*Anal.* Calcd. for $C_{30}H_{51}O_4N$: C, 73.57; H, 10.50; O, 13.07; N, 2.86. Found: C, 73.38; H, 10.40; O, 13.51; N, 3.17.

Elution with methylene dichloride containing 3–4% of methanol afforded 3β,6β-dihydroxy-19-oximinocholestane 19-O-methyl ether (XIX, R = R′ = H, R″ = Me). Crystallized from methanol this had m.p. 198–200°, $[\alpha]D$ − 15° (*c* 0.86), $\gamma_{max}^{KB}$ 3500 and 1070 cm.$^{-1}$. An authentic specimen was prepared by hydrolysis of the corresponding 3β-acetate (see above) with 5% ethanolic potassium hydroxide.

*Anal.* Calcd. for $C_{28}H_{49}O_3N$: C, 75.12; H, 11.03; O, 10.72; N, 3.13; OMe, 6.32. Found: C, 74.98; H, 10.86; O, 11.24; N, 3.50; OMe, 6.18.

Elution with methylene dichloride containing 4–6% of methanol furnished 3β,6β-dihydroxy-19-oximinocholestane (XIX, R = R′ = R″ = H), identical with a specimen obtained by alkaline hydrolysis of the corresponding 3β-acetate (see above). Recrystallized from acetonitrile this had m.p. 194–195°, $[\alpha]D$ − 7° (*c* 0.875), $\gamma_{max}^{KBr}$ 3400 and 3300 cm.$^{-1}$.

*Anal.* Calcd. for $C_{27}H_{47}O_3N$: C, 74.78; H, 10.92; O, 11.07; N, 3.23. Found: C, 74.45; H, 10.89; O, 11.17; N, 3.35.

**3β-Acetoxy-19-oximinocholest-5-ene 19-O-Methyl Ether** (XXVI, R = Ac).—Treatment of 3β-acetoxy-19-oximinocholestan-6β-ol 19-O-methyl ether (XIX, R = Ac, R′ = H, R″ = Me) in pyridine with excess of methanesulfonyl chloride for 2 hours at room temperature followed by refluxing of the product with collidine for 2 hours gave 3β-acetoxy-19-oximinocholest-5-ene O-methyl ether (XXVI, R = Ac; 86%). Crystallized from methanol or acetonitrile this had m.p. 117–118°, $[\alpha]D$ −129° (*c* 0.96), $\gamma_{max}^{CCl_4}$ 1750 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{48}O_3N$: C, 76.38; H, 10.47; N, 2.97; OMe, 6.58. Found: C, 75.98; H, 10.23; N, 2.54; OMe, 6.44.

Alkaline hydrolysis with refluxing 5% ethanolic potassium hydroxide for 30 minutes gave the corresponding alcohol XXVI (R = H). Crystallized from methanol this had m.p. 114–115°, $[\alpha]D$ −127° (*c* 0.94); $\gamma_{max}^{CHCl_3}$ 3700, 3500 and 1620 cm.$^{-1}$.

*Anal.* Calcd. for $C_{28}H_{27}O_2N$: C, 78.32; H, 10.94; O, 7.45; OMe, 8.32. Found: C, 77.96; H, 11.24; O, 7.2; OMe, 7.05.

**3β,20β-Diacetoxy-6-nitropregn-5-ene.**—Fuming nitric acid (75 ml.) was added dropwise during 1 hour with stirring to 3β,20β-diacetoxypregn-5-ene (5 g.) in ether (100 ml.) at 0°.[16] The stirred solution was kept at −10° for 2 hours after which water (150 ml.) and ether (100 ml.) were added and the product separated in the usual way. Crystallization from methanol gave 3β,20β-diacetoxy-6-nitropregn-5-ene (3.2 g.), m.p. 153–155°, $[\alpha]D$ − 80° (*c* 1.07); $\lambda\lambda_{max}$ 263, 240 mμ (εε 1,200 and 236, resp.), $\gamma_{max}^{Nujol}$ 1740 and 1520 cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{37}O_6N$: C, 67.11; H, 8.27; N, 3.13. Found: C, 67.02; H, 8.40; N, 3.00.

**3β,20β-Diacetoxy-5α-pregnan-6-one.**—3β,20β-Diacetoxy-6-nitropregn-5-ene (5 g.) in acetic acid (100 ml.) and water (10 ml.) was stirred with zinc dust (10 g.) under reflux for 4 hours. The product, crystallized from methanol, afforded 3β,20β - diacetoxy - 5α - pregnan - 6 - one (almost quantitative yield), m.p. 183–185°, $[\alpha]D$ −14° (*c* 0.93).

*Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15; O, 19.11. Found: C, 71.78; H, 8.93; O, 18.84.

The diacetate (1.75 g.) in methanol (70 ml.) was left at 15° with sodium borohydride (500 mg.) in water (1.5 ml.) for 30 min. Crystallization of the product from acetone–hexane furnished 3β,20β-diacetoxy-5α-pregnan-6β-ol (XXVII, R = H, X = $H_2$), m.p. 170–173°, $[\alpha]D$ ±0° (*c* 1.10); $\gamma_{max}^{CCl_4}$ 3700, 3500 and 1735 cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{40}O_5$: C, 71.37; H, 9.59; O, 19.03. Found: C, 71.13; H, 9.42; O, 18.88.

**3β,20β-Diacetoxy-5α-pregnan-6β-yl Nitrite** (XXVII, R = NO, X = $H_2$).—The above-mentioned diacetate alcohol (2.0 g.) in pyridine (10 ml.) was treated at −30° with excess of nitrosyl chloride. Addition of water, filtration and crystallization from hexane gave 3β,20β-diacetoxy-5α-pregnan-6β-yl nitrite (XXVII, R = NO, X = $H_2$; approx. 2.0 g.), m.p. 156–157°, $[\alpha]D$ −36° (*c* 0.73), $\gamma_{max}^{Nujol}$ 1730 and 1653 cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{40}O_6N$: C, 66.64; H, 8.95; O, 21.30; N, 3.11. Found: C, 66.94; H, 8.74; O, 21.27; N, 2.58.

**Photolysis of 3β,20β-Diacetoxy-5α-pregnan-6β-yl Nitrite** (XXVII, R = NO, X = $H_2$).—The nitrite (2.0 g.) in toluene (70 ml.) was photolyzed at room temperature for 1 hour with a 200-watt mercury lamp. The solvent was removed *in vacuo* and the residue refluxed in isopropyl alcohol until the green color changed to orange-brown. The isopropyl alcohol was removed *in vacuo* and the residue chromatographed over Florisil (60 g.). After elution of 3β,20β-diacetoxy-5α-pregnan-6-one and 3β,20β-diacetoxy-5α-pregnan-6β-ol, there was obtained the desired 3β,20β-diacetoxy-19-oximino-5α-pregnan-6β-ol (XXVII, R = H, X = NOH; 1.08 g.). Recrystallized from ethyl acetate and then acetonitrile this had m.p. 219–220°, $[\alpha]D$ −25° (*c* 0.90); $\gamma_{max}^{KBr}$ 3600, 3450, 1740 and 1715 cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{38}O_6N$: C, 66.94; H, 8.54; O, 21.40. Found: C, 66.91; H, 8.90; O, 20.96.

