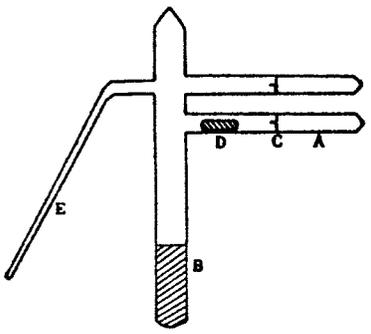

Figure 7.—Reaction vessel: A, *t*-butyl hydroperoxide; B, solution of hydrazine derivative; C, breakable seal; E, this part was inserted into the cavity.

phenylamine (white plates, mp 54°), nitrosobenzene, and a small amount of unidentified colored matter were isolated from the residue. For the other hydrazine derivatives, the reaction procedure and analyses of the reaction products were essentially identical with the above. Trinitronitrosobenzene which was obtained from the reaction mixture of diphenylpicrylhydrazine with hydroperoxide was crystallized as brown plates, mp 194–195°. This was identified by elemental analysis (*Anal.* Calcd for N: 23.14. Found: 24.15.), by nmr (τ 5.55), by thin layer chromatography, by its absorption maxima at 239, 322, and 406 mμ, and by mixture melting point determination with the authentic sample.[11]

Studies by Esr Spectrometer.—Esr measurements on the reaction mixture containing hydrazine derivative and hydroperoxide were done as follows using a 3BX-Type spectrometer with 100-kc modulation manufactured by Japan Electron Optics Lab. A known amount of the previously completely degased hydroperoxide was sealed in a small vessel with a break seal on one side. This side was fused to the other vessel in which a known amount of the completely degased benzene solution of the hydrazine derivative was sealed (see Figure 7). The break seal was destroyed at the desired temperature with a hammer, the reaction components were mixed, and the progression of the reaction was followed in the cavity of the esr spectrometer.

Titration of Hydroperoxide.—The remaining hydroperoxide was extracted from the reaction mixture by a known amount of water at 15°. The hydroperoxide extract was analyzed by the usual iodometry. The value obtained was corrected by a factor of 100/42.3.

(11) R. Nietzki and R. Ditschy, *ibid.*, **34**, 59 (1901).

Some Unusual Reactions of Hydrazines with a Hindered Steroidal α-Amino Ketone[1]

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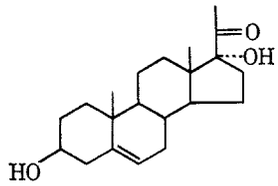
Received July 18, 1966

The reaction of 17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2c**) with hydrazine or methylhydrazine afforded, after mild acid hydrolysis, the reduced product, 17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2f**). Similar treatment of **2c** with 1,1-dimethylhydrazine yielded the oxidized product, 17a-methyl-D-homoandrosta-5,17-diene-3β,17-diol-16-one (**6a**). The hindered dimethylamino group of **2c** underwent a novel "pseudo-allylic" 1,3-displacement by primary and secondary amines (including hydrazines), affording the corresponding 16β-amino-17aβ-methyl-D-homo 17-ketones (**7**, **12**, **13**). The further reactions of the 16-hydrazino-17-keto intermediates (**7**) to the final products is discussed.

We have previously reported the rearrangement of 17α-hydroxy-20-keto steroids (**1**) to D-homo-17aα-amino 17-ketones (**2a**, **b**) when heated at 200° with ammonia or methylamine.[2] The structure of this series of compounds was well established by both chemical and physical methods.[2] During the course of our structure elucidation work, however, a series of anomalous reactions was encountered. This paper describes these reactions and the observations that resulted from them.



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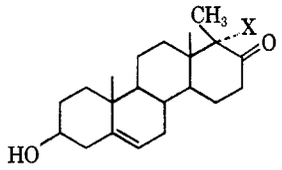


2a, X = NH_2
b, X = NHMe
c, X = NMe_2
d, X = $NMeCH_2C_6H_5$
e, X = OH
f, X = H
g, X = OAc of **f**

The nitrogen atom in compounds of series **2** is severely sterically crowded, as indicated by resistance of the secondary amine **2b** to acetylation, of the tertiary amine **2c** to quaternization with methyl iodide, and of the corresponding amino alcohols (from **2a** and **b**) to cleavage by periodate at 65°.[2] This loss in reactivity of the amine group in these compounds caused by the steric hindrance about C-17a led us to consider the Kishner reductive-elimination reaction as a means of structure elucidation.

The reaction of hydrazine or its derivatives with ketones having a variety of α substitutents (*e.g.*, hydroxyl, epoxy, halo, cyclopropyl, etc.) affords olefins in many instances.[3] Leonard has shown that even an α-amino ketone can be reduced to an olefin by this reaction if the amino group is sufficiently hindered.[4] It was already shown that the corresponding D-homo-α-hydroxy ketone (**2e**) readily underwent Kishner reductive elimination to the D-homo 17-olefin (**3a**).[3c,5] On the basis of Leonard's work, it

(1) Presented at the Gordon Research Conference on Steroids and Other Natural Products, New Hampton, N. H., Aug 5, 1966.

