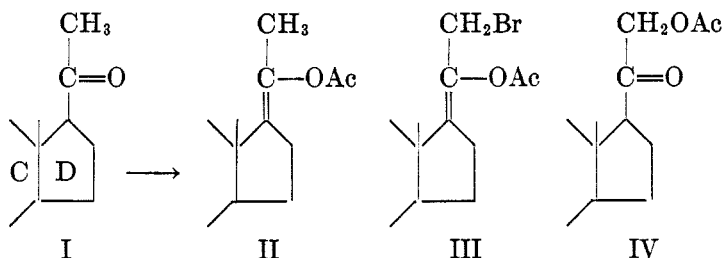


THE WOHL-ZIEGLER BROMINATION OF ENOL ACETATES OF 20-KETO STEROIDS

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The reaction of N-bromosuccinimide (Wohl-Ziegler reaction) with enol esters or ethers does not seem to have been studied as yet (1). Recently, Gallagher

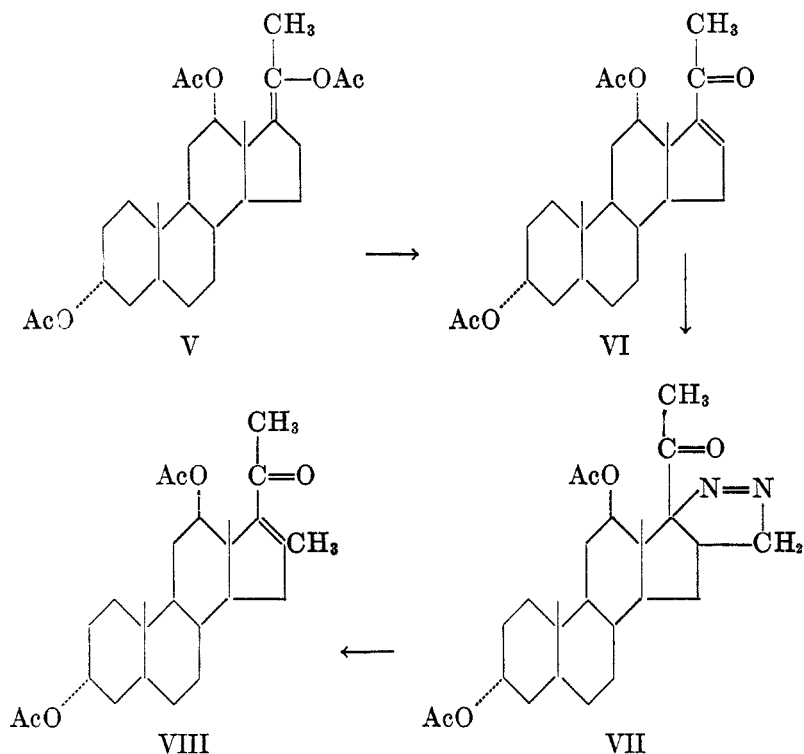


and co-workers (2) described a satisfactory method for the conversion of 20-keto steroids (I) into their enol acetates (II) by refluxing with acetic anhydride and *p*-toluenesulfonic acid. It was of interest to investigate the action of N-bromosuccinimide (NBS) on such enol acetates (II), since if a 21-bromo derivative (III) were formed, acetolysis followed by cleavage of the enol acetate grouping would afford a new method for converting 20-keto pregnane derivatives (I) into members of the cortical hormone series (IV).

Initial bromination experiments were carried out with the readily available, crystalline $\Delta^{17-3(\alpha),12(\alpha),20}$ -triacetoxypregnene (V) in the presence of peroxide; after removal of succinimide and solvent, the residue was refluxed with potassium acetate in acetone solution to effect substitution with any reactive bromide. The crystalline product thus obtained contained by analysis only two acetoxy groups and exhibited a pronounced maximum at 238 $m\mu$. On that basis, it seemed almost certain that the substance was the previously unknown $\Delta^{16-3(\alpha),12(\alpha)}$ -diacetoxy-20-ketopregnene (VI). Its structure was confirmed further when it was noted that the compound underwent the Azzarello reaction (3) with diazomethane to afford a pyrazoline (VII), a behavior characteristic of Δ^{16-20} -keto steroids (4). Finally, in agreement with related pyrazolines (4), VII readily lost the elements of nitrogen on sublimation to lead to a new unsaturated ketone. According to Wettstein (4), the most probable structure for the product of such a thermal treatment is that of a Δ^{16-16} -methyl-20-ketone (VIII).¹

Further investigation of this unexpected reaction between NBS and the enol acetate (V) indicated that the treatment with acetate could be omitted and that

¹ Ring enlargement to a Δ^{17} -D-homo-20-ketone is not excluded, but the observed ultra-violet absorption maximum at 248 $m\mu$ is in good agreement with that predicted (247 $m\mu$) on the basis of Woodward's rule [*J. Am. Chem. Soc.*, **64**, 76 (1942)] for the ketone (VIII) (the possible effect of the five-membered ring is not considered in this calculation).



after refluxing for five minutes with NBS, followed by filtration, removal of carbon tetrachloride, and direct crystallization, 45-50% of the unsaturated ketone (VI) could be isolated. Increasing the reflux time to one-half hour did not raise the yield and the absence of light and peroxide had no deleterious effect. This rapid rate of reaction of the enol acetates (II) with NBS is in marked contrast to the behavior of the corresponding 20-keto steroids (I) (5).

