type intermediate,[11] one could simply envisage that the formation of **14** takes place *via* a tertiary carbonium ion **15** derived from the mixed peroxide **12**.



12 15

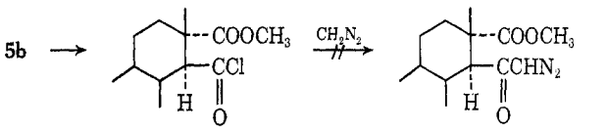
A mechanism which is better identified with a concerted E2 elimination may, however, have greater justification than an E1 intermediate which is depicted by formula **15**. If, in fact, **15** is a true intermediate, it is difficult to see why the product of the reaction is not the tetrasubstituted olefin **16**. An E2-type elimination on **12** would require the loss of a proton from the methyl group since loss of the C-14 H to give **14** would constitute a cis elimination.



15 16

The isolation of the methylene derivative **14** together with the previously discussed anomalous nmr data for the diacetoxy and the monoacetoxy compounds clearly suggests that the acid ester (mp 204°) described in the literature[3] was erroneously reported to be compound **5b** and is in fact the isomer **8b**. Furthermore, the diacetoxy compound which was obtained from the degradation of **8b** must have structure **10a** which would be consistent with the observed nmr.

When the conversion of **5b** (mp 163°) to the diacetoxy compound **9** was attempted, it was found that the acid chloride **17** *did not* react with diazomethane to form the diazo ketone **18**.

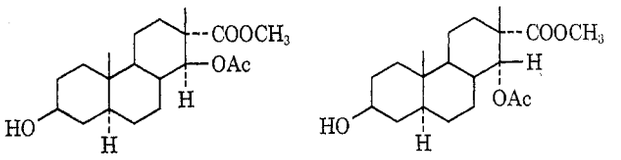


17 18

Since the formation of the diazo ketone must take place by an initial attack at the carbonyl carbon of the acid chloride, the unreactivity of **17** is quite consistent with the result obtained from the partial hydrolysis of **7** to give **8**. Here then is an example of a carbonyl function of a tertiary ester showing a greater degree of reactivity than the carbonyl function of a less substituted secondary ester.[12] Based on these results it was apparent, therefore, that the degradation of **5** to the diacetate **9** could not be accomplished by an initial reaction which would require a reagent addition to the carbonyl carbon of the acid.

The oxidation of an acid with lead tetraacetate has been shown to give rise to an olefin, an acetoxy compound, or a combination of both. The initial step is an attack at the hydroxyl oxygen atom which derivative **19** then purportedly breaks down to a carbonium-ion intermediate **20**.[13] When this reaction was applied to **5b**, all of the anticipated products which could arise from a carbonium-ion intermediate **20** were indeed found (Scheme III).

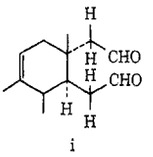
The total crude reaction mixture (**9**, **21**, and **22**) was partially hydrolyzed, to give the desired 3β-hydroxy derivate **23** in 60% yield as well as a small amount of its isomer **24**.



23 24

Reacetylation of **23** afforded the diacetate **9**. The nmr of **23**, δ 4.98 (d, 1, J = 10 Hz), is consistent with the position of the acetoxy group (C-14) and its equitorial conformation. The nmr of **24**, δ 5.14 (d, 1, J = 2 Hz), clearly indicates the axial conformation of the acetoxy group. Compound **22** (obtained by column chromatography before hydrolysis) is believed to be a 1:1 mixture of the $\Delta^{8(11)}$ and $\Delta^{7(8)}$ olefins.

(12) A similar selectivity has previously been postulated for the dialdehyde i [R. B. WOODWARD, *et al.*, *J. Amer. Chem. Soc.*, **74**, 4223 (1962)]. Based on

