[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

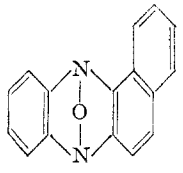
The Wohl–Aue Reaction. I. Structure of Benzo[a]phenazine Oxides and Syntheses of 1,6-Dimethoxyphenazine and 1,6-Dichlorophenazine[1]

BY IRWIN J. PACHTER AND MILTON C. KLOETZEL

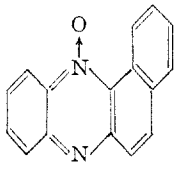
The Wohl–Aue reaction between nitrobenzene and 2-naphthylamine in the presence of alkali yielded benzo[a]phenazine-12-oxide which was not identical with benzo[a]phenazine-7-oxide derived from the oxidation of benzo[a]phenazine. Of the two monoöxides, only the Wohl–Aue compound readily yielded benzo[a]phenazine-7,12-dioxide on oxidation. The dioxide was reduced to the 7-oxide on treatment with a warm solution of hydrogen peroxide in acetic acid. This novel reduction was not effected by hot acetic acid in the absence of peroxide.

1,6-Dimethoxy- and 1,6-dichlorophenazine were prepared by the Wohl–Aue method in attempts to establish the structure of, and to conveniently synthesize, the antibiotic pigment iodinin.

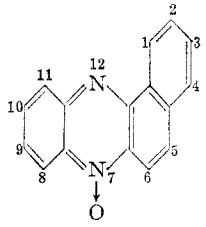
From the reaction of nitrobenzene with 2-naphthylamine and sodium hydroxide, Wohl and Aue[2] reported the isolation of a yellow benzo[a]phenazine oxide, m.p. 182° (cor.), to which they ascribed the now unacceptable[3] formula I. More recently Maffei[4] made a study of the peroxide oxidation products of phenazines and quinoxalines and found that sterically unhindered compounds of this group are capable of forming dioxides, whereas substances having a hindered nitrogen atom, such as benzo[a]phenazine, form only monoöxides. Other workers[5] observed similar steric effects. Maffei concluded that the yellow oxide, m.p. 181°, derived from benzo[a]phenazine by peroxide oxidation, was benzo[a]phenazine-7-oxide (II) and that on the basis of melting point and mixed melting point determinations, it was identical with the product obtained by Wohl and Aue.



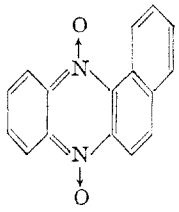
I



III



II



IV

If Maffei's conclusions were correct, the Wohl–Aue reaction would be remarkable, in that the oxygen atom in structure II is located on the nitrogen atom which was originally in 2-naphthylamine.

In our hands the reactions of Maffei and of Wohl and Aue yielded compounds that were indeed similar in melting point. Upon admixture, however, the melting point of the compounds was depressed 20°. Obviously they are not identical.

If the Wohl and Aue compound is not II but is benzo[a]phenazine-12-oxide (III), it should be readily convertible to benzo[a]phenazine-7,12-dioxide (IV), since oxidation at the 7-nitrogen atom is not sterically inhibited. This was found to be the case, for when the oxide obtained from the Wohl and Aue reaction was subjected to the action of excess 30% hydrogen peroxide in acetic acid at 50°, it was readily converted to an orange compound which contained an additional oxygen atom. As Maffei reported, authentic benzo[a]-phenazine-7-oxide remained essentially unchanged under the same conditions. It is evident that the Wohl and Aue product claimed by Maffei to be benzo[a]phenazine-7-oxide (II) is actually benzo-[a]phenazine-12-oxide (III). The oxygen atom in Wohl–Aue reaction products is therefore located on the nitrogen atom which was originally in the nitro group.

Actually it was found possible to oxidize benzo-[a]phenazine-7-oxide (II) to the dioxide (IV) when oxidation conditions were made sufficiently drastic. For example, treatment of oxide II with 30% hydrogen peroxide in acetic acid at 75° for 45 hours produced a 6% yield of dioxide IV. At 50°, only a trace of dioxide IV was produced.

