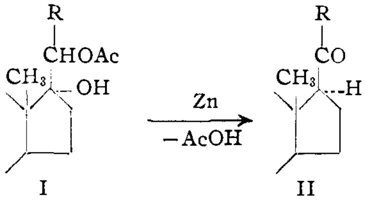
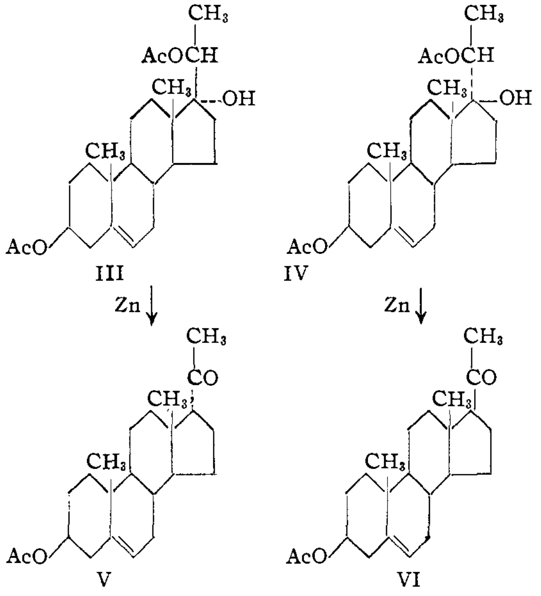
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Serini Reaction

BY LOUIS F. FIESER AND HUANG-MINLON

A reaction introduced to the steroid field by Serini and co-workers[1] that has found service in the partial synthesis of cortical steroids consists in the elimination of the elements of acetic acid from a 17-hydroxy-20-acetoxy compound (I) by treatment with zinc dust. Fieser and Fieser[2] pointed out that although in most of the reported instances the side chain at C_{17} suffers inversion from the α- to the β-orientation, or the reverse, an apparent exception to the rule is recorded by Butenandt.[3] At a time when the configurations of the compounds at C_{17} were completely unknown, Butenandt had conducted a synthesis that afforded two isomers that have been assigned the configurations shown in formulas III and IV on the basis of evidence, theoretical inferences, and a proposed convention for representation of absolute configurations at C_{20} presented in the article by Fieser and Fieser.[2] Butenandt recorded a full experimental description of the conversion of one of the triol diacetates (III or IV) into 17-iso-Δ^5-pregnene-3β-ol acetate (V) but did not indicate which diacetate had been employed. He stated, without experimental documentation, that the isopregnenolone acetate (V) could be obtained from either diacetate or from the unseparated mixture of the two resulting from the synthetic operations. If this is indeed the case, then one of the reactions proceeds without inversion.





In a repetition of Butenandt's work we found the synthesis of the isomers III and IV to be a tedious process because the initial addition of ethylmagnesium halide (or of ethyllithium, as we found) to dehydroepiandrosterone[4] is attended with extensive reduction of the carbonyl group. The remaining steps of dehydration and osmium tetroxide hydroxylation of the *cis–trans* mixture of 17-ethylenes proceed satisfactorily, and the two triol diacetates III and IV were prepared in pure form and each was submitted to the Serini reaction. This reaction also is less smooth than would be inferred from the literature and actually requires repeated reprocessing. Δ^5-Pregnene-3β,17α,20β-triol,3,20-diacetate (III) afforded 17-isopregnenolone acetate (V), the product isolated by Butenandt. 17-Iso-Δ^5-pregnene-3β,17β,20β-triol-3,20-diacetate (IV), however, yielded pregnenolone acetate (VI). Therefore Butenandt's statement is in error and both reactions proceed with inversion as in all other examples of the Serini reaction, including the case of a 20α-acetoxy compound recently reported by Shoppee.[5]

Fieser and Fieser[2] noted that the Serini reaction may possibly proceed through a Δ^{17}-enol-20-acetate, a 17,20-oxide, or a cyclic ortho ester. Marshall, *et al.*,[6] have found that Δ^{17}-enol-20-acetates can be prepared from 20-ketones by the action of acetic anhydride and *p*-toluenesulfonic acid and in one instance they isolated the *cis* and *trans* isomers. We have now prepared a further pair of such isomers in order to see if they behave like intermediates in the Serini reaction. Treatment of pregnenolone with acetic anhydride and an acid catalyst and extensive chromatography of the reaction mixture afforded two isomeric enol diacetates, m. p. 147 and 172°. That the double bond in both isomers is at the 17,20- and not the 20,21-position was established by bromination, when both compounds gave the same tribromo derivative identical with 3β-acetoxy-20-keto-5,6,17-tribromopregnane (IX), prepared by bromination of pregnenolone acetate according to Plattner and co-workers.[7] The substances thus appear to be

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[1] Serini, Logemann and Hildebrand, *Ber.*, **72**, 391 (1939).