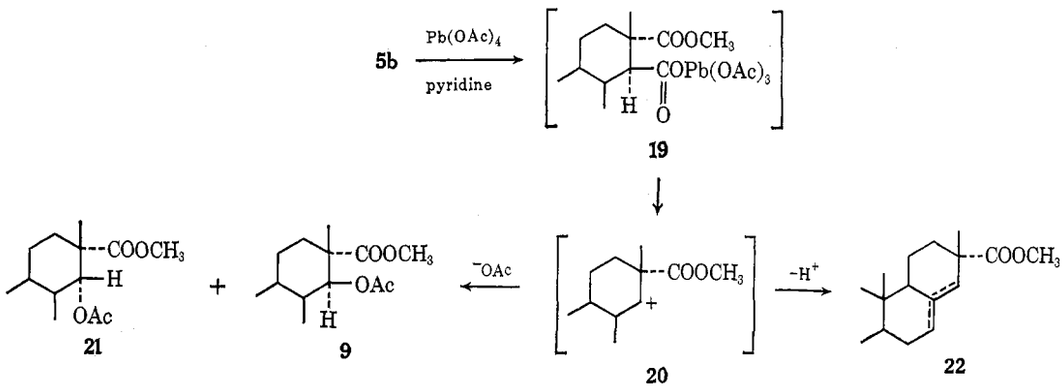


i

model studies, it was concluded that the upper activated methylene group was relatively less crowded compared with the lower.

(13) E. J. Corey and J. Casanova, Jr., *J. Amer. Chem. Soc.*, **85**, 165 (1963).

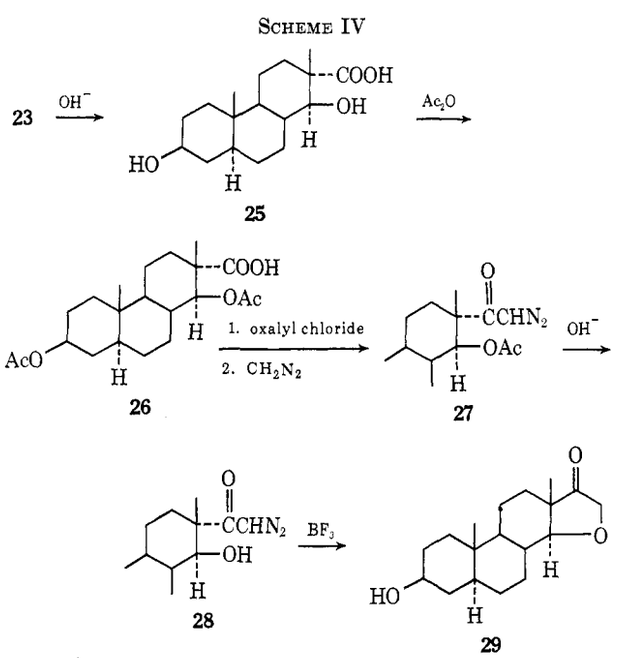
Scheme III



The nmr spectra of **22** reveals two equal singlets for each of the C-10 and C-13 methyl groups as well as weak absorption in the olefinic region.

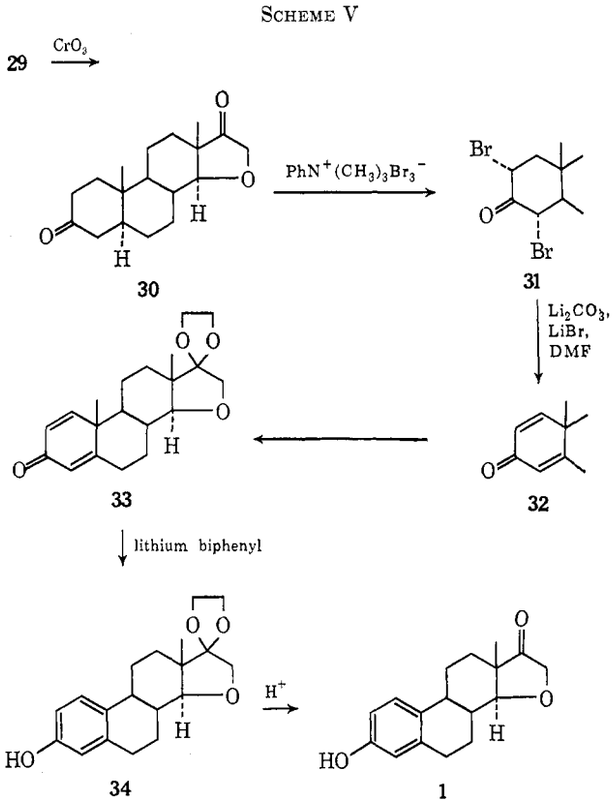
Compound **23** was hydrolyzed to the dihydroxy acid **25** which was reacetylated to give the diacetate **26**.[14] Compound **26** was converted to the diazo ketone **27** *via* the acid chloride and then hydrolyzed to the hydroxy derivative **28** (both **26** and **27** were used as crude intermediates). Treatment of a suspension of **28** in benzene with boron trifluoride etherate afforded **29** in excellent yield[15] (Scheme IV).