(16) See C. Anagnostopoulos and L. Fieser, *J. Am. Chem. Soc.*, **76**, 532 (1954); A. Bowers, M. Sanchez and H. Ringold, *ibid.*, **81**, 3702 (1959).

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[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

# A Synthesis of Aldosterone Acetate[1]

BY D. H. R. BARTON AND J. M. BEATON

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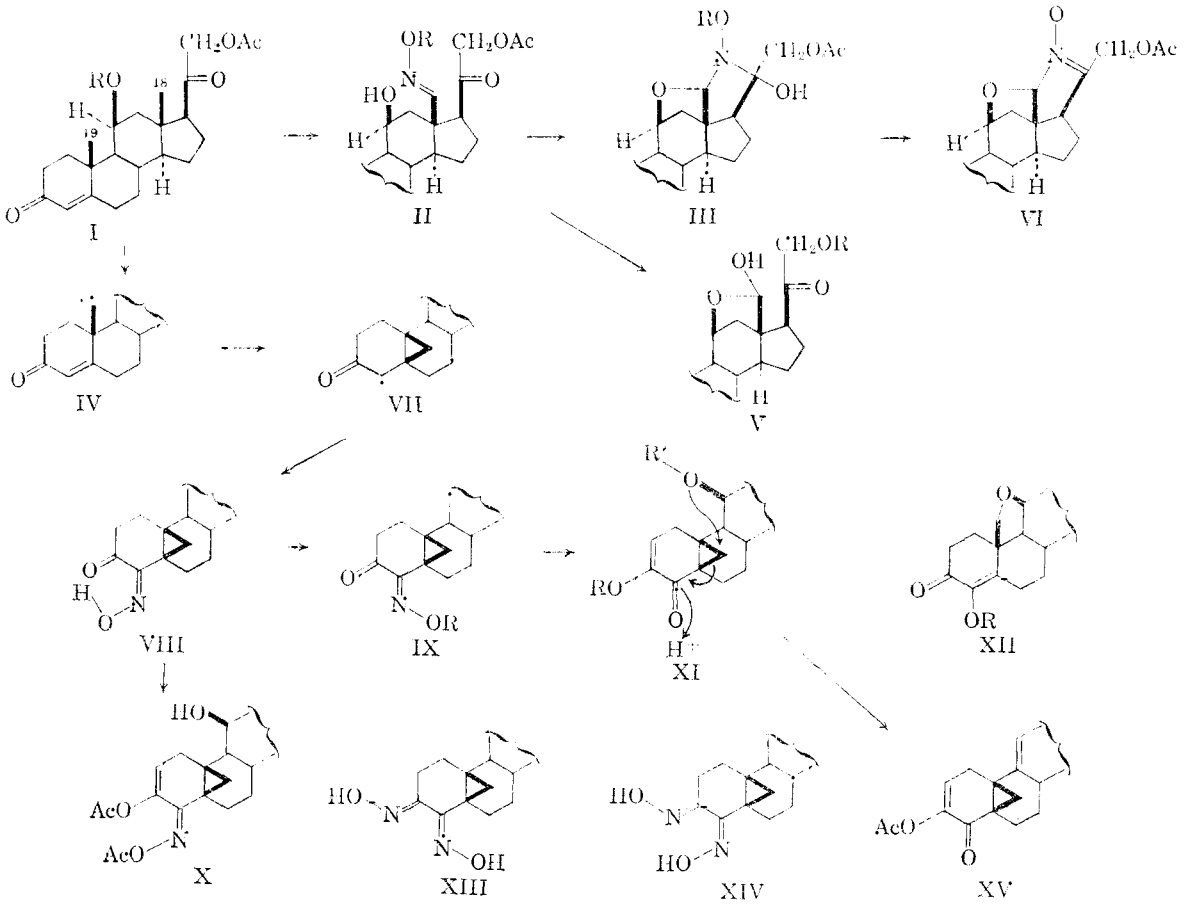
Photolysis of corticosterone acetate nitrite affords aldosterone acetate oxime which with nitrous acid gives aldosterone acetate. The over-all yield based on corticosterone acetate is about 15%. Products resulting from intramolecular attack of the activated $C_{11}$ alkoxyl radical involved in this reaction upon the methyl group at $C_{19}$ have been isolated and their structures determined. A novel rearrangement reaction is involved in the genesis of these compounds.

The elucidation of the constitution (V, R = H) of aldosterone[2] has presented organic chemists with a challenging problem of synthesis. Several total syntheses have been effected[3] but, at the time

(1) This paper is Communication No. 12 from the Research Institute for Medicine and Chemistry. For a preliminary report see D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **82**, 2641 (1960).

(2) S. A. Simpson, T. F. Tait, A. Wettstein, R. Neber, J. v. Euw, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163, 1200 (1954).

(3) J. Schmidlin, G. Anner, J.-R. Billeter and A. Wettstein, *Experientia*, **11**, 365 (1955), and many later papers from the Ciba group; W. S. Johnson, J. C. Collins, R. Pappo and M. B. Rubin, *J. Am. Chem. Soc.*, **80**, 2585 (1958); S. A. Szpilfogel, W. J. van der Burg, C. M. Siegmann and D. A. van Dorp, *Rec. trav. chim.*, **77**, 157 (1958); W. J. van der Burg, D. A. van Dorp, O. Schindler, C. M. Siegmann and S. A. Szpilfogel, *ibid.*, **77**, 171 (1958).



when we began our work, no partial synthesis had been reported. Just prior to the appearance of our preliminary communication[1] two multi-step partial syntheses were described[4] using the interesting lead tetraacetate induced cyclization of alcohols to give tetrahydrofurans described earlier.[5] Also, this year a multi-step method based upon the Hofmann–Loeffler–Freytag reaction[6] has been described.[7]

In the present paper we describe[1] a simple partial synthesis of aldosterone acetate. The procedure uses the new photochemical reaction described in the preceding paper.[8] Corticosterone acetate (I, R = H) readily afforded in nearly quantitative yield an 11$\beta$-nitrite (I, R = NO), which on photolysis in toluene solution under carefully defined conditions furnished crystalline aldosterone acetate oxime (II, R = H) in 21.2% yield. This compound, characterized as its acetate, gave aldosterone acetate (V, R = Ac) on treatment with nitrous acid.[9]

The over-all yield from corticosterone acetate (I, R = H) was about 15%. The identity of the aldosterone acetate was confirmed by comparison with racemic material,[3] by hydrolysis to aldosterone and by determination of its biological activity.[10a] Subsequently about 70 g. of aldosterone was made by our method.[10b]

The constitution of aldosterone acetate oxime (II, R = H) was confirmed by the fact that on melting or warming in methanol it was smoothly converted into the nitrone VI. In this reaction a new chromophore appears showing strong ultraviolet absorption indicative of the nitrone grouping.[11] The cyclization must proceed through the hydroxylamine III (R = H). It must be pointed out that we have, for convenience, represented the oxime as II (R = H), but the alternative formula III (R = H) is not excluded by the evidence available to us. Indeed the acetate of the oxime (see above) appears to have the constitution III (R = Ac), since it is resistant to chromic acid oxidation. In both the oxime and its derived acetate it is not possible to see clearly a 20-ketone carbonyl band in the infrared spectrum.