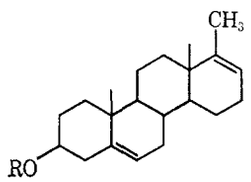
(2) D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

(3) (a) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 973 (1913); (b) N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704 (1952); (c) R. B. Turner, R. Anliker, R. Helbling, J. Meier, and H. Heusser, *Helv. Chim. Acta*, **38**, 411 (1955); (d) D. H. R. Barton, N. J. Holness, and W. Klyne, *J. Chem. Soc.*, 2456 (1949); (e) D. E. Ames and R. E. Bowman, *ibid.*, 2752 (1951); (f) E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963); (g) W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964); (h) P. S. Wharton, S. Dunny, and L. S. Krebs, *ibid.*, **29**, 958 (1964); (i) C. L. Bumgardner and J. P. Freeman, *Tetrahedron Letters*, 737 (1964); (j) S. M. Kupchan and E. Abushanab, *ibid.*, 3075 (1965); (k) Huang-Minlon and Chung-Tungshun, *ibid.*, 666 (1961); (l) C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, **27**, 2205 (1962); (m) C. Djerassi and G. von Mutzenbecker, *Proc. Chem. Soc.*, 377 (1963); (n) B. T. Gillis and J. D. Hagarty, *J. Am. Chem. Soc.*, **87**, 4576 (1965).

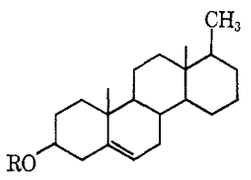
(4) N. J. Leonard and S. Gelfand, *ibid.*, **77**, 3269, 3272 (1955).

(5) (a) H. Heusser, N. Wahba, and F. Winternitz, *Helv. Chim. Acta*, **37**, 1052 (1954); (b) L. Ruzicka and H. F. Meldahl, *ibid.*, **23**, 513 (1940).

therefore seemed probable that the same olefin **3a** would also be formed by treatment of the highly hindered α-dimethylamino ketone **2c** with hydrazine. Instead, however, an entirely unexpected product was obtained.



3a, R = H
b, R = Ac



4a, R = H
b, R = Ac
c, R = Ac, 5α-dihydro

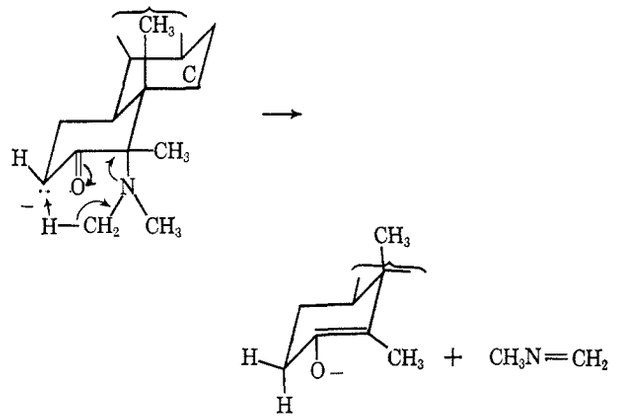
Heating the *t*-amino ketone **2c** with hydrazine and potassium hydroxide in diethylene glycol at 180° afforded, as expected, no basic product, but only neutral material. This was, however, not the anticipated 5,17-diene **3a**, but rather the D-ring saturated analog **4a**, which was identified by comparison with an authentic sample prepared by selective reduction of the diene **3a**.[5]

Other examples of "overreduction" of α-substituted keto steroids in a Wolff–Kishner reaction have been reported.[3d,6] However, air was not excluded from these reactions, and it is now known that hydrazine can be oxidized by oxygen to diimide, which can then reduce the normal olefinic products to saturated hydrocarbons.[7] The formation of **4a**, however, cannot be explained by a diimide reduction of an initially formed diene **3a**, for when the reduction of **2c** was rerun under an atmosphere of nitrogen, the same product (**4a**) was isolated in about the same yield. Furthermore, when either the corresponding α-hydroxy ketone (**2e**) or the α-monomethylamino ketone (**2b**) was subjected to the same conditions, only the diene **3a** (and no **4a**) could be isolated from the reactions.

The mechanism of this reductive cleavage of the C-17a–N bond was an intriguing problem, and the first step leading to its solution appeared to be the identification of the actual reducing agent, which must itself be oxidized during the reaction. Since it was evident that the second N-methyl group played some essential role in this anomalous overreduction, a base-catalyzed cyclic mechanism could be proposed in which the N-methyl group was oxidized to the N-methylimine of formaldehyde (Scheme I).

However, this mechanism, which should proceed equally readily in the absence of hydrazine, was shown to be incorrect. No reaction occurred upon treatment of **2c** or the presumably more reactive N-benzyl analog **2d** with sodium hydride in boiling toluene or in dimethyl sulfoxide. When **2c** was gradually heated with potassium hydroxide in diethylene glycol until some reaction occurred (*ca.* 150°),[8] dimethylamine was evolved and the steroid residue was decomposed and could not be identified. Heat alone was also found to be ineffective, for **2c** was recovered in *ca.* 90% yield when heated at 175° for 2 hr under an atmosphere of nitrogen. Thus, a base- or heat-catalyzed degradation of the amino ketone itself with an internal oxidation–reduction of one N-methyl group accompanied by reductive cleavage of the C-17a–N bond was ruled out.

SCHEME I



The active reducing agent responsible for the added reduction was found to be hydrazine itself. Treatment of **2c** with hydrazine in diethylene glycol at 160° afforded a yellow solid, shown to be mostly the hydrazone of the deaminated saturated ketone **5**, presumably accompanied by some of the corresponding azine.[9] Acid hydrolysis of this intermediate hydrazone afforded the known 17-ketone **2f**.[10]

An alternate mechanism, similar to that in Scheme I, in which the *hydrazone* of **2c** underwent an internal oxidation–reduction to formaldehyde, methylamine, and the reduced steroid seemed unlikely. A mechanism involving an oxidation of the N–N bond of a hydrazine moiety (either the reagent itself or a hydrazino steroid) to either nitrogen or diimide seemed more plausible, but the driving force for this and the necessity for a dimethylamine group at C-17a were not at all clear. Fortunately, these two mechanisms could be easily distinguished. If one of the nitrogens of the hydrazine molecule were alkylated, the latter oxidation of the hydrazine function to diimide or nitrogen would be impossible, whereas the former oxidation of the dimethylamino group to formaldehyde and methylamine should proceed as before. Therefore, the reactions of **2c** with methylhydrazine and 1,1-dimethylhydrazine were investigated.