Scheme IV



We next turned our attention to the conversion of **29** to the estrone derivative **1**. Oxidation of **29** afforded the diketone **30** which with 2 equiv of phenyltrimethylammonium perbromide gave the diequatorial dibromide **31**. Dehydrobromination afforded the dienone **32** which was then ketalized to give **33**. Aromatization of **33** was accomplished by treatment with lithium biphenyl[16] and the crude estrone derivative **34** was deketalized to give the 15-oxaestrone **1** (Scheme V). The biological activity of **1** and the

Scheme V

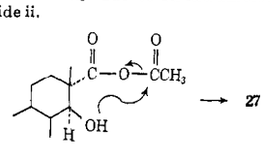


various analogs derived from **1** will be reported elsewhere.

Experimental Section[17]

3β-Hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic acid (3) was obtained from isoandrosterone as previously described (59%), mp 272–274° (lit.[7] mp 258–260° dec).

(14) The ability to acetylate the highly hindered C-14 hydroxyl group of compound **26** is most likely due to an intramolecular trans-acetylation *via* the mixed anhydride ii.



ii

(15) This reaction is an intramolecular version of the general route to α-alkoxy ketones from diazo ketones and alcohol in the presence of a catalytic amount of boron trifluoride etherate: M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, **72**, 5161 (1952).

(16) H. L. Dryden, Jr., G. M. Webber, and J. J. Wieczorek, *J. Amer. Chem. Soc.*, **86**, 742 (1964).

(17) All melting points were taken in glass capillaries and are corrected. The nmr spectra were determined using a Varian A-60 spectrometer with tetramethylsilane as the internal standard. The high-resolution mass spectra were obtained with a Consolidated Electrodynamics Corporation 21-110 mass spectrometer.

3β-Hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic Acid 17-Methyl Ester (4a).—To a mixture of 356 g of **3** in 3 l. of methanol was added dropwise 40 ml of acetyl chloride. After the mixture refluxed for 4 hr, the methanol was removed under reduced pressure and 2 l. of water was added to the residue. The resulting precipitate was filtered, washed with water, and dried. The product was then dissolved in a minimum of methylene chloride and treated with Norit and dried ($MgSO_4$). The mixture was filtered and the methylene chloride removed under reduced pressure. Trituration of the residue with ether afforded 325 g (87%) of **4a**, mp 258–261° (lit.[7] mp 263–265°).

3β-Acetoxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic Acid 17-Methyl Ester (4b).—A solution of 325 g of **4a**, 325 ml of acetic anhydride, and 1300 ml of pyridine was stirred overnight. The mixture was divided into three portions and each then was added to 3 l. of cold (0°) 3 *N* hydrochloric acid. The resulting precipitates were filtered and the combined product was washed with water and dried to give 350 g (93%) of **4b**, mp 260–262° (lit.[7] mp 261–262°).

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic Acid 17-Methyl Ester (5b).—To a suspension of 350 g of **4b** in 5 l. of glacial acetic acid was added dropwise 290 ml of a 90% aqueous chromium trioxide solution.[18] Solution soon occurred with the evolution of heat (the temperature was kept below 70° with external cooling). After the solution was stirred overnight, the acetic acid was removed under high vacuum and the residue treated with 4 l. of water. The precipitate was filtered, washed thoroughly with water, and dried. The product was then dissolved in benzene and the solution treated with Norit and anhydrous magnesium sulfate. The mixture was filtered and the benzene removed under reduced pressure. Trituration of the residue with hexane afforded 250 g (98%) of **5b**, mp 152–158° (lit.[8] mp 158–160°).