When benzo[a]phenazine-12-oxide (III) was oxidized to the dioxide at 50° the product obtained was contaminated by a yellow compound which proved to be the 7-oxide (II) rather than unreacted starting material. The formation of the 7-oxide apparently resulted from partial decomposition of the 7,12-dioxide, since compound II was also formed when a purified sample of compound IV was subjected to the oxidative conditions. The isolation of oxide II from the reaction mixture emphasizes the fact that under conditions sufficient to convert the 12-oxide (III) to the dioxide, the 7-oxide (II) resists oxidation.

The oxidation of the 12-oxide (III) was effected advantageously at room temperature in a previously warmed solution of hydrogen peroxide and acetic acid to yield 84% of the dioxide IV. Under these conditions oxidative decomposition of the benzophenazine nucleus and formation of benzo-[a]phenazine-7-oxide, which occur to considerable extents at higher temperatures, were minimized.

It was of interest to determine whether the 12-oxygen atom was the only one lost or whether the 7-oxygen atom was also lost during the treatment of dioxide IV with peroxide in warm acetic acid solution. The fact that the 12-oxide (III) was not detected in the mixture was not surprising since

(1) Abstracted from a portion of the dissertation submitted by Irwin J. Pachter to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

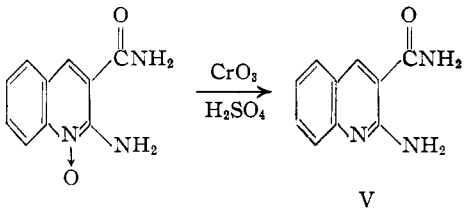
(2) A. Wohl and W. Aue, *Ber.*, **34**, 2442 (1901).

(3) Z. V. Pushkareva and G. I. Agibalova, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 151 (1938) [*C. A.*, **32**, 5404 (1938)].

(4) S. Maffei, *Gazz. chim. ital.*, **76**, 239 (1946).

(5) F. Linsker and R. L. Evans, THIS JOURNAL, **68**, 874 (1946).

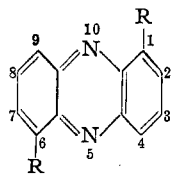
this substance, if formed, would have been reoxidized to the dioxide. To avoid reoxidation, compound IV was heated in acetic acid at 75° for 120 hours in the absence of peroxide. Unchanged dioxide was recovered nearly quantitatively from the reaction mixture. Apparently the deoxygenation of dioxide IV is not effected by hot acetic acid but requires the presence of peroxide. Deoxygenations in the presence of oxidizing agents are not without precedent in amine oxide chemistry. Heller and Wunderlich[6] previously found that 2-aminoquinoline-3-carboxamide-1-oxide (erroneously reported as α-cyano-α-carboxamido-N-hydroxydihydroindole by Heller and Wunderlich) yielded 2-aminoquinoline-3-carboxamide (V) on treatment with chromic anhydride in sulfuric acid, even though more vigorous treatment with acid alone resulted in no loss of oxygen. Other workers[7,8] have reported similar occurrences. The present instance is, however, the first in which such a deoxygenation was observed to occur under the influence of peroxide.



V

It is likely that reactions of this type have occurred during the preparation of amine oxides from tertiary amines and peroxides, but were not previously observed because of the readiness with which the oxides were regenerated by excess peroxide normally employed. It is only when the amine, once formed, cannot be reconverted to the oxide that the deoxygenating effect of peroxides becomes evident.

The Wohl and Aue reaction also was adapted to the syntheses of 1,6-dimethoxyphenazine (VI) and 1,6-dichlorophenazine (VII) in attempts to establish the structure of, and to conveniently synthesize, the antibiotic pigment iodinin (1,6-dihydroxyphenazine dioxide). When *o*-anisidine and *o*-nitroanisole were subjected to the mild conditions of the Wohl and Aue reaction as modified by Soule,[9] 1,6-dimethoxyphenazine was obtained in 12% yield.