The treatment of **2c** with methylhydrazine under the same conditions as before afforded a methylhydrazone, which was not characterized but was hydrolyzed with acid to the deaminated saturated ketone **2f**. However, a similar reaction of **2c** with 1,1-dimethylhydrazine yielded a very crude "dimethylhydrazone," which could not be purified. Acid hydrolysis of this intermediate yielded surprisingly the known diosphenol **6a**.[11] We were now in the position of having to explain not only why hydrazine and methylhydrazine *reduced*

(6) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944).

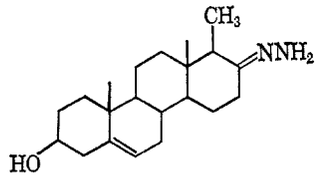
(7) Diimide has been shown to be responsible in several cases for the reduction of double bonds during Wolff–Kishner reactions: E. J. Corey, W. L. Mock, and D. J. Pasto, *Tetrahedron Letters*, 347 (1961); S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem. Intern. Ed. Engl.*, **4**, 271 (1965); A. Furst, R. C. Berlo, and S. Hooton, *Chem. Rev.*, **65**, 51 (1965).

(8) No reaction occurred when **2c** was heated with potassium hydroxide in diethylene glycol at 100° for 2 hr.

(9) Only starting material was recovered from the reaction of the dimethylamino ketone **2c** with hydrazine in refluxing amyl alcohol, refluxing dimethylformamide, and diethylene glycol heated at 135°. Neither acetic nor *p*-toluenesulfonic acid was effective in catalyzing the reaction.

(10) K. Miescher and H. Kägi, *Helv. Chim. Acta*, **22**, 184 (1939); L. Ruzicka and H. Meldahl, *ibid.*, **22**, 421 (1939).

(11) (a) J. Romo and A. Romo de Vivar, *J. Org. Chem.*, **21**, 902 (1956); (b) G. Cooley, B. Ellis, F. Hartley, and V. Petrow, *J. Chem. Soc.*, 4377 (1955); (c) H. H. Inhoffen, F. Blomeyer, and K. Brückner, *Chem. Ber.*, **87**, 593 (1954).



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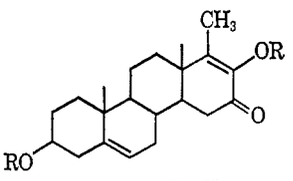


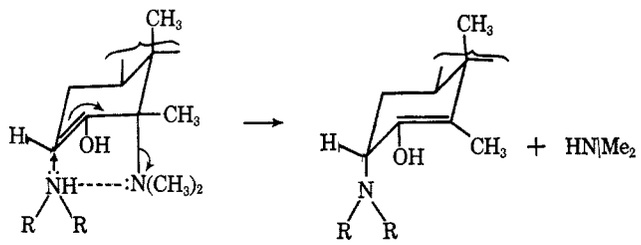
6a, R = H
b, R = Ac

2c to a derivative of 2f, but also why similar treatment of the same amino ketone with dimethylhydrazine *oxidized* it to the α-diketone 6a.

The isolation of 6a was the first indication that C-16 was somehow involved in this reaction, and several new mechanisms were considered. However, the discovery that the less-hindered monomethylamino ketone 2b was unchanged when heated with 1,1-dimethylhydrazine at 160° led us to what we believe is the correct explanation for this series of reactions.

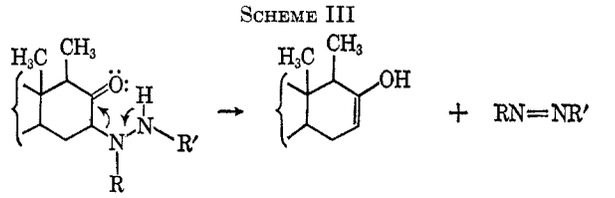
If the less-hindered 2b did not form a dimethylhydrazone, then the reaction of dimethylhydrazine with the more-hindered 2c could not occur at the carbonyl carbon (C-17). However, the strain produced by the highly hindered dimethylamino group could provide the driving force for an SN2′ displacement of the C-17a-amine group by an incoming hydrazine molecule at C-16 (see Scheme II).[12] There are several analogous SN2′ displacements in the steroid literature; for example, the formation of 12α-acetoxy 11-ketones from 9α-bromo 11-ketones,[13] 2α-acetoxy steroids from 6β-bromo Δ4-3-ketones,[14] and 4α-acetoxy 3-ketones from 2α-bromo-3-keto steroids.[14c]

SCHEME II



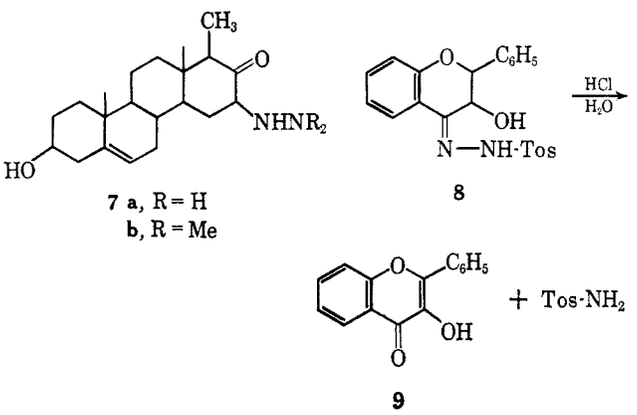
The α-hydrazino ketone formed in this manner, if a proton were available on the "outside" nitrogen atom (7a), could be expected to decompose at 160° to diimide and the 16-unsubstituted ketone 2f by a reverse aldol type of reaction (Scheme III). This unhindered ketone would then react with excess reagent to form the hydrazone 5 (or N-methylhydrazone), which, in the presence of alkoxide at 160°, would be reduced to the D-saturated product 4a. However, the 16-dimethylhydrazino ketone (7b) could not be expected to undergo this pyrolytic degradation and would be isolated, most likely as a mixture with the isomeric 17-hydroxy-16-dimethylhydrazone and 17-hydroxy-16-dimethylhydrazino 16-olefin.