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15-formyl-17-oic Acid Methyl Ester (6).—A solution of 5 g of **4b** in 500 ml of methylene chloride was cooled to −70° and ozonized until the appearance of a blue-green coloration. The solution was then purged with a nitrogen stream and the resulting yellow solution added dropwise at 0° to a suspension of 12.5 g of zinc in 50 ml of glacial acetic acid. After stirring for 3 hr at 0°, the mixture was filtered and most of the solvent removed under reduced pressure. Water was added to the residue and the mixture extracted with methylene chloride. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Trituration of the residue with ether gave 3.4 g (92%) of **6**, mp 148–151°. Crystallization from methanol afforded an analytical sample, mp 152–154°, $[\alpha]^{25}D$ +12.49° (*c* 0.9927, $CHCl_3$).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.96; H, 8.90.

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic Acid Dimethyl Ester (7).—A solution of 500 mg of **5b** and 470 mg of dimethylformamide dimethyl acetal in 5 ml of dry benzene was refluxed for 15 min. The solution was cooled, diluted with ether, and washed successively with 0.1 *N* hydrochloric acid, water, and saturated sodium chloride solution. The ether solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Crystallization from petroleum ether (30–60°) afforded 400 mg (83%) of **7**, mp 119–121° (lit.[3] mp 120–121°).

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic Acid 15-Methyl Ester (8b).—To a solution of 600 ml of methanol and 600 ml of 6% aqueous potassium hydroxide was added 75 g of **7**. The resulting mixture was refluxed for 4.5 hr, followed by removal of the methanol under reduced pressure. The remaining aqueous solution was then cooled (0°) and acidified (pH ~3) with 1 *N* hydrochloric acid. The product was filtered and air dried to give 64.5 g (99%) of the 3β-hydroxy derivative **8a**, mp 230–232° [lit.[3] (incorrectly assigned as **5a**) mp 234–235°].

To a solution of 97.5 ml of acetic anhydride and 97.5 ml of pyridine was added 64.5 g of the above alcohol **8a**. The mixture was stirred for 6 hr and then diluted at 0° with 130 ml of methanol and 97.5 ml of 2 *N* hydrochloric acid. After stirring for 30 min at 0°, the mixture was then poured into 4 l. of water. The precipitate was filtered, washed thoroughly with water, and dried. Crystallization from ether–hexane afforded three crops of product **8b**: 45.2 g, mp 209–211°; 15.1 g, mp 209–211°; and 4.8 g, mp 208–210°. The total yield of **8b** was 65.1 g (90%) [lit.[3] (incorrectly assigned as **5b**) mp 205–207°].

(18) This solution is prepared by dissolving 90 g of chromium trioxide in 100 ml of water.

Reaction of the Acid Chloride 11 with *m*-Chloroperbenzoic Acid. Formation of 10b, 10c, and 14.—To 1 ml of oxalyl chloride was added 1 g of **8b**. The solution was stirred at room temperature for 4 hr and the excess oxalyl chloride then removed under reduced pressure. Hexane was added to the residue and the solvent again removed under reduced pressure to give 500 mg of the acid chloride **11**, mp 99–101° [lit.[10] (incorrectly assigned as **17**) mp 94°]. The acid chloride was then dissolved in 25 ml of dry ether to which was added at 0° 474 mg of *m*-chloroperbenzoic acid (98% purity) and 0.22 ml of pyridine. After the mixture was stirred overnight at 0°, the precipitated pyridine hydrochloride was filtered off and washed with ether. The combined filtrate was washed with 1 *N* hydrochloric acid followed by 5% sodium bicarbonate solution. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was then dissolved in 13 ml of 1 *N* methanolic potassium hydroxide and was stirred at room temperature for 0.5 hr. To the solution was added 50 ml of water and the resulting mixture extracted with methylene chloride and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue triturated with ether to give 370 mg of 3β,13α-dihydroxy-13,15-seco-*D*-bisnor-5α-androstan-15-oic acid methyl ester (**10c**), mp 168–172°, contaminated with a small amount of **14**. Acetylation afforded **10b**, mp 133–134°, $[\alpha]^{25}D$ −29.18° (*c* 1.0966, $CHCl_3$).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.06; H, 8.89.