After removal of crystalline aldosterone acetate oxime by filtration the residual material was

(4) K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni and O. Jeger, *Experientia*, **16**, 21 (1960); *Helv. Chim. Acta*, **44**, 502 (1961); L. Velluz, G. Muller, R. Bardoneschi and A. Poittevin, *Compt. rend.*, 725 (1960).

(5) G. Cainelli, M. L. Mihailovic, D. Arigoni and O. Jeger, *Helv Chim. Acta*, **42**, 1124 (1959); B. Kamber, G. Cainelli, D. Arigoni and O. Jerger, *ibid.*, **43**, 347 (1960).

(6) For leading references see K. Schaffner, D. Arigoni and O. Jeger, *Experientia*, **16**, 169 (1960).

(7) M. E. Wolff, J. F. Kerwin, F. F. Owings, B. B. Lewis, P. Blank, A. Magnani and V. Georgian, *J. Am. Chem. Soc.*, **82**, 4117 (1960).

(8) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *ibid.*, **83**, 4076 (1961).

(9) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney and L. J. Wyman, *J. Chem Soc.*, 4614 (1958).

(10) (a) Personal communication from Dr. M. M. Pechet of this Institute. (b) Personal communication from Dr. Herschel Herzog of the Schering Corp., Bloomfield, N. J.

(11) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and A. Todd, *J. Chem. Soc.*, 2094 (1959).

chromatographed over alumina. This furnished 11-dehydrocorticosterone acetate (about 10%), the nitrone VI already described, and two compounds isomeric with aldosterone acetate oxime (II, R = H), the combined total of which represented about 45% of the starting material. Since the total yield of oxime II (R = H) and nitrone was also about 40% it seemed probable, in view of the fact that $C_{18}$ and $C_{19}$ are comparably situated from the geometrical point of view with respect to the $C_{11}$-$\beta$-nitrite of (I, R = NO), that these compounds represented intramolecular attack upon the $C_{19}$-methyl group. Indeed, nuclear magnetic resonance studies showed that the $C_{19}$-methyl group had disappeared in both compounds. The less polar (more easily eluted) of the isomers rearranged on heating to give the more polar isomer. In both compounds the $\alpha,\beta$-unsaturated ketone system present in ring A of I (R = NO) had disappeared. These and other facts outlined in the sequel are best explained if the unstable isomer is formulated as VIII and the more stable isomer as IX (R = H). The compounds thus originate from attack upon $C_{19}$ to give the radical IV which then cyclizes to radical VII. Combination of the latter with NO and isomerization of the thereby formed C-nitroso compound would furnish the two $\alpha$-oximino-ketones VIII and IX (R = H).

The unstable isomer shows an ultraviolet maximum at 276 m$\mu$ ($\epsilon$ 2,500) which is intensified, but not shifted, by the addition of alkali. The stable isomer has an ultraviolet maximum at 245 m$\mu$ ($\epsilon$ 7,400) which changes with alkali to 297 m$\mu$ ($\epsilon$ 11,700). The behavior of the two benzil monoximes under the same conditions is similar. $\beta$-(*syn*)-Benzil monoxime has a maximum at 252 m$\mu$ ($\epsilon$ 27,600), essentially unchanged on addition of alkali, whilst the $\alpha$-(*anti*)-benzil monoxime shows a single maximum at 249 m$\mu$ ($\epsilon$ 18,000) in neutral solution and develops an additional maximum at 300 m$\mu$ ($\epsilon$ 8,000) on addition of alkali.[12] The stability relationship of the two benzil monoximes is, in fact, the opposite of that found for the isomers VIII and IX (R = H), but the camphorquinone monoximes[13] show a comparable relationship. It is clear that the relative stabilities of pairs of $\alpha$-oximino-ketones represent a delicate balance between hydrogen bonding effects stabilizing the *syn*-oximes and dipolar interactions which should favor the *anti* isomers. In addition, of course, steric factors play a variable but important role.

The assignment of *syn* and *anti* configurations reached on the above evidence is confirmed by infrared considerations. In solution the stable $\alpha$-oximino-ketone IX (R = H) shows a sharp unassociated hydroxyl band at 3650 cm.$^{-1}$ and a fairly strong band at 3300 cm.$^{-1}$ due to associated hydroxyl as is common in the spectra of oximes. The unstable $\alpha$-oximino-ketone VIII has a small sharp band at 3650 cm.$^{-1}$ but no discernible associated hydroxyl absorption. In the carbonyl region, IX (R = H) shows a spectrum indicative of one acetate and two ($C_3$ and $C_{20}$) ketone groups as well as a strong (>C = N---) band at 1595 cm.$^{-1}$. In contrast, VIII shows acetate and $C_{20}$-ketone bands as well as quite strong bands at 1650 and 1540 cm.$^{-1}$, the former being assigned to the hydrogen bonded $C_3$-ketone.

Treatment of the *syn*-oximino-ketone VIII with pyridine-acetic anhydride at 100° for 15 min. gave a triacetate formulated as X. It showed an ultraviolet maximum at 242 m$\mu$ ($\epsilon$ 11,300) changing on addition of alkali to the spectrum characteristic of VIII (in alkali). The *anti*-oximino-ketone IX (R = H) on mild acetylation afforded a diacetate (IX, R = Ac), the infrared spectrum of which indicated the retention of ketone groups at both $C_3$ and $C_{20}$. The retention of the difficulty acetylatable 11$\beta$-hydroxyl group in the triacetate X and the diacetate IX (R = Ac) was shown by oxidation with pyridine-chromium trioxide to give the corresponding 11-ketones. The infrared spectra of these ketones showed the absence of any OH or NH absorption.

The assignment of configuration to the two oximino-ketones was further confirmed by oximation under mild conditions. The *anti* compound IX (R = H) gave a 3,4,20-trioxime (as XIII) which afforded a crimson complex with divalent nickel ion. In contrast, the *syn* isomer VIII gave a 3,4,20-trioxime (as XIV) which furnished no colored precipitate with nickel ion. Since complexing with nickel is restricted to an *anti* configuration of the $\alpha$-dioxime grouping,[14] the formation of such a grouping is only possible from an *anti*-oximino-ketone of the type IX (R = H). The *syn* isomer VIII could not, therefore, furnish a complex yielding $\alpha$-dioxime.

Treatment of either of the stereoisomeric oximino-ketones VIII or IX (R = H) with aqueous hydrochloric acid in acetone solution under mild conditions afforded the same oxime-free compound XI (R = R′ = H) retaining the 21-acetate residue. This compound gave an intense purple ferric reaction. It furnished a diacetate (XI, R = Ac, R′ = H) and, on more vigorous acetylation, a triacetate (XI, R = R′ = Ac). Oximination of XI (R = R′ = H) afforded a mixture separated into the same two 3,4,20-trioximes XIII and XIV as already obtained from IX (R = H) and VIII, respectively, on oximation (see above). The deoximination does not, therefore, involve any rearrangement of the carbon skeleton. On warming with methanesulfonyl chloride in dimethylformamide solution containing pyridine, the diacetate XI (R = Ac, R′ = H) gave an anhydro-derivative (XV). Whereas the starting diacetate XI (R = Ac, R′ = H) had ultraviolet absorption at 226 m$\mu$ ($\epsilon$ 7,900), its anhydro-derivative showed strong end absorption at 208 m$\mu$ ($\epsilon$ 12,000), obscuring the absorption at higher wave length. Whilst the diacetate XI (R = Ac, R′ = H) gave no color with tetranitromethane, its anhydro-derivative gave a strong yellow color. Clearly there is an ethylenic linkage present which is not conjugated directly with the $\alpha,\beta$-unsaturated ketone system. Cross-conjugated vinylcyclo-

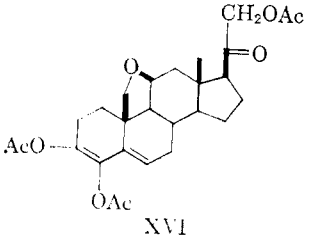
(12) We thank Mr. H. C. Browning for these measurements.