SCHEME III



R,R′ = H, Me

The conversion of such an intermediate (7b) into the diosphenol 6a can be compared with two analogous reactions recently reported in the literature. It was shown that heating α-hydrazino ketones in the presence of hydrazine hydrobromide caused an internal oxidation–reduction to occur, affording cleavage of the N–N bond to give ammonia and an α-imino ketone.[15] A similar reaction was found when an α-hydroxytosylhydrazone (8) was heated with hydrochloric acid, the products isolated being *p*-toluenesulfonamide and 3-hydroxyflavone (9).[16] It seems reasonable, therefore, to postulate that acid hydrolysis of the α-dimethylhydrazino ketone (7b) could lead to dimethylamine and the diosphenol 6a by a similar process (Scheme IV).

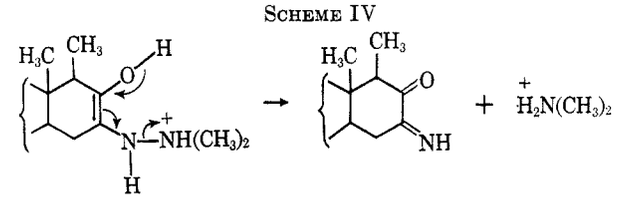


7 a, R = H
b, R = Me

8

9

SCHEME IV



Thus, both the *reduction* of 2c when heated with hydrazine or methylhydrazine and the *oxidation* of 2c when dimethylhydrazine (followed by acid hydrolysis) was used can be logically explained by accepting one basic postulate: that at elevated temperature the dimethylamino group of 2c can be displaced by other amines entering at C-16. The nucleophilic displacement of one amine by another is very unusual, but very recently a somewhat analogous allylic displacement of another highly hindered amine by piperidine (10 → 11) was reported.[17,18] The possibility that such a displacement could occur with 2c to produce an intermediate α-hydrazino ketone (7) was verified by heating

(12) Hydrogen bonding between the incoming hydrazine molecule and the axial C-17a-dimethylamine group could lead to a concerted mechanism with transfer of a proton between the nitrogen atoms to prevent the formation of any high-energy-charged species, such as dimethylamide anion.

(13) (a) J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960); (b) P. A. Diassi and R. M. Palmere, *J. Org. Chem.*, **26**, 5240 (1961); (c) E. J. Becker, R. M. Palmere, A. I. Cohen, and P. A. Diassi, *ibid.*, **30**, 2169 (1965).

(14) (a) J. Herran, G. Rosencranz, and F. Sondheimer, *Chem. Ind.* (London), 824 (1953); (b) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosencranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953); (c) L. F. Fieser and M. A. Romero, *ibid.*, **75**, 4716 (1953).

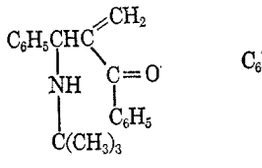
(15) S. Hauptmann, M. Kluge, K.-D. Seidig, and H. Wilde, *Angew. Chem. Intern. Ed. Engl.*, **4**, 688 (1965).

(16) G. Janzso, F. Kallay, and I. Koczor, *Tetrahedron Letters*, 2269 (1965).

(17) R. R. Rebman and N. H. Cromwell, *ibid.*, 4833 (1965).

(18) We wish to thank Dr. S. G. Levine of North Carolina State University for pointing out that this reaction may not be a truly analogous displacement reaction but rather a Michael addition of piperidine followed by a reverse Michael elimination of *t*-butylamine.

2c with both a primary amine (aniline) and a secondary amine (dimethylamine) and obtaining the corresponding 16β-amino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-ones (**12** and **13**). The 16β-anilino steroid **12** underwent Oppenauer oxidation smoothly to give the corresponding Δ^4-3-ketone (**14**). The structures of these products were established with the help of their nmr spectra. A doublet (J = 7–8 cps) for the 17a-methyl group confirmed the loss of the dimethylamino group at that position, and the appearance of a broad hump at 3.7–4.2 ppm in the spectra of **12** and **14** (in the case of the aliphatic amine **13**, this hump was shifted upfield to coincide approximately with that of the 3α proton to give a broad two-proton hump at 2.8–3.8 ppm) indicated a proton adjacent to both a nitrogen atom and a carbonyl group (C-16). The width of this peak suggested an equatorial configuration for the amine,[19] and this was confirmed by the ultraviolet spectrum of **13**. We have previously shown that the introduction of an *axial* amine group adjacent to a ketone caused a marked bathochromic shift of the absorption maximum of the carbonyl group, whereas the introduction of an *equatorial* amine produced only a very slight shift of this maximum.[2] The absorption maximum of **13** (290 mμ) compares well with that of other α-equatorial amino ketones (*ca.* 285–293 mμ) and lies far below the region of absorption of α-axial amino ketones (*ca.* 300–315 mμ).[2] An equatorial configuration of the 16-amino group would seem reasonable even if it initially entered the molecule in the axial position as proposed, for at the temperature of the reaction, self-catalyzed epimerization of a 16α-amino 17-ketone to the more stable 16β position would be expected. The pK_a values for **12** and **13** were consistent for amines adjacent to a carbonyl group.[2] The alternate structure **15** for the 16,17-amino ketone was ruled out on the basis of a deuterium exchange study. The nmr spectrum of the deuterated compound obtained from **13** by equilibration with base in deuterium oxide exhibited no absorption in the 2.8–3.2 region (16α-D) and at 0.87 ppm. Instead, a new singlet at 0.93 ppm (17aβ-Me, 17aα-D) appeared, and the absence of coupling indicated that the carbonyl group in ring D was adjacent to this methyl group.