The solvent from the above mother liquor was removed under reduced pressure and the residue acetylated with 0.45 ml of pyridine and 0.45 ml of acetic anhydride. To the solution was added 10 ml of water and 0.5 ml of 2 *N* hydrochloric acid and the resulting mixture was extracted with ether. The ether solution was washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 310 mg of material which was chromatographed on 15 g of silica gel. Elution with benzene gave a product which when triturated with pentane afforded 110 mg of 3β-acetoxy-13,15-seco-*D*-bisnor-5α-androst-$\Delta^{13(18)}$-en-15-oic acid methyl ester (**14**), mp 122–125°, $[\alpha]^{25}D$ −16.9° (*c* 0.2120, $CHCl_3$).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.03. Found: C, 71.99; H, 9.17.

Reaction of 5 with Lead Tetraacetate. Preparation of 9, 22, 23, and 24.—A mixture of 255 g of **5b**, 745 g of lead tetraacetate,[19] 108 ml of pyridine, and 3.8 l. of dry benzene was stirred and refluxed for 7 hr. The mixture was cooled and the lead salts were filtered and thoroughly washed with ether. The filtrate was washed with a 10% solution of sodium thiosulfate, 1 *N* hydrochloric acid, and then a saturated sodium chloride solution. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 270 g of crude product. One gram of material was chromatographed on 25 g of silica gel. Elution with benzene afforded a small amount of **22**. The remaining material was then dissolved in a minimum of benzene and washed through 1300 g of neutral alumina (grade I). Elution with 3 l. of benzene followed by 1 l. of a 1% ethyl acetate benzene solution afforded 215 g of crude material. This product was then dissolved in 1.23 l. of 3% methanolic potassium hydroxide and stirred at 0° for 1 hr. The mixture was acidified with 700 ml of 1 *N* hydrochloric acid at 0° and the precipitate filtered and dried to give 108 g of 3β-hydroxy-14β-acetoxy-14,17-seco-*D*-bisnor-5α-androstan-17-oic acid methyl ester (**23**), mp 127–130°. The methanol was removed from the filtrate under reduced pressure, the mixture extracted with methylene chloride, and the resulting solution dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue triturated with methanol to give 2 g of **23**, mp 126–130°. A third crop of 3 g, mp 124–128°, of **23** was obtained by removing a portion of the methanol under reduced pressure. The total yield of **23** was 113 g (49%). Crystallization from methnaol afforded an analytical sample containing 1 mol of methanol, mp 134–136°, $[\alpha]^{26}D$ −164.76° (*c* 1.1113, $CHCl_3$).

Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.59; H, 9.44. Found: C, 65.85; H, 10.09.

Acetylation with pyridine–acetic anhydride afforded the 3β-acetoxy derivate **9**, mp 105–106°, $[\alpha]^{25}D$ −16.23° (*c* 0.7579, $CHCl_3$).

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.11; H, 8.93.

(19) The lead tetraacetate was placed under high vacuum over phosphorus pentoxide for 24 hr prior to use.

The mother liquor obtained from the above trituration was treated with cyclohexane to give 60 g of crude **24** contaminated with **22**. Crystallization from hexane afforded 23 g (10%) of 3β-hydroxy-14α-acetoxy-14,17-seco-*D*-bisnor-5α-androstan-17-oic acid methyl ester (**24**), mp 140–147°.

A second crystallization from cyclohexane afforded an analytical sample, mp 152–153°, $[\alpha]^{25}D$ −22.82° (*c* 0.5390, $CHCl_3$).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.45; H, 8.99.

3β,14β-Dihydroxy-14,17-seco-*D*-bisnor-5α-androstan-17-oic Acid (25).—A solution of 86 g of **23** in 2.74 l. of 3% methanolic potassium hydroxide was refluxed for 6 hr. The methanol was removed under reduced pressure and 200 ml of water added to the residue. The solution was cooled to 0° and acidified with concentrated hydrochloric acid. The precipitate was filtered and dried to give 72.2 g (98%) of **25**, mp 285–287°. Crystallization from methanol afforded an analytical sample, mp 285–287°, $[\alpha]^{25}D$ +11.94° (*c* 0.9047, CH_3OH).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52. Found: C, 69.16; H, 9.71.

3β,14β-Dihydroxy-16-diazo-17-oxo-14,16-seco-*D*-nor-5α-androstane (28).—To a solution of 350 ml of acetic anhydride in 350 ml of pyridine was added 70 g of **25**. The solution was stirred at room temperature overnight and then poured into 6 l. of ice water. The mixture was stirred for 2 hr and then extracted with ether. The ether solution was washed with 1 *N* hydrochloric acid and then water to neutrality. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 83 g of crude **26** as an oil.