The Wohl-Ziegler reaction was next applied to the crude 20-enol acetate of 3(β)-acetoxy-20-ketoallopregnane, which appears to consist of a mixture of *cis* and *trans* isomers (2), and led to the known (6, 7) Δ^{16} -3(β)-acetoxy-20-ketoallopregnene in 25% over-all yield (based on allopregnanolone acetate). Recently (8), Δ^{16} -20-keto steroids have gained increased importance as starting materials for the preparation of 17(α)-hydroxypregnanes, and a new synthesis of such unsaturated ketones is clearly desirable. While in certain instances (6, 7) the conventional procedure (involving bromination of the 20-ketone followed by dehydrobromination with pyridine) is satisfactory, it fails in other cases such as the 3(α),12(α)-diacetoxy-20-ketopregnane where bromination results in difficultly separable mixtures (9). The present investigation demonstrates that the Wohl-Ziegler reaction *via* the enol acetates represents a satisfactory alternative.

The mechanism of the reaction of NBS with enolic derivatives of 20-keto steroids is not quite clear, but assuming a free radical mechanism for allylic brominations with NBS (1), initial attack at C₁₆ followed by a shift of the double

bond (*i.e.* the single electron) would afford a reasonable path for the direct production of VI and acetyl bromide.

EXPERIMENTAL²

The Wohl-Ziegler reaction on Δ^{17} -3(α),12(α),20-triacetoxy pregnene (V). A solution of 230 mg. of the enol acetate (V), prepared according to Gallagher (2), in 8 cc. of dry carbon tetrachloride was refluxed with 90 mg. of N-bromosuccinimide from five to thirty minutes. All of the reagent was consumed within four minutes and the colorless solution evolved considerable amounts of fumes (acetyl bromide and/or hydrogen bromide). The succinimide was removed by filtration and the filtrate was distilled to dryness under reduced pressure. Trituration of the residue with hexane afforded 100 mg. (48%) of colorless solid melting at 180–185°. The analytical sample of the unsaturated ketone (VI) crystallized from a mixture of hexane and acetone as colorless needles with m.p. 193–193.5°, $[\alpha]_D^{25} +113^\circ$, maxima at 238 $m\mu$ (log E 4.07) and 315 $m\mu$ (log E 2.02) and minimum at 281 $m\mu$ (log E 1.81).

Anal. Calc'd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; acetyl, 20.67.

Found: C, 71.71; H, 8.37; acetyl, 20.53.

The pyrazoline derivative (VII) was prepared according to Wettstein's method (4) by allowing an ethereal solution of 255 mg. of the Δ^{16} -20-ketone (VI) to stand with an excess of diazomethane for twenty hours. Evaporation in a current of air and recrystallization from hexane-acetone gave 220 mg. (79%) of colorless needles with m.p. 175–176° (gas; on cooling and remelting, a melting point of 207–210° was observed), $[\alpha]_D^{25} +142^\circ$.

Anal. Calc'd for $C_{25}H_{34}N_2O_5$: C, 68.09; H, 8.35; N, 6.11.

Found: C, 67.82; H, 8.24; N, 6.59.

Fifty milligrams of the pyrazoline (VII) was sublimed at 170° and 0.002 mm., and the sublimate was recrystallized from hexane-acetone affording 40 mg. (85%) of the Δ^{16} -16-methyl-20-ketone (VIII) with m.p. 213–214°, $[\alpha]_D^{25} +128^\circ$, maximum at 248 $m\mu$ (log E 4.00).

Anal. Calc'd for $C_{25}H_{38}O_5$: C, 72.53; H, 8.90.

Found: C, 72.23; H, 8.49.

The Wohl-Ziegler reaction on Δ^{17} -3(β),20-diacetoxyallopregnene. Δ^5 -Pregnenolone acetate was hydrogenated completely in acetic acid solution with platinum oxide catalyst and the product was oxidized with chromic anhydride in the same solvent. The resulting 3(β)-acetoxy-20-ketoallopregnane (1.4 g.) was converted to the enol acetate (2), and the colored impurities were removed by passage through a short column of alumina. The colorless, oily enol acetate (1.55 g.) thus obtained was refluxed with 0.7 g. of N-bromosuccinimide and 15 mg. of benzoyl peroxide in 40 cc. of carbon tetrachloride for seven minutes. The usual work-up including chromatography gave 0.35 g. (25% over-all yield based on 20-ketone) of Δ^{16} -3(β)-acetoxy-20-ketoallopregnene with m.p. 154–157°, which according to Plattner, *et al.* (6), represents satisfactory material for subsequent reactions. Several recrystallizations from hexane gave colorless crystals with m.p. 161–163°, $[\alpha]_D^{25} +43.6^\circ$, maxima at 240 $m\mu$ (log E 4.01) and 310 $m\mu$ (log E 2.70) and minimum at 275 $m\mu$ (log E 2.32); reported: m.p. 163–165° (7), 166–167° (vac.) (6), $[\alpha]_D +42.2^\circ$ (6).³

Anal. Calc'd for $C_{23}H_{34}O_5$: C, 77.05; H, 9.56.

Found: C, 77.30; H, 9.56.

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² Melting points are corrected. All rotations were determined in a 0.5% chloroform solution and absorption spectra in 95% ethanol. The microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N. J.

³ KLYNE, *et al.*, (10) obtained the following constants on a sample supplied by Plattner (6): m.p. 165–167°, $[\alpha]_D^{25} +36.3^\circ \pm 7^\circ$, maxima at 240 $m\mu$ (log E 3.93) and 320 $m\mu$ (log E 1.92) in ethanol.

SUMMARY

As demonstrated by the two examples, enol acetates of 20-keto steroids react rapidly with N-bromosuccinimide with formation of the corresponding Δ^{16} -20-keto steroids in one step.

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