(13) See J. Simonsen and L. N. Owen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, 1949, pp. 472–475.

(14) See N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1937, pp. 196 and 197.

propane and $\alpha,\beta$-unsaturated ketone systems of the type shown in XV explain these spectral relationships in a satisfactory manner.

When the stable $\alpha$-oximino-ketone IX (R = H) was subjected to more vigorous treatment with acid than that specified above it gave, as main product, a deacetylated compound (as XI, R = R′ = H) the constitution of which was shown by acetylation to the diacetate XI (R = Ac, R′ = H) described above, as well as a minor amount of a new monoacetate. This is formulated as XII (R = H) on the basis of the following evidence. It gave a diosphenol ferric test and showed an ultraviolet spectrum identical with that of known $\Delta^4$-4-hydroxy-3-keto-steroids.[15] On acetylation under mild conditions it afforded a diacetate (XII, R = Ac) with the expected ultraviolet absorption maximum at 247 m$\mu$ ($\epsilon$ 15,500). The diacetate XII (R = Ac) showed the expected carbonyl absorption but *no* hydroxyl absorption in the infrared. It could not be dehydrated with methanesulfonyl chloride and pyridine. Vigorous acetylation of the diacetate furnished an interesting triacetate. This is formulated as XVI in agreement with its strong ultraviolet absorption at 237 m$\mu$ ($\epsilon$ 18,000), the strong negative shift in rotation with respect to the parent diacetate XII (R = Ac), its strong tetranitromethane color relative to that for XII (R = Ac) which was negative, and from inspection of the carbonyl region of its infrared spectrum. It is clear from these experiments that the monoacetate XII (R = H), and its derived diacetate XII (R = Ac) and triacetate XVI are formed by an acid-catalyzed transformation which converts the 11$\beta$-hydroxyl into ethereal oxygen and at the same time removes the bond at $C_5$ which prevents the 3,4-diosphenol of XI (R = H) behaving like a normal steroidal 3,4-diosphenol as it does in XII (R = H). The formulations given explain these facts in a satisfactory manner. When the stable $\alpha$-oximino-ketone IX (R = H) was subjected to still more vigorous acid treatment it afforded a deacetylated rearranged product (as XII, R = H) which gave the above-mentioned diacetate XII (R = Ac) on acetylation.




XVI

In all experiments described above we have not given a direct proof of the presence of a cyclopropane ring in the compounds derived from attack on $C_{19}$. However, such a formulation is plausible from the mechanistic point of view and explains all the results in a satisfactory manner. Incidentally, the fact that the NO which is initially part of the 11$\beta$-nitrite residue ultimately attaches itself to $C_4$ is good evidence for the "cage" radical type of mechanism and against the direct "switching" mechanism. Both mechanisms are discussed in the preceding paper.[8]

**Acknowledgment.**—We thank Dr. M. M. Pechet for his continued interest and encouragement. Skillful technical assistance was provided by Misses R. A. Holland and M. A. Kennedy and by Mr. P. C. Ludwig. We also thank Dr. M. Akhtar for his helpful comments on the theoretical aspects of this work and the Schering Corporation for a generous gift of the $\alpha$-oximoketone IX (R = H).

## Experimental

Microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim (Ruhr), Germany. Infrared spectra were determined using an Infracord model 137 spectrophotometer. Ultraviolet spectra were measured in methanol by means of a Cary model II spectrophotometer; where alkaline spectra are recorded 1% methanolic sodium hydroxide was used. Unless otherwise stated, optical rotations were determined in chloroform and melting points on a Köfler-type hot-stage.

**Corticosterone 11-Nitrite 21-Acetate** (I, R = NO).—A solution of corticosterone 21-acetate (25 g.) in pyridine (100 ml.) was swirled while nitrosyl chloride was passed into it. The color was discharged almost completely at first and addition of nitrosyl chloride was continued until a definite brown or green color persisted. The solution was treated with water (*ca.* 2 l.) and stirred until the precipitate became solid and the supernatant liquid clear. The solid was separated by filtration, washed with water and recrystallized from methylene chloride–hexane to give a first crop of needles (23.1 g.), m.p. 174–176°, and a second crop (2.0 g.), m.p. 170–172°. The analytical sample of the 11$\beta$-nitrite (I, R = NO), obtained as plates from methylene chloride–hexane, had m.p. 174–176°, $[\alpha]D$ +316, +321° (*c* 1.1, 1.4); $\lambda_{max}$ 239, 346, 358, 372 and 386 m$\mu$ ($\epsilon$ 16100, 64, 65, 63 and 41, resp.), $\nu_{max}^{KBr}$ 1735, 1670, 1640 and 1600 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1750, 1730, 1665 and 1625 cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.49; N, 3.36. Found: C, 66.17; H, 7.71; N, 3.16.

**Photolysis of Corticosterone 11-Nitrite 21-Acetate** (I, R = NO).—A solution of corticosterone 11-nitrite 21-acetate (4.00 g.) in toluene (200 ml.) was irradiated by means of a Hanovia 200 watt high pressure mercury arc lamp placed inside a water-cooled Pyrex immersion well. Slight agitation of the solution was maintained by means of a stream of pure nitrogen and the reaction temperature was kept near 32° by regulating the temperature of the cooling water. After 35 min. the solid was removed by filtration (885 mg., 21.2%) and identified as aldosterone acetate oxime (II or III, R = H). A sample recrystallized from methylene chloride–benzene had m.p. 175–194°, $[\alpha]^{27}D$ + 198° (*c* 1.3), $\lambda_{max}$ 240 m$\mu$ ($\epsilon$ 16,500); $\nu_{max}^{KBr}$ 3500, 3300, 1735, 1665 and 1610 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3550, 3350, 1740, 1665 and 1615 cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.49; O, 22.99; N, 3.36. Found: C, 66.07; H, 7.42; O, 22.83; N, 3.46.

The toluene filtrate from a similar experiment conducted at a slightly higher temperature (*ca.* 36°), which gave only 0.43 g. of the oxime, was chromatographed on alumina (Merck acid-washed, 100 g.) and fractions were eluted with methylene chloride containing increasing amounts of methanol. The first fractions (210 mg.) crystallized from ethyl acetate to give 11-dehydrocorticosterone acetate as needles (70 mg.), m.p. 177–180°, identical (mixture m.p. and infrared) with an authentic specimen. The next fraction (350 mg.) was a mixture and was not examined further. The next fractions (1.27 g.) were crystallized from ethyl acetate to give the unstable $\alpha$-oximinoketone monoacetate VIII as needles (400 mg.), m.p. 173–176° and 211–214°, $[\alpha]^{24}D$ + 138° (*c* 1.0), $\lambda_{max}$ (neutral) 276 m$\mu$ ($\epsilon$ 250°), $\lambda_{max}$ (alkaline) 276 m$\mu$ ($\epsilon$ 6900); $\nu_{max}^{KBr}$ 3500(s), 3300(s), 1750(s), 1720(s), 1660(w) and 1615(m); $\nu_{max}^{CH_2Cl_2}$ 3650(m), 1745(s), 1720(s), 1650(ms), 1610(w) and 1540(m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.49; O, 22.99; N, 3.36. Found: C, 65.97; H, 7.51; O, 23.16; N, 3.53.