VI, R = OCH_3; VII, R = Cl

After our work had been completed, we were notified[10] that 1,6-dimethoxyphenazine had been synthesized in an unequivocal, though more complicated, fashion by Clemo and Daglish.[11] Our product was found to be identical in melting point, and to give no melting point depression upon admixture, with a sample of 1,6-dimethoxyphenazine which was kindly furnished by Professor Clemo. The structure of our compound was further confirmed by its conversion to 1,6-dihydroxyphenazine, m.p. 274–275°, under demethylation conditions similar to those employed by Clemo and Daglish.[11] It is of interest that Clemo and Daglish reported the failure of the unmodified Wohl and Aue reaction to yield any dimethoxyphenazine derivative.

Since McIlwain[12] has shown that 1,6-dihydroxyphenazine could be oxidized to iodinin, a three-step synthesis of the pigment now exists. However, in view of the low yields obtained from the ether-cleavage of 1,6-dimethoxyphenazine and from the oxidation of 1,6-dihydroxyphenazine, an alternate synthesis of the antibiotic pigment seemed desirable.

Vivian[13] has recently reported that 2,7-dichlorophenazine dioxide yielded 2,7-dihydroxyphenazine dioxide on hydrolysis with aqueous alcoholic alkali. 1,6-Dichlorophenazine dioxide might be expected to react similarly to yield iodinin. We have found that the Wohl–Aue reaction between *o*-chloronitrobenzene and *o*-chloroaniline yielded 1,6-dichlorophenazine (VII) but that the latter completely resisted attempts to convert it into the dioxide by reaction with hydrogen peroxide in acetic acid at 60° and at 95°. At 95°, the starting material underwent extensive oxidative decomposition. The synthesis of iodinin therefore could not be effected by this method.

The formation of 1,6-disubstituted phenazines rather than the corresponding oxides in these Wohl–Aue reactions is of interest, particularly since the oxygen atom was not lost in the preparation of sterically hindered benzo[a]phenazine-12-oxide.

The reaction of *o*-anisidine with *o*-nitroanisole yielded 2,2′-azoxydianisole and 2-methoxy-2′-nitrodiphenylamine as by-products. The formation of an azoxy compound rather than an azo compound in a Wohl–Aue reaction is unusual but appears to be unrelated to the concurrent formation of an unoxidized phenazine nucleus, since *o*-chloroaniline and *o*-chloronitrobenzene reacted to give 2,2′-dichloroazobenzene and 2-chloro-2′-nitrodiphenylamine as by-products.

Experimental[14]

Benzo[a]phenazine-7-oxide, the Maffei Product (II).—Benzo[a]phenazine was prepared by the method of Witt[15] with the exception that the product was purified chromatographically on alumina instead of by distillation. The oxide was prepared according to the directions of Maffei.[4] It melted at 181.5–182.5°.

Anal. Calcd. for $C_{16}H_{10}N_2O$: C, 78.03; H, 4.09. Found: C, 77.88; H, 4.20.

(6) G. Heller and P. Wunderlich, *Ber.*, **47**, 1617 (1914).
(7) P. Friedlander and H. Ostermaier, *ibid.*, **14**, 1916 (1881).
(8) L. H. Briggs, W. E. Harvey, R. H. Locker, W. A. McGillivray and R. N. Seelye, *J. Chem. Soc.*, 3013 (1950).
(9) E. C. Soule, U. S. Patent 2,332,179.
(10) G. R. Clemo, private communication, May 4, 1950.
(11) G. R. Clemo and A. F. Daglish, *J. Chem. Soc.*, 1481 (1950).
(12) H. McIlwain, *ibid.*, 322 (1943).
(13) D. L. Vivian, THIS JOURNAL, **73**, 457 (1951).
(14) All m.p.'s are uncorrected unless otherwise specified. Microanalyses are by Mr. Joseph Pirie of the University of Southern California.
(15) O. N. Witt, *Ber.*, **20**, 571 (1887).