The crude diacetate **26** (83 g) was treated with 90 ml of oxalyl chloride and stirred at room temperature overnight. The excess oxalyl chloride was then removed under reduced pressure, the residue diluted with hexane, and the solvent again removed under reduced pressure to give 85 g of crude acid chloride.

To an ethereal solution of diazomethane prepared from 150 g of *n*-methylnitrosourea was added dropwise with stirring at 0° a solution of 85 g of the crude acid chloride in 200 ml of ether. The solution was stirred at 0° for 2 hr and the solvent and excess diazomethane were then evaporated under a stream of nitrogen. The crude diazo ketone **27** was then added to 790 ml of a 6% methanolic potassium hydroxide solution and stirred at room temperature for 5 hr. The reaction mixture was then cooled to 5° and the precipitate filtered to give 63 g (83%) of **28**, mp 145–150°. Crystallization from ether–methylene chloride afforded an anaytical sample, mp 154–156°, $[\alpha]^{25}D$ −8.46° (*c* 0.9697, $CHCl_3$).

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.47; H, 8.81. Found: C, 67.22; H, 8.91.

3β-Hydroxy-15-oxa-5α-androstan-17-one (29).—To a suspension of 63 g of **28** in 1.2 l. of dry benzene was added dropwise with stirring a solution of 15 ml of boron trifluoride etherate in 20 ml of benzene. The evolution of nitrogen began immediately, and after the addition was completed (~15 min) the reaction was stirred for an additional 10 min. The benzene soluton was then washed with 5% sodium bicarbonate solution and the aqueous extracts were back-washed with ether. The organic layers were then combined, dried ($MgSO_4$), heated with Norit, and then filtered. The solvent was removed under reduced pressure and the residue triturated with hexane to give 54.5 g (92%) of **29**, mp 145–150°. Crystallization from ether–methylene chloride afforded an analytical sample, mp 152–154°, $[\alpha]^{25}D$ +54.07° (*c* 0.5049, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.90; H, 9.82.

Acetylation with pyridine–acetic anhydride followed by crystallization from methanol afforded the 3β-acetoxy derivative, mp 164–167°, $[\alpha]^{25}D$ +45.19° (*c* 0.9249, $CHCl_3$).

Anal. Calcd fof $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.56; H, 8.86.

15-Oxa-5α-androstane-3,17-dione (30).—To a cooled (0°) solution of 10 g of **29** in 100 ml of acetone was added dropwise with stirring 10 ml of Jones reagent. After the addition was complete, the mixture was stirred at 0° for 10 min. The solvent was then removed under reduced pressure and the residue treated with 300 ml of ice water. The precipitate was filtered and washed thoroughly with water and dried. The product was then dissolved in a minimum of methylene chloride and the solution was treated with Norit and filtered. The solvent was removed under reduced pressure to give 9.2 g (93%) of **30**, mp 176–180°. Crystallization from ether–methylene chloride afforded an analytical sample, mp 182–185°, $[\alpha]^{25}D$ +77.39° (*c* 1.1798, $CHCl_3$).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.18; H, 9.01.

2α,4α-Dibromo-15-oxa-5α-androstane-3,17-dione (31).—To a solution of 16.5 g of **30** in 160 ml of dry tetrahydrofuran was added 216 g of phenyltrimethylammonium perbromide. The brominating agent quickly dissolved and after a short time phenyltrimethylammonium bromide began to precipitate. The mixture was stirred for 4.5 hr and the precipitate was filtered and washed with benzene. An additional 100 ml of benzene was added to the filtrate and the resulting solution was then washed with a 5% solution of sodium sulfite and water and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue triturated with cold ether to give 14.2 g (55%) of **31**, mp 212–214°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 213–215° dec, $[\alpha]^{25}D$ +18.05° (*c* 0.9861, $CHCl_3$).

Anal. Calcd for $C_{18}H_{24}Br_2O_3$: C, 48.24; H, 5.40. Found: C, 48.20; H, 5.50.