The unstable $\alpha$-oximinoketone monoacetate VIII gives a strong tetrazolium blue reaction, a fairly strong Zimmerman

(15) See L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1728 (1954), and references there cited.

reaction and a very strong, rapidly developing purple color with ferric chloride in ethanol. The colorless crystals gave a pale yellow-green solution in chloroform, not changed noticeably by the addition of tetranitromethane. When a solution of VIII is heated, or when the crystals are heated past the first m.p., the stable α-oximinoketone monoacetate (IX, R = H) (*vide infra*) is formed (m.p. mixed m.p., infrared and ultraviolet spectra).

Following some non-crystalline fractions (110 mg.) came another crystalline substance (950 mg.) identified as the nitrone VI. Recrystallization from ethyl acetate gave needles (420 mg.), m.p. 194–197°, $[\alpha]_D$ + 167° (*c* 1.2),[16] $\lambda_{max}$ 239 mμ (ε 27,400); $\nu_{max}^{KBr}$ 1740(s), 1665(s), 1610(m) and 1545(ms) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1650(s), 1670(s), 1620(m) and 1575(ms) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{29}O_5N$: C, 69.15; H, 7.32; O, 20.03; N, 3.51. Found: C, 69.07; H, 7.72; O, 19.91; N, 3.46.

The nitrone is formed from aldosterone acetate oxime (II, R = H) on melting or on refluxing in methanol for 1 hr.

The last group of crystalline fractions (630 mg.) eluted from the chromatogram was recrystallized from ethyl acetate to give the stable α-oximinoketone monoacetate IX (R = H) as needles, m.p. 214 – 219°, $[\alpha]^{28}D$ + 296° (*c* 1.0), $\lambda_{max}$ (neutral) 245 mμ, (ε 7400), $\lambda_{max}$ (alkaline) 297 mμ (ε 11,700); $\nu_{max}^{KBr}$ 3650(s), 3300(s), 1750(s), 1720(s) and 1620(m); $\nu_{max}^{CH_2Cl_2}$ 3650(m), 3300(m), 1745(s), 1720(s), 1595(m) and 1545(w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.49; O, 22.99; N, 3.36. Found: C, 66.16; H, 7.29; O, 22.96; N, 3.31.

The stable α-oximinoketone monoacetate IX (R = H) gives a strong reaction with tetrazolium blue, a strong Zimmermann reaction, a slowly developing but ultimately strong purple color with ferric chloride in ethanol and no color with tetranitromethane in chloroform. It is much more polar than the unstable α-oximinoketone monoacetate VIII on paper chromatography as well as by adsorption on alumina.

**Aldosterone Oxime Diacetate** (II or III, R = Ac).—A solution of crude aldosterone acetate oxime (II or III, R = H; 250 mg.) in pyridine (10 ml.) and acetic anhydride (5 ml.) was heated on the steam-bath for 5 min. After evaporation of solvent, the residual gum was crystallized several times from ethyl acetate to give aldosterone oxime diacetate (II or III, R = Ac) as prisms, m.p. 183 –187°, $[\alpha]_D$ +171°, +175° (*c* 1.1, 1.1), $\lambda_{max}$ 240 mμ (ε 16,600); $\nu_{max}^{CHCl_3}$ 3650 (m), 1780(s), 1750(s), 1675(s) and 1625(m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{33}O_7N$: C, 65.34; H, 7.24; O, 24.37; N, 3.05. Found: C, 65.48; H, 7.23; O, 24.48; N, 3.30.

It was recovered unchanged from treatment with nitrous-acetic acid mixture under conditions which effected cleavage of the free oxime II or III (R = H) to aldosterone acetate. The oxime diacetate was recovered unchanged after attempted oxidation with chromium trioxide in pyridine solution at room temperature for 2 hr.

**Aldosterone 21-Acetate** (V, R = Ac).—Crude aldosterone acetate oxime (II or III, R = H; 505 mg.) was added at 10° to a mixture of acetic acid (8 ml.) and aqueous sodium nitrite (5%, 4 ml.) and stirred for 5 min. Neutralization of the acid with dilute sodium bicarbonate and extraction with methylene chloride gave aldosterone 21-acetate (V, R = Ac) as needles from ethyl acetate (320 mg.), m.p. 194–201°, $[\alpha]^{23}D$ +127° (*c* 1.2), $\lambda_{max}$ 240 mμ (ε 16,100); $\nu_{max}^{CHCl_3}$ 3600-(m), 1750(s), 1675(s) and 1620(m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.61; H, 7.51; O, 23.85. Found: C, 68.60; H, 7.40; O, 23.92.

A comparison of spectra and paper chromatographic behavior of this sample with a specimen of synthetic (±)-aldosterone 21-acetate confirmed their identity. The physiological potency of our synthetic aldosterone 21-acetate was the same as that of the natural hormone.

**Aldosterone** (V, R = H).—To a solution of aldosterone 21-acetate (V, R = Ac; 120 mg.) in methylene chloride (4 ml.) was added 8 ml. of a 0.5 *M* solution of potassium carbonate in 75% aqueous methanol. The mixture was stirred for 4 min., then solid carbon dioxide and water (3 ml.) were added and the solution concentrated under reduced pressure until cloudiness appeared. Water (5 ml.) was added and the mixture was extracted with methylene chloride (3 × 15 ml.). Crystallization of the product from acetone–ether gave slightly impure aldosterone (V, R = H; 47 mg.), m.p. 168–175°, $[\alpha]_D$ +159° (*c* 1.0); $\nu_{max}^{CHCl_3}$ 3500(m), 1705(m), 1670(s) and 1620(m) cm.$^{-1}$. Paper chromatography revealed the presence of a contaminant of similar polarity, probably 17-isoaldosterone.

(16) The value of +119° previously reported is incorrect.

**The Triacetate X Derived from the Unstable α-Oximinoketone** VIII.—A solution of the unstable α-oximinoketone monoacetate VIII (200 mg.) in pyridine (10 ml.) and acetic anhydride (5 ml.) was heated on the steam-bath for 15 min., then cooled and diluted gradually with water until precipitation was complete. The solid was separated by filtration and recrystallized from ethyl acetate–hexane to give the triacetate X as needles (110 mg.), m.p. 203–209°, $[\alpha]_D$ + 84°, + 90° (*c* 1.0, 1.1), $\lambda_{max}$ (neutral) 242 mμ (ε 11,300), $\lambda_{max}$ (alkaline) 276 mμ (ε 7100); $\nu_{max}^{KBr}$ 3600(m), 1785(s), 1755(s), 1745(s), 1730(s), 1650(w), 1590(m), 1240(s) and 1200(s) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3650(m), 1765(s, broad), 1730-(s), 1665(w), 1580(m), 1240(s) and 1190(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{27}H_{35}O_8N$: C, 64.65; H, 7.03; O, 25.52; N, 2.79; Ac, 25.74. Found: C, 64.66; H, 6.95; O, 25.20; N, 2.93; Ac, 30.02.