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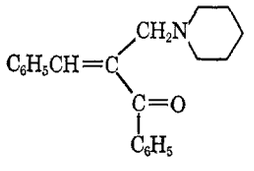

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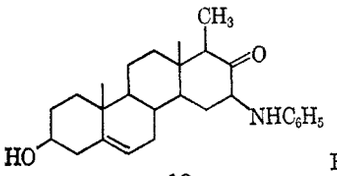

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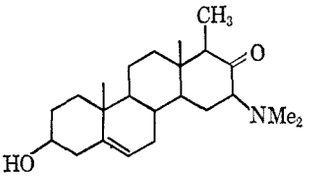

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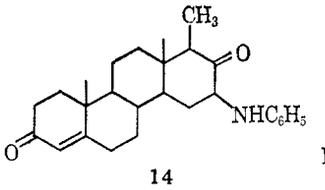

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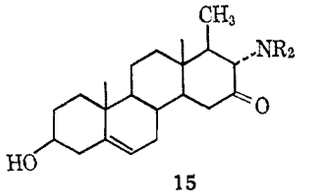

15

The formation of the 16β-amino steroids **12** and **13** by the highly unusual "pseudo-allylic" 1,3-displacement of a hindered amine (**2c**) by another amine substantiates the postulate that the initial step in the syntheses of **2f** and **6a** from **2c** is the formation of the corresponding 16-hydrazino-17aβ-methyl-D-homo 17-ketones (**7**). Once the existence of these key intermediates is established, the formation of the final products is readily explained, and thus this entire set of unusual reactions can be rationalized. The applicability of this series of reactions to other hindered α-amino ketones has yet to be determined.

Experimental Section[20]

Kishner Reduction–Elimination of 17aα-Dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one.—A solution of 1.0 g of 17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2c**), 5.5 g of potassium hydroxide, and 16 ml of 95% hydrazine in 50 ml of diethylene glycol was refluxed under an atmosphere of nitrogen for 1.75 hr (the pot temperature was 145°). The water was then removed by distillation over a 15-min period as the pot temperature was increased to 180°. The solution was refluxed under nitrogen an additional 1.75 hr, holding the pot temperature at 180–190°. The solution was cooled, poured into water, and filtered. (In another run, this crude product was dissolved in ether and treated with anhydrous hydrogen chloride to precipitate any amino steroids. No precipitate was formed.) The crude product, 1.07 g, mp 129–130°, was recrystallized twice from methanol to give 0.58 g (68%) of **17aβ-methyl-D-homoandrost-5-en-3β-ol** (**4a**), mp 144–146°. An analytical sample had mp 147.5–148.5°, $[\alpha]^{23}D$ −92.5°. The residual steroid obtained by concentration of the mother liquors was acetylated and chromatographed on thin layer alumina plates. Elution with benzene–hexane (1:3) indicated little, if any, **3b** to be present, most of the impurities remaining at the origin.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.27; H, 11.34.

When mixed with an independently synthesized sample of 17aβ-methyl-D-homoandrost-5-en-3β-ol (see below), the mixture showed no depression of melting point, mp 148.5–149.5°.

A solution of 34 mg of 17aβ-methyl-D-homoandrost-5-en-3β-ol (**4a**) in 20 ml of acetic anhydride was refluxed for 1 hr, the excess anhydride was decomposed with methanol, and the solution was concentrated under reduced pressure. The residue was recrystallized from methanol, yielding 23 mg (59%) of the **3-acetate of 17aβ-methyl-D-homoandrost-5-en-3β-ol** (**4b**), mp 145–146°, $[\alpha]^{23}D$ −90°. The reported constants for the compound are mp 141–142°, $[\alpha]^{19}D$ −80°.[5a]

Hydrogenation of 10.6 mg of the acetate of 17aβ-methyl-D-homoandrost-5-en-3β-ol with platinum oxide in acetic acid at room temperature and atmospheric pressure and recrystallization of the product from methanol yielded 5.7 mg (54%) of the **3-acetate** (**4c**) **of 17aβ-methyl-D-homo-5α-androstan-3β-ol**, mp 129–130°. The reported melting point of this compound is 128–129°,[5b] and a mixture of this compound and an independently synthesized sample melted at 128–129°.

Independent Synthesis of 17aβ-Methyl-D-homoandrost-5-en-3β-ol (**4a**).—Following the procedure of Heusser, *et al.*,[5a] 125 mg of the acetate of 17a-methyl-D-homoandrosta-5,17-dien-3β-ol (**3b**) was selectively reduced with Pd–$BaSO_4$ catalyst. The product was recrystallized from methanol, yielding 88 mg. (70%) of the **acetate** (**4b**) **of 17aβ-methyl-D-homoandrost-5-en-3β-ol**, mp 139–140°. The infrared spectrum of this acetate was identical

(19) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 79–82.