15-Oxaandrosta-1,4-diene-3,17-dione (32).—To a solution of 19.6 g of lithium bromide and 19.6 g of lithium carbonate in 200 ml of dry dimethylformamide at 95° was added dropwise a solution of 14.7 g of **31** in 150 ml of the same solvent. The mixture was stirred and maintained at 95° for 18 hr and most of the dimethylformamide was then removed under high vacuum. To the residue was then added 200 ml of ice water followed by 50 ml of 1 *N* hydrochloric acid. The precipitated semisolid was then extracted with methylene chloride and the organic layer washed thoroughly with water and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was dissolved in a minimum of methylene chloride and passed through 50 g of neutral alumina (grade I). Elution with methylene chloride gave 9.5 g of crude product which when triturated with ether afforded 7 g (74%) of **32**, mp 181–185°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 185–187°, $[\alpha]^{25}D$ +70.50° (*c* 0.9050, $CHCl_3$).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.77; H, 7.97.

15-Oxaandrosta-1,4-diene-3,17-dione 17-Ethylene Ketal (33).—A mixture of 7 g of **32**, 14 ml of ethylene glycol, 0.28 g of *p*-toluenesulfonic acid, and 350 ml of benzene was placed in a 500-ml flask fitted with a Soxhlet extractor which was charged with Linde 3A Molecular Sieves. After refluxing for 6 hr, the reaction was cooled and washed with a 5% sodium bicarbonate solution and water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue triturated with ether to give 6.5 g (78%) of **33**, mp 147–150°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 147–150°, $[\alpha]^{25}D$ +6.50° (*c* 0.9545, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70, H, 7.93. Found: C, 72.76; H, 7.89.

15-Oxaestrone 17-Ethylene Ketal (34).—To a solution of 86.2 g of biphenyl in 1.5 l. of dry tetrahydrofuran was added 4.35 g of lithium wire. The mixture was stirred at room temperature for 4 hr after which time the lithium had completely dissolved. The dark blue solution was then warmed to 50° and a solution of 25.4 g of **33** and 38.8 g of diphenylmethane in 100 ml of tetrahydrofuran was added dropwise over a period of 30 min. The temperature was maintained at 50–52° and the mixture was stirred for an additional hour. The reaction was then cooled to 0° and 45 g of ammonium chloride was added in small portions (color changed from dark green to light brown). Small pieces of ice were then cautiously added causing the reaction to become colorless, followed by the addition of 100 ml of ice water. The resulting two layers were separated and the aqueous solution was extracted with methylene chloride. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oily residue. Hexane (800 ml) was added and the mixture stirred until precipitation took place. The crude precipitate (25 g) was dissolved in a minimum of methylene chloride and passed through 250 g of silica gel. Elution with 2 l. of methylene chloride gave 0.9 g of a green-tinted by-product, 4 l. of 1% ethyl acetate–benzene gave 7 g of crude product, and 5 l. of a 5% ethyl acetate–benzene gave an additional 8.5 g of material. The combined product (15.5 g) was triturated with hexane–ether to give 12.5 g (54%) of **34**, mp 212–215°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 214–216°, $[\alpha]^{25}D$ +18.99° (*c* 0.8900, $CHCl_3$).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.98; H, 7.53.

15-Oxaestrone (1).—A solution of 12 g of **34**, 250 ml of dioxane, and 20 ml of an 8% aqueous sulfuric acid solution was stirred and refluxed for 4 hr. The solution was cooled and poured into 2 l. of ice water, and the precipitate was filtered. The product was washed thoroughly with water and air dried. The crude material was then dissolved in a minimum of 1:1 methylene chloride–tetrahydrofuran solution, dried ($MgSO_4$), and heated with charcoal. The mixture was filtered and the solvent removed under reduced pressure. The resulting residue was triturated with ether to give 9.2 g of crude product. Crystallization from methanol afforded two crops of product: 7.0 g, mp 254–256°; and 1.4 g, mp 252–254°. The total yield of 1 was 8.4 g (81%). Crystallization from methanol of the first crop afforded an analytical sample, mp 255–256°, $[\alpha]^{15}D$ +108.45° (*c* 0.8760, $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.28; H, 7.84.