**Acetylation of the Stable α-Oximinoketone Monoacetate** (IX, R = H).—A solution of the stable α-oximinoketone monoacetate (IX, R = H; 0.50 g.) in pyridine (4 ml.) and acetic anhydride (2 ml.) was kept at room temp. for 10 min., then decomposed carefully by the slow addition of water. The product which separated was recrystallized from methylene chloride–ethyl acetate–hexane to give needles (470 mg.), m.p. 167–177°. Recrystallization from methylene chloride–hexane gave the diacetate IX (R = Ac) as needles, m.p. 170–178°, $[\alpha]^{26}D$ +235° (*c* 1.3), $\epsilon_{210m}$ 4700 (neutral), $\lambda_{max}$ (alkaline) 248 and 297 mμ (ε 1900 and 2550); $\nu_{max}^{KBr}$ 3600(s), 3500(m), 1770(s, broad), 1720(s), 1650(m) and 1595(m) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3600(w), 1780(s), 1745(s) 1720(s) and 1590-(m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{33}O_7N \cdot H_2O$: C, 62.87; H, 7.39; O, 26.80; N, 2.93. Calcd. for $C_{25}H_{33}O_7N$: C, 65.34; H, 7.24; O, 24.37; N, 3.05; Ac, 18.73. Found (Sample crystallized from ethyl acetate): C, 62.92; H, 7.10; O, 26.49; N, 3.18. (Sample from methylene chloride–hexane): C, 62.98; H, 7.37; O, 26.40; N, 3.11. (After thorough drying): C, 64.98; H, 7.24; O, 24.71; Ac, 19.42.

**Oximation of the Stable α-Oximinoketone Monoacetate** (IX, R = H).—A solution of the stable α-oximinoketone monoacetate (IX, R = H; 2.00 g.) in pyridine (80 ml.) was treated with hydroxylamine hydrochloride (2 g.) and the mixture kept at room temperature overnight. When the mixture was added to ice-water, only slight precipitation occurred. Sodium chloride was added until the cold solution was nearly saturated, then the mixture was extracted with tetrahydrofuran. The extract was dried with sodium sulfate and evaporated. Crystallization from ethyl acetate gave the trioxime XIII (1.33 g.), m.p. 203–209°, $[\alpha]^{23}D$ +148, +155° (*c* 1.0, 1.0 in dioxane), $\lambda_{max}$ (neutral) 234 mμ (ε 7700), $\lambda_{max}$ (alkaline) 266 mμ (ε 7,400); $\nu_{max}^{KBr}$ 3500(s), 1735(s) and 1650(w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{33}O_6N_3$: C, 61.73; H, 7.43; O, 21.45; N, 9.39. Found: C, 61.67; H, 7.37; O, 21.32; N, 9.17.

Addition of 5% aqueous nickel acetate to a fairly concentrated ethanolic solution of the trioxime gave a crimson precipitate.

**Oximation of the Unstable α-Oximinoketone Monoacetate VIII.**—A solution of the unstable α-oximinoketone monoacetate VIII (200 mg.) in pyridine (8 ml.) was kept for 21 hr. at room temperature with hydroxylamine hydrochloride (200 mg.). The mixture was poured into ice-water, the precipitate collected by filtration and crystallized from tetrahydrofuran–methylene chloride to give the trioxime XIV (100 mg.), m.p. 135–140°, $[\alpha]^{26}D$ + 33° (*c* 1.0 in methanol), $\lambda_{max}$ (neutral) at 225 and 265 mμ (ε 8500 and 3900, resp.), $\lambda_{max}$ (alkaline) 236 and 265 mμ (ε 9000 and 10,000 resp.); $\nu_{max}^{KBr}$ 3400(s), 1745(s) and 1650(w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{33}O_6N_3$: C, 61.73; H, 7.43; O, 21.45; N, 9.39. Calcd. for $C_{23}H_{33}O_6N_3 \cdot {}^1/_2H_2O$: C, 60.51; H, 7.51; O, 22.78; N, 9.20. Found: C, 60.59; H, 7.25; O, 21.76; N, 9.44.

When a drop of 5% aqueous nickel acetate is added to an ethanolic solution of this trioxime, no colored precipitate is formed.

**Preparation of the Monoacetate** (XI, R = R′ = H). (a).—A solution of the stable α-oximinoketone monoacetate (IX, R = Ac; 1.00 g.) in acetone (50 ml.) and water (10 ml.) containing concentrated hydrochloric acid (2.5 ml.) was kept at 25° for 16 hours. After dilution with water and extraction with methylene chloride, the product was chromatographed on alumina (30 g.), the composition of the fractions being followed by infrared spectra. The early fractions were combined (730 mg.) and crystallized from ethyl acetate to give the monoacetate XI (R = R′ = H) as needles (295 mg.), m.p. 213–224°. A second crop (100 mg.) had m.p. 208–221°. The analytical sample had m.p. 216–224°, $[\alpha]^{26}D$ +230° (*c* 1.1), $\lambda_{max}$ (neutral) 234 and 264 mμ (ε 5,900 and 4,450, resp.), $\lambda_{max}$ (alkaline) 226 and 304 mμ (ε 4,700 and 3,400, resp.); $\nu_{max}^{KBr}$ 3650(m), 3400(s), 1750(s), 1715(s), 1665(w), 1630(s) and 1220(s) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3650(w), 3550(m), 1750(s), 1725(s), 1680(w), 1640(s) and 1610(w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; O, 23.85; Ac, 10.69. Found: C, 68.78; H, 7.27; O, 24.15; Ac, 11.03.

The monoacetate XI (R = R′ = H) gave a strong purple color with ferric chloride in ethanol, a strong reaction with tetrazolium blue, and no reaction with the Zimmermann reagent.

(b).—When a mixture of the unstable α-oximinoketone monoacetate VIII (20 mg.), acetone (1 ml.), water (0.2 ml.) and concentrated hydrochloric acid (0.1 ml.) was kept at room temperature overnight and worked up as described above, the product was the same monoacetate (XI, R = R′ = H).

**Preparation of the Monoacetate** (XII, R = H).—A solution of the stable α-oximinoketone monoacetate (IX, R = H; 2.5 g.) in acetone (125 ml.), water (25 ml.) and concentrated hydrochloric acid (21.5 ml.) was kept at room temperature overnight and then concentrated under reduced pressure on the steam-bath. Addition of water and extraction with methylene chloride gave a gum which was chromatographed on alumina (75 g.). The major product crystallized from ethyl acetate to give the 21-alcohol (as XI, R = R′ = H) as needles (500 mg.), m.p. 208–220°, $[\alpha]^{25}D$ +237° (*c* 1.0), $\lambda_{max}$ (neutral) 233 and 258 mμ (ε 5,500 and 4,300, resp.), $\lambda_{max}$ (alkaline) 225 and 305 mμ (ε 5,000 and 3,200, resp.); $\nu_{max}^{KBr}$ 3650(s), 3400(s), 1700(s), and 1650(s) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3650(w), 3500(s), 1705(s), 1680(m) and 1640(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; O, 22.19. Found: C, 69.84; H, 7.90; O, 22.35.