(20) Melting points were determined on a Fisher-Johns block and are corrected. The ultraviolet spectra were run in methanol. Optical rotations were determined on an approximately 1% solution in chloroform unless otherwise noted. The nmr spectra were obtained on a Varian A-60 instrument; the spectra were determined in deuteriochloroform solution; and the shifts are expressed as parts per million downfield from tetramethylsilane, used as an internal standard. The pK_a values were determined in 50% aqueous methanol. All compounds had infrared spectra which agreed with the assigned structures.

with that of the acetate of the Kishner reduction–elimination product, with the exception of a small band in the OH region, showing that some hydrolysis had occurred, accounting for the lower melting point.

Saponification of 42 mg of the acetate at room temperature and recrystallization of the product from methanol afforded 17 mg (46%) of **17aβ-methyl-D-homoandrost-5-en-3β-ol (4a)**, mp 149–150°. The infrared spectrum of this material was identical with that of the Kishner elimination product, and a mixture of the two had mp 148.5–149.5°.

Complete hydrogenation of 129 mg of the diene acetate **3b** and recrystallization of the product from methanol afforded 96 mg (74%) of the **acetate (4c) of 17aβ-methyl-D-homo-5α-androstan-3β-ol**, mp 128–130°. The infrared spectrum of this compound was identical with that of the acetate of the hydrogenated Kishner reduction–elimination product, and a mixture of the two compounds had mp 128–129°.

Kishner Reduction–Elimination of 17aα-Methylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one. Similar treatment of 0.98 g of **2b** afforded, after acetylation and recrystallization from methanol, 0.63 g (65%) of the **3-acetate (3b) of 17a-methyl-D-homoandrosta-5,17-diene**, mp 119–120°. The melting point was not depressed when mixed with an authentic sample prepared above. Chromatography of the residue from concentration of the mother liquors on thin layer alumina plates with benzene–hexane (1:3) indicated little if any **4b** was present, most of the impurities remaining at the origin.

Kishner Reduction–Elimination of 17aβ-Methyl-D-homoandrost-5-ene-3β,17aα-diol-17-one.—Similar treatment of 0.48 g of **2d** afforded, after acetylation and recrystallization from methanol, 0.26 g (51%) of **3b**, mp 120–121°.

Base Degradation of 17aα-Dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one.—A solution of 500 mg of **2c** and 2.5 g of potassium hydroxide in 25 ml of diethylene glycol was stirred and heated at 160° for 3 hr. A stream of nitrogen was passed over the solution and into a solution of anhydrous hydrogen bromide in ether. The precipitate which formed (75 mg, 40% of theory) was collected and found to be dimethylamine hydrobromide, mp 129–130°, by comparison of its infrared spectrum with that of an authentic sample (mp 133°). No solid product could be isolated from the diethylene glycol solution.

Preparation of the Hydrazone of 17aβ-Methyl-D-homoandrost-5-en-3β-ol-17-one (5). A. From 17aβ-Methyl-D-homoandrost-5-en-3β-ol-17-one.—A solution of 250 mg of **2f** in 25 ml of ethanol was treated with 4 ml of triethylamine and 8 ml of 95% hydrazine and refluxed for 1.5 hr. The cooled solution was concentrated to a small volume under reduced pressure, poured into water, and filtered. The precipitate was recrystallized from aqueous ethanol to give 169 mg (64%) of hydrazone **5**, mp 207–217° dec. The analytical sample was recrystallized from MeOH, mp 210–213° dec.

Anal. Calcd for $C_{21}H_{34}N_2O$: C, 76.31; H, 10.37; N, 8.48. Found: C, 76.52; H, 10.36; N, 8.63.

B. From 17aα-Dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one.—A solution of 2.50 g of **2c** in 125 ml of diethylene glycol and 25 ml of anhydrous hydrazine was refluxed under an atmosphere of nitrogen for 2 hr. The cooled solution was poured into water and the precipitate was extracted with ether. The ether solution was dried, concentrated to a small volume, cooled, and filtered to give 1.77 g of yellow crystals, mp 151–170°. Successive recrystallizations from benzene and ether–petroleum ether (bp 35–60°) raised the melting point to 199–213°. The infrared and nmr spectra of this sample were nearly identical with those of the authentic sample prepared above.

Hydrolysis of the Hydrazone of 17aβ-Methyl-D-homoandrost-5-en-3β-ol-17-one.—A solution of 1.00 g of the crude yellow "hydrazone" (obtained from **2c** by treatment with hydrazine at *ca.* 160°) in 100 ml of ethanol was treated with 20 ml of 18 *N* sulfuric acid, refluxed for 2 hr, and poured into water. The precipitate was extracted with ether, washed with water, and dried. The crude product had no ultraviolet absorption at 276 mμ. The ether solution was concentrated to dryness and the residue was recrystallized from methanol several times to give 0.16 g (17%) of **17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (2f)**, mp 215–218°.

The mother liquors were combined and concentrated, and the residue was dissolved in 20 ml of acetic anhydride, refluxed for 1 hr, treated with 20 ml of methanol, and left overnight. The solution was concentrated to dryness under reduced pressure and the residue was chromatographed on alumina (Woelm No. I). Elution with 10% ether in benzene followed by recrystallization from methanol afforded 0.17 g (16%) of the **3-acetate (2g) of 17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one**, mp 173–174°. A mixture melting point with an authentic sample was not depressed, mp 172–174°.[10]

Reaction of 17aα-Dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one with Methylhydrazine.—A solution of 500 mg of **2c** in 25 ml of diethylene glycol and 5 ml of methylhydrazine was refluxed under an atmosphere of nitrogen for 2 hr. The cooled solution was poured into water, filtered, washed, and dried. The residue, which weighed 443 mg, was not characterized, but was dissolved in 50 ml of ethanol, treated with 10 ml of 18 *N* sulfuric acid, and refluxed for 2 hr. The solution was poured into concentrated salt solution and the precipitate was filtered, washed with water, and dried under reduced pressure to give 175 mg of crude ketone. This was dissolved in 15 ml of acetic anhydride and refluxed for 1 hr; the solution was then treated with 15 ml of methanol, refluxed briefly, and concentrated under reduced pressure. The residue was chromatographed on alumina (Woelm No. I). Elution with 10% ether in benzene, followed by recrystallization from methanol, afforded 32 mg (7% based on starting material, 17% based on acid-insoluble hydrolysis product) of the **3-acetate (2g) of 17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one**, mp 173–175°. A mixture melting point with an authentic sample was not depressed, mp 172–174°.