Maffei surprisingly reported C, 73.15; H, 3.94 found for this compound.

Benzo[a]phenazine-12-oxide, the Wohl-Aue product (III), was prepared by a Wohl-Aue reaction employing the modification described by Soule[9] for the preparation of phenazine oxide. The 12-oxide obtained in this way was identical with a sample prepared by the original procedure described by Wohl and Aue.[2] Although benzo[a]phenazine was found as a by-product by Wohl and Aue, it was not obtained under the conditions of the Soule modification.

A mixture of 36 g. of 2-naphthylamine, 70 cc. of nitrobenzene, 200 cc. of benzene[9] and 100 g. of powdered potassium hydroxide was refluxed and stirred for 12 hours. The benzene solution was filtered while hot and the solid residue was extracted with a fresh 100-cc. portion of hot benzene. The desired product (III) was extracted from the combined benzene solutions with hydrochloric acid and precipitated by treatment of the hydrochloric acid solution with excess ammonium hydroxide. Recrystallization from benzene–ethanol with the aid of a small amount of decolorizing carbon yielded 9.8 g. (16%) of yellow benzo[a]phenazine-12-oxide, m.p. 179–180°. A mixture of II and III melted at 159–166°.

Benzo[a]phenazine-7,12-dioxide (IV) from the 12-Oxide (III). (a) **At 50°.**—A mixture of 0.700 g. of benzo[a]phenazine-12-oxide (III), 25 cc. of glacial acetic acid and 4 cc. of superoxol was heated at 50° for 48 hours. On dilution of the solution with 50 cc. of water, an orange solid separated and was filtered. A small additional yield was obtained by extracting the filtrate with benzene. The combined products were dissolved in benzene and chromatographed on alumina. A dark-colored band of decomposed material remained at the top of the column. A yellow band, which passed through first, contained 0.092 g. of benzo[a]phenazine-7-oxide (II), m.p. and m.p. of the mixture with the Maffei product, 181–182°. This was followed by an orange band which yielded 0.394 g. (52%) of orange benzo[a]phenazine-7,12-dioxide (IV), m.p. 191° (dec.). If the m.p. of IV is approached slowly, the compound gradually darkens and decomposes considerably below 191°. Prolonged contact of IV with the alumina column results in its decomposition.

(b) **At 25°.**—Thirty cc. of a mixture of three volumes of acetic acid and one volume of superoxol was heated at 50° for 24 hours in order to permit the peracetic acid concentration to approach equilibrium.[16] The mixture was cooled and added to a solution of 1.500 g. of benzo[a]phenazine-12-oxide (III) in 30 cc. of acetic acid. The resulting solution stood at 25° for five days. It was then diluted with 120 cc. of water and treated in the aforedescribed manner. A yield of 1.34 g. (84%) of orange dioxide, m.p. 191° (dec.), was obtained together with 0.07 g. of yellow material, m.p. 161–165°. The m.p. of the yellow substance was raised on admixture with either II or III. It is probable that this substance was a mixture of these compounds.

Anal. Calcd. for IV, $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84. Found: C, 73.31; H, 3.83.

Benzo[a]phenazine-7,12-dioxide from the 7-Oxide (II).—A 1.00-g. sample of benzo[a]phenazine-7-oxide was dissolved in 35 cc. of acetic acid and 5 cc. of superoxol. The solution was heated at 75° for 45 hours, diluted with 100 cc. of water and treated as described for the preparation of IV from III at 50°. A yellow band again passed through the column first followed by an orange band. The latter yielded 0.06 g. (6%) of benzo[a]phenazine-7,12-dioxide (IV), m.p. 190° (dec.), which gave no depression of melting point upon admixture with a sample of dioxide prepared from the Wohl–Aue product (III). The yellow band yielded 0.41 g. of unreacted II, m.p. and m.p. on admixture with II, 181–182°. Much deep-seated decomposition of the starting material occurred during this reaction.