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Registry No.—**1**, 40715-31-9; **3**, 6217-96-5; **4a**, 6217-97-6; **4b**, 6217-98-7; **5b**, 19018-70-3; **6**, 40715-35-3; **7**, 19018-71-4; **8a**, 40715-37-5; **8b**, 26362-62-9; **9**, 21491-12-3; **10b**, 40715-40-0; **10c**, 40715-41-1; **11**, 40715-42-2; **14**, 40715-43-3; **23**, 40715-44-4; **24**, 40715-45-5; **25**, 40715-46-6; **26**, 40715-47-7; **27**, 40715-48-8; **28**, 40715-49-9; **29**, 40830-80-6; **29** 3β-acetoxy derivative, 40715-51-3; **30**, 40715-52-4; **31**, 40715-53-5; **32**, 40715-54-6; **33**, 40715-55-7; **34**, 40715-56-8; *m*-chloroperbenzoic acid, 937-14-4; lead tetraacetate, 546-67-8.

Notes

Purine *N*-Oxides. XLVIII. 1-Hydroxyguanine[1]

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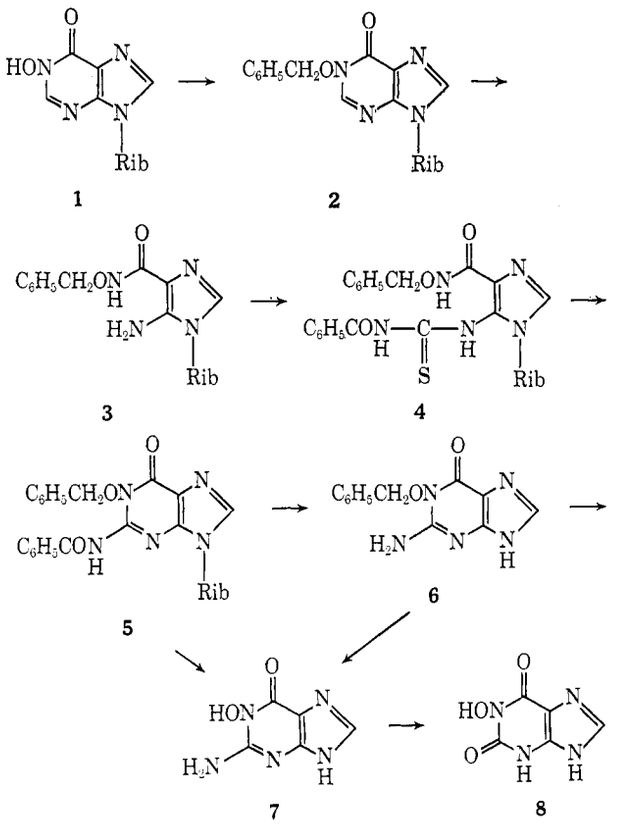
The 1- and 3-*N*-oxide isomers of adenine,[2,3] hypoxanthine,[3,4] and xanthine[5,6] are available, but only the 3 isomer of guanine.[6] By an adaptation of the synthetic route which led *via* substituted imidazoles to a series of 9-hydroxypurines,[7,8] it has now been possible to obtain 1-hydroxyguanine. 1-Hydroxyinosine (**1**), obtained by the nitrosation of adenosine 1-*N*-oxide,[9a] was converted to 1-benzyloxyinosine[9a] (**2**) by reaction with benzyl bromide in DMF in the presence of K_2CO_3. By refluxing **2** in ethanol containing 0.2 volumes of 6 *N* NaOH, the pyrimidine ring was opened to yield 5-amino-1-β-D-ribofuranosylimidazole-4-*N*-benzyloxycarboxamide (**3**). Refluxing **3** with 1 equiv of benzoyl isothiocyanate in acetone yielded 5-(*N'*-benzoylthiocarbamoyl)amino-1-β-D-ribofuranosylimidazole-4-*N*-benzyloxycarboxamide (**4**). Treatment of this with



methyl iodide in 0.1 *N* NaOH at room temperature did not give the expected methylmercapto derivative, but the odor of methylmercaptan was observed when the solution was acidified. The white, crystalline product obtained was assigned the structure **5** from its nmr and its subsequent hydrolysis products. In 32% HBr in glacial acetic acid **5** was hydrolyzed to 1-hydroxyguanine (**7**), and was hydrolyzed to 1-benzyloxyguanine (**6**) in refluxing 1 *N* HCl. Debenzylation of **6** with 32% HBr in glacial acetic acid gave 1-hydroxyguanine (Table I). Further proof of the structure of **7** was ob-

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