Reaction of 17aα-Dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one with 1,1-Dimethylhydrazine.—A solution of 2.35 g of **2c** in 115 ml of diethylene glycol and 23 ml of 1,1-dimethylhydrazine was refluxed under an atmosphere of nitrogen for 3 hr. The cooled solution was poured into water, and the product was extracted with ether, washed well with water, and dried. The ether solution was concentrated to a gum, 2.52 g, which could not be characterized adequately.

The gum was dissolved in 250 ml of ethanol, treated with 50 ml of 18 *N* sulfuric acid, and refluxed for 2 hr. The solution was poured into dilute hydrochloric acid, sodium chloride was added, and the precipitate was filtered, washed with water, and dried. The acid-insoluble product weighed 1.17 g and exhibited λ_{max} 276 mμ (ε 6150), λ_{max}^{KOH} 312 mμ (ε 3570). Calculating from the known ε values for the pure diosphenol (see below), the yield of **17a-methyl-D-homoandrosta-5,17-diene-3β,17-diol-16-one (6a)** is 0.77 g (36%). Recrystallization of the crude product twice from methanol and once from acetonitrile afforded 0.44 g (21%) of pure **6a**, mp 192–193°, $[\alpha]^{25}D$ −77°, λ_{max} 275 mμ (ε 9350), λ_{max}^{KOH} 313 mμ (ε 5750). The reported constants for this compound are mp 192–3,[11a] 196,[11b] and 186–7°;[11c] $[\alpha]D$ −54[11a] and −67°;[11b] λ_{max} 276 mμ (ε 9300)[11a] and 277 mμ (ε 8000).[11b]

A solution of 68 mg of the diosphenol **6a** in 6 ml of acetic anhydride was refluxed for 1 hr, treated with 6 ml of methanol, refluxed briefly, and concentrated to dryness under reduced pressure. The residue was recrystallized from methanol, affording 59 mg (69%) of **3β,17-diacetoxy-17a-methyl-D-homo-androsta-5,17-dien-16-one (6b)**, mp 203–204°, $[\alpha]^{25}D$ −71°, λ_{max} 242 mμ (ε 11,500). The literature values for this compound are mp 204–206,[11a] 209–210,[11b] and 197–198°;[11c] $[\alpha]D$ −64,[11a] −66,[11b] and −68.4°;[11c] λ_{max} 244 mμ (ε 12,100)[11a] and 245 mμ (ε 11,830).[11b]

16β-Anilino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (12).—A solution of 2.00 g of 17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2c**) in 100 ml of diethylene glycol and 15 ml of aniline was refluxed under an atmosphere of nitrogen for 2 hr. The cooled solution was poured into water (*ca.* 1.5 l.) and the precipitate was filtered, washed with water, and dried under reduced pressure. The crude product was dissolved in ether and treated with anhydrous hydrogen chloride. The precipitated salt was filtered and recrystallized twice from methanol–acetonitrile, affording 1.10 g (45%) of the **hydrochloride salt of 12**, mp 184–188° dec, $[\alpha]^{25}D$ −50° (*c* 0.8, MeOH), pK_a' 2.1.

Anal. Calcd for $C_{27}H_{33}ClNO_2$: C, 73.03; H, 8.63; Cl, 7.98; N, 3.15. Found: C, 72.98; H, 8.42; Cl, 8.22; N, 3.16.

The free base, prepared from the salt in the usual manner, was recrystallized from aqueous methanol, mp 171–172°, $[\alpha]^{25}D$ −23°, λ_{max} 245 mμ (ε 13,700) and 292 mμ (ε 1930), λ_{max}^{HCl} 253 mμ (ε 270). The nmr spectrum exhibited two three-proton singlets at 0.67 (18-Me) and 0.98 (19-Me), a three-proton doublet (J = 7 cps) centered at 0.99 (17a-Me), a broad one-proton hump at 3.2–3.7 (3α proton), another at 3.7–4.2 (16α proton), a one-proton singlet at 3.45 (NH), a one-proton hump at 5.4 (6 proton), and a five-proton multiplet at 6.5–7.2 ppm.

Anal. Calcd for $C_{27}H_{37}NO_2$: C, 79.56; H, 9.15; N, 3.44. Found: C, 79.40; H, 9.12; N, 3.44.

16β-Anilino-17aβ-methyl-D-homoandrost-4-ene-3,17-dione (14).—A solution of 0.78 g of **12** in 30 ml of toluene and 8 ml of cyclohexanone was treated with 1.0 g of aluminum isopropoxide and stirred and refluxed for 1.5 hr. The cooled solution was diluted with ether, washed several times with potassium sodium tartrate solution, dried, and concentrated under reduced pressure. Trituration of the residual oil with ether afforded, after filtration, 0.23 g (30%) of product, λ_{max} 243 mμ (ε 28,900). A sample was recrystallized for analysis from methanol–acetone, mp 239–243° dec, $[\alpha]^{25}D$ +42°, λ_{max} 243 mμ (ε 30,200) and 292 mμ (ε 1960), λ_{max}^{HCl} 240 mμ (ε 17,100). The nmr spectrum exhibited two three-proton singlets at 0.87 (18-Me) and 1.17 (19-Me), a three-proton doublet (J = 7 cps) centered at 0.99 (17a-Me), a broad one-proton hump at 3.7–4.2 (16α proton), a one-proton singlet at 5.80 (4 proton), and a five-proton multiplet at 6.5–7.4 ppm.