One of the less polar fractions from the chromatogram crystallized from ethyl acetate to give the monoacetate XII (R = H) as needles (40 mg.), m.p. 200–207°, $[\alpha]^{26}D$ +190° (*c* 1.0), $\lambda_{max}$ (neutral) 278 mμ (ε 12,300), $\lambda_{max}$ (alkaline) 320 mμ (ε 7,800); $\nu_{max}^{KBr}$ 3600(s), 1750(s), 1725(s), 1660(s), 1630(s) and 1240(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{36}O_6$: C, 68.63; H, 7.51; O, 23.85, 10.69. Found: C, 68.75; H, 7.49; O, 24.05; Ac, 10.76.

**Preparation of the 21-Alcohol (as XII, R = H).**—A solution of the stable α-oximinoketone monoacetate (IX, R = H) (500 mg.) in acetone (25 ml.) containing water (10 ml.) and concentrated hydrochloric acid (15 ml.) was kept at room temperature overnight. The mixture was concentrated under reduced pressure, diluted with water and extracted with methylene chloride. The crude product was chromatographed on alumina (15 g.) to give a series of fractions having $\lambda_{max}$ 278 mμ. These were combined and recrystallized from ethyl acetate–hexane to give the alcohol (as XII, R = H) as needles (280 mg.), m.p. 198–214°. The analytical sample had m.p. 199–213°, $[\alpha]^{22}D$ +174° (*c* 1.1), $\lambda_{max}$ (neutral) 278 mμ (ε 11,300), $\lambda_{max}$ (alkaline) 321 mμ (ε 7,700); $\nu_{max}^{KBr}$ 3450(s), 1690(s), 1665(s) and 1635(m) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3550(s), 1705(s), 1665(s) and 1635(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; O, 22.19. Found: C, 69.88; H, 7.84; O, 22.41.

The same 21-alcohol (as XII, R = H) was also obtained from the 21-alcohol (as XI, R = R′ = H) (91 mg.) in acetone (4.5 ml.) containing water (1.8 ml.) by treatment with concd. hydrochloric acid (2.7 ml.) at room temperature for 16 hr. The product was isolated by addition of water and extraction into methylene dichloride. Crystallization from ethyl acetate–hexane afforded the 21-alcohol (as XII, R = H) (33 mg.).

**Preparation of the Diacetate** (XI, R = Ac, R′ = H) (a) **From the Monoacetate** (XI, R = R′ = H).—A solution of this monoacetate (100 mg.) in pyridine (4 ml.) and acetic anhydride (2 ml.) was heated on the steam-bath for 5 min. After dilution with water and extraction with methylene chloride, the product was crystallized from ethyl acetate to give the diacetate XI (R = Ac, R′ = H) as needles (80 mg.), m.p. 195–198°. The analytical sample was obtained as needles from ethyl acetate, m.p. 197–201°, $[\alpha]^{23}D$ +194° (*c* 1.1), $\lambda_{max}$ (neutral) 226 mμ (ε 7900), $\lambda_{max}$ (alkaline) 224 and 305 mμ (ε 5,400 and 3,300, resp.); $\nu_{max}^{KBr}$ 3600(s), 1765(s), 1745(s), 1710(s), 1660(s), 1230(s) and 1190(s) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 3650(m), 1755(s), 1725(s), 1665(s), 1240(s) and 1180(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26; Ac, 19.36. Found: C, 67.38; H, 7.30; Ac, 18.47.

(b) **From the Alcohol** (as XI, R = R′ = H). Acetylation of 21-alcohol (100 mg.) in the same way as described above gave the same diacetate (XI, R = Ac, R′ = H) as needles (40 mg.).

(c) **From the Stable α-Oximinoketone Monoacetate (IX, R = H) without Isolation of Intermediates.**—A solution of the stable α-oximinoketone monoacetate (IX, R = H; 500 mg.) in acetone (25 ml.) containing water (5 ml.) and concentrated hydrochloric acid (2.5 ml.) was kept at 25° for 16 hr. Addition of water and extraction with methylene chloride gave a gum which was acetylated by means of acetic anhydride (5 ml.) and pyridine (10 ml.) at 100° for 5 min., then treated with water to give a crystalline solid. Recrystallization of the solid from methylene chloride–hexane gave the diacetate (XI, R = Ac, R′ = H; 370 mg.). A solution of the diacetate (XI, R = Ac, R′ = H; 200 mg.) in methanol (40 ml.) containing aqueous sodium hydroxide (4.96 ml., 56.5 mg. NaOH) was refluxed for 15 min., concentrated under reduced pressure, diluted with water, acidified with acetic acid and extracted with methylene chloride. Two crystallizations of the product from ethyl acetate gave the 21-alcohol (as XI, R = R′ = H) as prisms (20 mg.) identical with the compound previously described.

**Preparation of the Triacetate** (XI, R = R′ = Ac).—A solution of the 21-alcohol (as XI, R = R′ = H) (102 mg.) in pyridine (4 ml.) and acetic anhydride (2 ml.) was heated on the steam-bath for 2 hours. The crude product (105 mg.) was chromatographed on alumina (3 g.) and the least polar fractions (87 mg.) were crystallized from ethyl acetate to give the triacetate (XI, R = R′ = Ac) as prisms (75 mg.), m.p. 195–199°, $[\alpha]^{21}D$ +181° (*c* 1.0), $\lambda_{max}$ (neutral) 227 mμ (ε 7,500), $\lambda_{max}$ (alkaline) 222 and 306 mμ (ε 5100 and 3200, resp.).

*Anal.* Calcd. for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04; O, 26.31; Ac, 26.54. Found: C, 66.37; H, 7.24; O, 26.24; Ac, 26.57.

Similar acetylation of the diacetate (XII, R = Ac; see below) caused no change.

**Preparation of the Diacetate** (XV).—A solution of the diacetate (XI, R = Ac, R′ = H; 60 mg.) in dimethylformamide (5 ml.), pyridine (1 ml.) and methanesulfonyl chloride (0.5 ml.) was heated on the steam-bath for 30 min. Treatment of the solution with water gave a solid which was recrystallized from ethyl acetate to give the diacetate XV as needles, m.p. 206–216°, end absorption (at 208 mμ, ε, 12,000) in neutral solution, $\lambda_{max}$ (alkaline) 220 and 307 mμ (ε 5,700 and 3,100, resp.); $\nu_{max}^{KBr}$ 1750(s), 1730(s), 1665(s), 1240(s), 1220(s) and 1200(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09; O, 22.51. Found: C, 70.39; H, 6.95; O, 22.22.

In contrast to its precursor, the diacetate XV gives a yellow color with tetranitromethane in chloroform.

The diacetate (XII, R = Ac; see below) was recovered unchanged after being subjected to the same dehydration conditions.

**Preparation of the Diacetate** (XII, R = Ac). (a). **From the 21-Alcohol** (as XII, R = H).—A solution of this alcohol (300 mg.) in pyridine (15 ml.) and acetic anhydride (7.5 ml.) was heated on the steam-bath for 10 min. The product was precipitated with water and recrystallized from ethyl acetate to give the diacetate XII (R = Ac), as needles (260 mg.), m.p. 210–216°. The analytical sample, obtained by recrystallization from the same solvent, had

m.p. 213–219°, $[\alpha]^{23}D$ +155°, +160° (*c* 1.1), $\lambda_{max}$ (neutral) 247 mμ (ε 15,500), $\lambda_{max}$ (alkaline) 321 mμ (ε 2,200); $\nu_{max}^{KBr}$ 1760(s), 1740(s), 1720(s), 1685(s), 1620(m), 1240(s) and 1200 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1755(s), 1725(s), 1685(s) and 1620(m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26; O, 25.20; Ac, 19.31. Found: C, 67.66; H, 7.26; O, 25.33; Ac, 21.60.