Benzo[a]phenazine-7-oxide (II) from the 7,12-Dioxide (IV).—A mixture of 0.500 g. of pure benzo[a]phenazine-7,12-dioxide, 20 cc. of glacial acetic acid and 3 cc. of superoxol was heated at 49° for 95 hours, diluted with 50 cc. of water and treated as described for the preparation of IV from III at 50°. There was obtained 0.083 g. of benzo[a]phenazine-7-oxide, which gave no depression of m.p. on admixture with the Maffei product, and 0.181 g. of unchanged dioxide. The balance of the original material underwent deep-seated oxidation.

(16) W. C. Smit, *Rec. trav. chim.*, **49**, 675 (1930).

Attempted Decomposition of Benzo[a]phenazine-7,12-dioxide in Hot Acetic Acid.—A 0.50-g. sample of pure dioxide was dissolved in 20 cc. of acetic acid and 2.5 cc. of water (which was added in place of superoxol). The solution was heated at 75° for 120 hours and diluted with 75 cc. of water. The orange product which separated at this point was filtered and the filtrate was extracted with benzene. The filtered product was dissolved in the benzene extract and, after drying over potassium carbonate, the benzene solution was chromatographed. No yellow band separated. The orange band was eluted with benzene–acetone; the eluate on evaporation yielded 0.48 g. of orange material, m.p. 191° (dec.). A mixed m.p. with IV gave no depression.

1,6-Dimethoxyphenazine (VI).—To 180 cc. of dry benzene was added 31 g. of *o*-anisidine, 70 g. of *o*-nitroanisole and 70 g. of powdered potassium hydroxide. The mixture was refluxed under vigorous stirring for seven hours. After cooling, the benzene solution was decanted and extracted with 200 cc. of 15% hydrochloric acid. Upon making the acid solution basic, 1,6-dimethoxyphenazine (VI) separated. To the residue in the reaction vessel was added 500 cc. of water and the black lumps were broken up. The water-insoluble material was collected by filtration and dissolved in 40 cc. of hot acetic acid. On cooling, needles of a tarnished gold color formed. When the needles were washed with ethanol, a color change to bright yellow accompanied by a change in crystal form occurred. The product (VI) thus obtained was combined with that from the benzene solution and recrystallized from ethanol–dioxane. The yield of 1,6-dimethoxyphenazine, m.p. 246–247°, was 7.1 g. (12%).

Anal. Calcd. for $C_{14}H_{12}O_2N_2$: C, 69.98; H, 5.04; OCH_3, 25.83. Found: C, 70.20; H, 4.95; OCH_3, 25.88, 25.90.

After removal of the dimethoxyphenazine, the benzene mother liquor was concentrated by evaporation. Upon standing for three months, a mixture of red and very pale yellow crystals was obtained. These compounds were separated by treating the mixture with petroleum ether. The red crystals dissolved readily in this solvent. The pale yellow compound (3.1 g.) was removed by filtration and, after recrystallization from methanol, melted at 81°. The pale yellow compound was found to be identical in m.p. and mixed m.p. with a sample of 2,2′-azoxydianisole prepared by the method of Starke.[17]

The red crystals were recovered from the petroleum ether solution after chromatographic removal of a small amount of dissolved pale yellow product. A yield of 2.4 g. of needles, m.p. 82–83°, was obtained which gave no depression of m.p. on admixture with a sample of 2-methoxy-2′-nitrodiphenylamine prepared by the method of McCombie, Scarborough and Waters.[18]

1,6-Dichlorophenazine.—To 150 cc. of benzene was added 20 g. of *o*-chloroaniline and 60 g. of *o*-chloronitrobenzene. The mixture was stirred and 50 g. of powdered potassium hydroxide was added. After eight hours of refluxing under vigorous stirring, the mixture was poured into a liter of water to dissolve potassium salts. Filtration yielded crude product which was only sparingly soluble in cold benzene. Extraction of the benzene mother liquor with concentrated hydrochloric acid gave a small additional yield. The product was dissolved in benzene and purified chromatographically on alumina to yield 2.15 g. (5.5%) of 1,6-dichlorophenazine; short yellow needles, m.p. 266–267°.