Anal. Calcd for $C_{27}H_{35}NO_2$: C, 79.96; H, 8.70; N, 3.45. Found: C, 80.25; H, 8.58; N, 3.26.

16β-Dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (13).—A solution of 4.24 g of 17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one (**2c**) in 210 ml of diethylene glycol was treated with 32 ml of dimethylamine and heated in a sealed bomb at 170° for 2 hr. The cooled solution was poured into water, and the precipitate was filtered, washed, and dried. Two recrystallizations from acetonitrile afforded 1.91 g (45%) of **13**, mp 154–156°, $[\alpha]^{25}D$ −94° (*c* 0.5, MeOH), λ_{max} 290 mμ (ε 36). The nmr spectrum exhibited a three-proton singlet at 0.67 (18-Me), a 1.5 proton singlet at 0.87 and a 4.5 proton singlet at 1.00 (17a-Me doublet and 19-Me singlet overlapping, J = 8 cps), a six-proton singlet at 2.44 (N-Me_2), a broad two-proton hump at 2.8–3.8 (3α and 16α protons), and a one-proton hump at 5.40 ppm (6 proton).

Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.61; H, 10.28; N, 3.95.

The **hydrochloride salt**, prepared in the usual manner, was recrystallized from isopropyl alcohol–ethyl acetate, mp 282–283° dec (put on the block at 280°), $[\alpha]^{25}D$ −105° (*c* 0.8, MeOH), pK'_a 7.7, λ_{max} 283 mμ (ε 36).

Anal. Calcd for $C_{23}H_{38}ClNO_2$: C, 69.76; H, 9.67; Cl, 8.95; N, 3.54. Found: C, 69.50; H, 9.65; Cl, 8.94; N, 3.32.

A solution of 100 mg of **13** in 6 ml of purified dioxane and 6 ml of deuterium oxide was treated with 300 mg of sodium methoxide and heated at 70° under an atmosphere of nitrogen for 16 hr. The solution was concentrated and the steroid was extracted with ether. The ether solution was dried, concentrated to a small volume, and diluted with petroleum ether. The precipitate was collected and dried under reduced pressure, affording 53 mg of 3-O,16α,17aα-d_3-16β-dimethylamino-17aβ-methyl-D-homoandrost-3-en-3β-ol-17-one, mp 146–149°. The nmr spectrum exhibited two three-proton singlets at 0.67 (18-Me) and 1.00 (19-Me), a singlet integrating for 2.4 protons at 0.93 (17a-Me), a six-proton singlet at 2.44 (NMe_2), a broad one-proton hump at 3.2–3.8 (3α-H), and a one-proton hump at 5.40 ppm (6 proton).

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Acylated Hydrazine Mustards[1]

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The synthesis of some new 1-acyl-2,2-dialkylhydrazines (**3a–f**), 1-acyl-2-isopropenylhydrazines (**6a–d**), and 1-acyl-2,2-bis(2-chloroethyl)hydrazines (**8a–c**) is reported. Catalytic reduction of 1-acyl-2,2-bis(2-chloroallyl)-hydrazines was found to cause extensive hydrogenolysis of the C–N and C–Cl bonds. Lithium aluminum hydride reduction of acylhydrazones **5b, 5c,** and **5d** and catalytic reduction of **5a** and **5e** was selective, resulting in 1-acyl-2-alkylhydrazines. However, reduction of α-haloacylhydrazones **6a** and **6b** was accompanied by considerable hydrogenolysis.

The synthesis and interesting biological activity of bis(2-chloroethyl)hydrazine[2] and a number of its acyl[3] and alkylidene[2c,3a,4] derivatives have recently been reported by other workers. The purpose of the present investigation was to obtain a wider variety of "hydrazine" mustards for screening purposes and to explore new methods of synthesis for these compounds. The syntheses of new acyl derivatives of bis(2-chloroethyl)-hydrazine, as well as the synthesis and reduction of acyl derivatives of bis(2-chloroallyl)hydrazines and chlorinated isopropenylhydrazones, were accomplished and are reported herein.

Alkylation of benzoylhydrazine (**1a**)[5] and isonicotinoylhydrazine (**1b**)[6] with alkyl halides has been shown to give 2,2-dialkylhydrazines (**2a** and **2b**)[5,6] despite earlier reports.[7] A large number of 1-acyl-2,2-dialkyl-hydrazines have also been prepared in this laboratory,[8] by direct alkylation.

In the present study, the acylhydrazines **1a**, **1c**, **1d**, **1e**, and **1f** were alkylated with 2,3-dichloropropene to give 1-acyl-2,2-dialkenylhydrazines **3a**, **3c**, **3d**, and **3f**, respectively. The nmr spectrum of the product from the reaction of **1a** with 2,3-dichloropropene clearly indicates structure **3a** in having peaks at 3.90 (allylic protons), 5.25 (*trans*-vinyl protons), 5.44 (*cis*-vinyl protons), and complex aromatic absorption above 7.2–8.0 ppm for aromatic and N–H protons. The nmr spectrum of **3d** at first appeared unusual in that splitting

(1) This investigation was supported by Public Health Service Research Grant No. CA-05777 from the National Cancer Institute.

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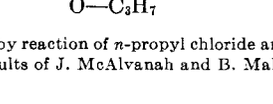

as the product formed by reaction of *n*-propyl chloride and benzoylhydrazine.

(8) Unpublished results of J. McAlvanah and B. Mallinger of this laboratory.