The diacetate XII (R = Ac) gave no color with ferric chloride in ethanol or with tetranitromethane.

(b) **From the Monoacetate** (XII, R = H).—Similar acetylation of this monoacetate (10 mg.) gave the same diacetate (XII, R = Ac).

Treatment of the diacetate (XII, R = Ac; 50 mg.) in methanol (10 ml.) with aqueous sodium hydroxide (1.24 ml.; 14.1 mg. of NaOH) under reflux for 15 min. gave, after crystallization from ethyl acetate, the 21-alcohol (as XII, R = H; 5 mg.) identical with material already described.

**Preparation of the Triacetate** (XVI).—The diacetate (XII, R = Ac; 20 mg.) in pyridine (8 ml.) and acetic anhydride (4 ml.) was refluxed for 48 hours. The dark mixture was decomposed with water, extracted with methylene chloride, and the product chromatographed on alumina (11 g.) The crystalline fractions of lowest polarity crystallized from ethyl acetate–hexane to give the triacetate XVI as colorless prisms, m.p. 190–209°, $[\alpha]D$ +32° (*c* 1.1), $\lambda_{max}$ 237 mμ (ε 18,000), $\lambda_{max}$ (alkaline) 232 and 346 mμ (ε 7,400 and 3,500, resp.); $\nu_{max}^{KBr}$ 1765(s), 1745(s), 1720(s), 1670(w), 1630(w), 1220(s) and 1180(s) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1760(s), 1740(s), 1630(w) and 1605(w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04; O, 26.31; Ac, 26.54. Found: C, 66.23; H, 7.05; O, 26.86; Ac, 25.12.

This triacetate gives a strong yellow color with tetranitromethane in chloroform, whereas the present diacetate (XII, R = Ac) gives no color under the same conditions

**Oximation of Monoacetate** (XI, R = R′ = H).—A solution of the monoacetate (250 mg.) and hydroxylamine hydrochloride (250 mg.) in pyridine (10 ml.) was kept at room temperature for 4 days. The mixture was extracted with tetrahydrofuran after the addition of aqueous sodium chloride, the extract dried ($MgSO_4$) and evaporated. The partially crystalline residue was dissolved in tetrahydrofuran–methylene chloride and chromatographed on alumina (7.5 g.). The first 10 ml. to be eluted gave a gum. The next 20 ml. gave a solid which was recrystallized from tetrahydrofuran–methylene chloride to give the trioxime XIV previously obtained by the oximation of the unstable α-oximinoketone monoacetate VIII. Later fractions, eluted with methylene dichloride–methanol (20:1), yielded the trioxime XIII derived by oximation of the stable α-oximinoketone monoacetate IX (R = H).

**Oxidation of the Diacetate** (IX, R = Ac).—A solution of the diacetate (IX, R = Ac; 500 mg.) in pyridine (10 ml.) was added to the chromium trioxide–pyridine complex (prepared from chromium trioxide (1.05 g.) and pyridine (15 ml.)) and kept at 25° for 5 min. Addition of water and extraction with methylene chloride–ether (1:3) by crystallization of the product from ethyl acetate, gave the derived 11-ketone as needles (310 mg.), m.p. 183–186°, $[\alpha]^{21}D$ + 266° (*c* 1.0 in $CHCl_3$), end absorption in methanol (ε at 214 mμ 3900) $\lambda_{max}$ (alkaline) 297 mμ (ε 4800); $\nu_{max}^{KBr}$ 1780(s), 1750(s), 1720(s), 1705(s), 1590(m) and 1230(s); $\nu_{max}^{CHCl_3}$ 1780(s), 1750(s), 1715(vs), 1590(m), 1220(s) and 1170(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{25}H_{31}O_7N$: C, 65.63; H, 6.83; O, 24.48; N, 3.06. Found: C, 65.06; H, 6.63; O, 24.87; N, 3.26.

**Oxidation of the Triacetate** (X).—A solution of the triacetate **X** (240 mg.) in pyridine (10 ml.) was added to the chromium trioxide–pyridine complex (from chromium trioxide (1.0 g.) and pyridine (15 ml.)) and kept at room temp. for 5 min. Addition of water and extraction with methylene chloride–ether (1:3), followed by crystallization from ethyl acetate gave needles (75 mg.), m.p. 160–175°, $[\alpha]D$ + 147° (*c* 1.0 in $CHCl_3$). Recrystallization from ethyl acetate ether (charcoal) gave a sample (55 mg.) of the derived 11-ketone, m.p. 176–178°, $\lambda_{max}^{MeOH}$ (neutral) 244 mμ (ε 12,200), $\lambda_{max}$ (alkaline) 278 mμ (ε 7,000); $\nu_{max}^{KBr}$ 1770–1750(vs), 1720–1705(s), 1585(m). 1230(vs) and 1190(s) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1750(vs), 1720(s), 1650(w), 1585(m), 1220(s) and 1180(s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{27}H_{33}O_8N$: C, 64.91; H, 6.66; O, 25.62; N, 2.80. Found: C, 65.14; H, 6.65; O, 25.41; N, 2.84.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE UNIVERSITY, AMES, IOWA]

# Preparation and Characterization of Dodecaphenylcyclohexasilane

BY H. J. S. WINKLER, A. W. P. JARVIE, D. J. PETERSON AND H. GILMAN

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The higher melting, perphenylated silicohydrocarbon isolated from the reaction of dichlorodiphenylsilane with sodium or lithium and designated compound B, has now been shown to be dodecaphenylcyclohexasilane and not octaphenylcyclotetrasilane as proposed.

It has been reported in a preliminary communication[1] that the higher melting compound obtained from the reaction of dichlorodiphenylsilane with sodium or lithium was dodecaphenylcyclohexasilane. Kipping, who designated this substance as compound B,[2] assigned the structure octaphenylcyclotetrasilane to it. We have assigned this structure to the lower melting material, compound A, on the basis of synthetic derivatives and ascribed the high reactivity of this compound in free radical type reactions to the ease of cleavage of the strained four-membered ring. The structure assigned to compound A by Kipping (. . .$SiPh_2$·$SiPh_2$·$SiPh_2$·$SiPh_2$. . .) contained two tervalent silicon atoms, but electron spin resonance studies excluded this biradical structure.[4] Their tervalent structure was altogether reasonable at that time in view of some uncommonly reactive transformations.

Since the structure octaphenylcyclotetrasilane was assigned to compound A by us and since this structure had already been assigned to compound B by Kipping, it was felt necessary to investigate further the structure of compound B.

The analytical data obtained for compound B suggested that the compound was composed of diphenylsilylene units, and the hydrogen value[2,3] showed that there was one silicon–silicon bond per diphenylsilylene unit. It was evident from this

(1) H. Gilman, D. J. Peterson, A. W. P. Jarvie and H. J. S. Winkler, *Tetrahedron Letters*, **23**, 5 (1960).

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