Anal. Calcd. for $C_{12}H_6N_2Cl_2$: C, 57.86; H, 2.43. Found: C, 57.86; H, 2.36.

From the column was also isolated 0.6 g. of 2-chloro-2′-nitrodiphenylamine, orange needles from ethanol, m.p. 114°. Campbell and MacLean[19] reported red prisms (rather than orange needles) from alcohol, m.p. 114°. In order to ascertain the structure of our compound, it was synthesized by heating a mixture of equal parts of *o*-chloroaniline, *o*-chloronitrobenzene and sodium acetate to 225° for several hours. The product obtained in this way crystallized from ethanol in the form of orange needles and gave

(17) P. Starke, *J. prakt. Chem.*, [2] **69**, 206 (1889).

(18) H. McCombie, H. A. Scarborough and W. A. Waters, *J. Chem. Soc.*, 353 (1928).

(19) N. Campbell and J. A. R. MacLean, *ibid.*, 504 (1942).

no depression of m.p. on admixture with the product derived from the Wohl–Aue mixture.

Concentration of the benzene mother liquor from the Wohl–Aue reaction yielded a mixture of *o*-chloronitrobenzene and 0.5 g. of 2,2′-dichloroazobenzene, orange needles and plates, m.p. 136°. A m.p. of 134° has previously been reported for this compound.[20]

(20) M. Meltsner, L. Greenstein, G. Gross and M. Cohen, THIS JOURNAL, **59**, 2660 (1937).

LOS ANGELES, CALIFORNIA RECEIVED APRIL 9, 1951

[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., AND THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

Steroids. XX.[1a] Cyclic Steroidal Hemithioketals[1b]

BY J. ROMO, G. ROSENKRANZ AND CARL DJERASSI

Unconjugated carbonyl groups of steroids at C-3, C-17 and C-20 react with β-mercaptoethanol to form cyclic ethylenehemithioketals. These substances are stable to base or lithium aluminum hydride, but on acid hydrolysis are reconverted to the parent ketones. In contrast to thioenol ethers or mercaptoles, the presently described ethylenehemithioketals on treatment with Raney nickel yield the original ketone rather than the corresponding hydrocarbon. Since α,β-unsaturated ketones do not react with β-mercaptoethanol under those conditions, it is possible in certain cases to protect a saturated carbonyl group in the presence of a Δ^4-3-keto moiety. Cyclic ethylenehemithioketals of Δ^4-3-ketosteroids can be prepared by the more drastic *p*-toluenesulfonic acid-catalyzed condensation, but the yields are poor. In the presence of piperidine, β-mercaptoethanol undergoes 1,4-addition with a sterically unhindered α,β-unsaturated keto grouping as illustrated with $\Delta^{5,16}$-pregnadien-3β-ol-20-one and 16-dehydroprogesterone (XI).

In an earlier article[2] there was described the reaction of a number of steroidal ketones with benzyl mercaptan. Under the reaction conditions employed, a saturated keto group did not react while an α,β-unsaturated carbonyl system underwent either 1,4-addition or thioenol ether formation. Using $\Delta^{4,16}$-pregnadiene-3,20-dione (XI) as an illustration, it was possible to either add benzyl mercaptan at the C-16 position (piperidine or hydrochloric acid catalysts), effect thioenol ether formation at C-3 (pyridine hydrochloride catalyst) or accomplish both reactions simultaneously at C-3 and C-16 (in the presence of *p*-toluenesulfonic acid); the 20-keto remained unaffected in every instance. It was thus found possible to protect a Δ^4-3-keto system in the presence of another saturated carbonyl group, since acid hydrolysis of the 3-benzylmercapto-$\Delta^{3,5}$-diene regenerated the original Δ^4-3-keto moiety. Raney nickel desulfurization, on the other hand, afforded the $\Delta^{3,5}$-diene.

Considerably different results were observed on extending this study to β-mercaptoethanol. In contrast to benzylmercaptan, β-mercaptoethanol reacted readily in the presence of zinc chloride[3] with *unconjugated* carbonyl groups to yield the corresponding cyclic ethylenehemithioketals. This was true of saturated 3-ketosteroids regardless of the configuration at C-5 [androstan-17β-ol-3-one 17-acetate (Ia), etiocholan-17β-ol-3-one 17-acetate (IIa)], of 17-ketosteroids [estrone acetate (IIIa), Δ^5-androsten-3β-ol-17-one 3-acetate (VIIa)] as well as of 20-ketosteroids [allopregnan-3β-ol-20-one 3-acetate (IVa), Δ^5-pregnen-3β-ol-20-one 3-acetate (Va)].

In the presence of a Δ^4-3-keto moiety a saturated carbonyl group could be attacked selectively under proper conditions. Again employing zinc chloride as the condensing agent, Δ^4-androstene-3,17-dione (VIIIa) afforded the corresponding 17-ethylenehemithioketal (VIIIb), whose structure was proved[4] by its ultraviolet absorption maximum at 240 mμ (log ε 4.29) and infrared carbonyl maximum at 1674 cm.$^{-1}$, typical of Δ^4-3-ketosteroids,[5] as well as by an independent synthesis involving Oppenauer oxidation of the 17-ethylenehemithioketal (VIIc) of Δ^5-androstene-3β-ol-17-one. The more drastic *p*-toluenesulfonic acid-catalyzed condensation of VIIIa led in poor yield to the 3,17-bisethylenehemithioketal (IXa) of Δ^4-androstene-3,17-dione, which did not show any selective absorption in the ultraviolet nor did it exhibit an infrared carbonyl band. Similarly, testosterone or its acetate were converted to the 3-ethylenehemithioketals IXb and IXc in less than 20% yield. In agreement with the results in the androstane series, Oppenauer oxidation of Δ^5-pregnen-3β-ol-20-one 20-ethylenehemithioketal (Vc) produced progesterone 20-ethylenehemithioketal (VIb).

The hemithioketal grouping remains unchanged in dilute base (*cf.* saponification of IIIb, Vb and VIIb) and is resistant toward reduction with lithium aluminum hydride as illustrated by the conversion of progesterone 20-ethylenehemithioketal (VIb) to Δ^4-pregnen-3-ol-20-one 20-ethylenehemithioketal (IXd). Although requiring somewhat more drastic conditions than the benzylthioenol ethers, acid hydrolysis of the various hemithioketals described in this paper readily regenerated the parent ketone, thus serving as further proof for the above structure assignments. It is possible, therefore, to achieve under certain conditions the selective protection of an unconjugated carbonyl group in the presence of a Δ^4-3-keto moiety using β-mercaptoethanol, in contrast to the reaction with benzyl mercaptan,[2] where the opposite aim was accomplished. It is interesting to note that while Raney nickel treatment of benzylthioenol

(1) (a) Paper XIX, *Experientia*, **7**, 2601 (1951). (b) Presented in part at the XIIth International Congress of Pure and Applied Chemistry, New York City, September, 1951.

(2) J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, THIS JOURNAL, **73**, 1528 (1951).

(3) G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949), showed that Δ^4-androstene-3,17-dione (VIIa) reacted with benzyl mercaptan in the presence of zinc chloride with formation of the 3-benzylthioenol ether, the isolated 17-keto group remaining untouched.

(4) It was believed earlier (ref. 3) that condensation had occurred at C-3 rather than at C-17.

(5) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, **72**, 956 (1950).