[2] Fieser and Fieser, *Experientia*, **4**, 285 (1948)

[3] Butenandt, Schmidt-Thomé and Paul, *Ber.*, **72**, 1112 (1939).

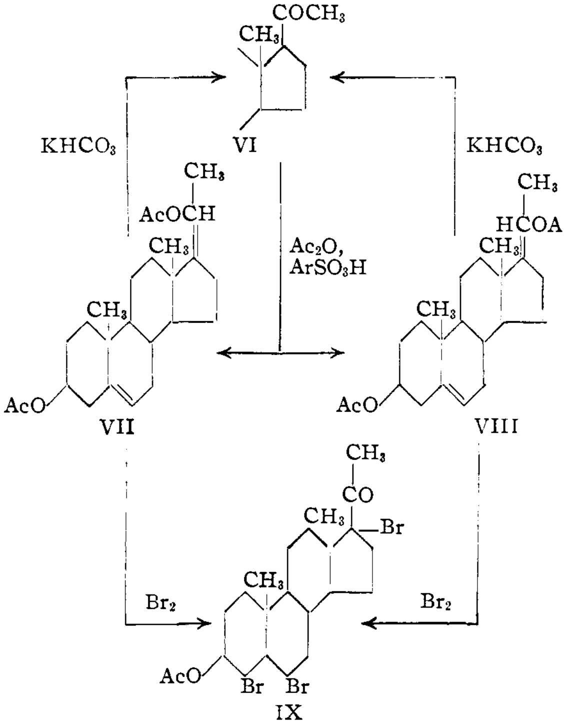
[4] Revised nomenclature proposed by Fieser and Fieser, ref. 2, and in "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publ. Corp., New York, N. Y., 1949.

[5] Shoppee, *Experientia*, **4**, 418 (1948).

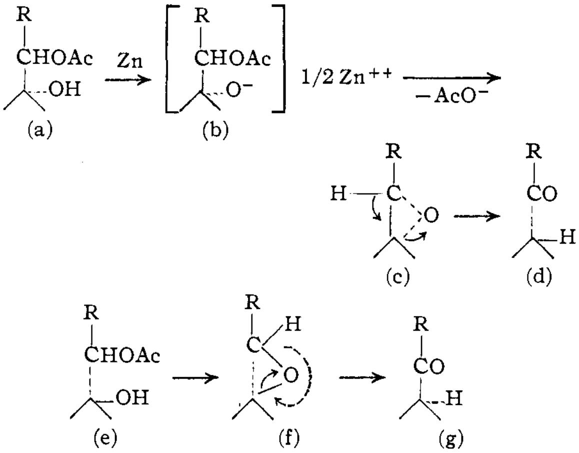
[6] Marshall, Kritchevsky, Lieberman and Gallagher, THIS JOURNAL, **70**, 1837 (1948).

[7] Plattner, Heusser and Boyce, *Helv. Chim. Acta*, **31**, 603 (1948).

the Δ^{17}-enol-20-acetates VII and VIII, but we cannot as yet distinguish between the two formulas. The isomer with the acetoxyl group *cis* to the ring system (VII) would be expected to be hydrolyzed with less ease than that of *trans* structure (VIII), but both substances are hydrolyzed rapidly by potassium bicarbonate in aqueous methanol at room temperature and any difference was not discernible under these conditions. If such an enol acetate were an intermediate in the Serini reaction, one isomer or the other should yield the ketone of the 17-iso series on hydrolysis. Both enol acetates, however, afforded the 17-normal pregnenolone as the sole product, and hence the Serini reaction must proceed by some other mechanism.



Shoppee[5] is of the opinion that the reaction proceeds through a 17,20-oxide, and this seems to us the most likely course. Shoppee's view that oxide formation is initiated by an attack by zinc at C_{20} with removal of an acetate ion appears less plausible, because an acetoxyl group at C_3, and sometimes also one at C_{21}, escapes attack, and because the reaction can be effected with the free alcohol as well as with the acetate.[8] The initiating reaction more likely involves attack by zinc of the 17-hydroxyl group, which is always present, with removal of hydrogen (b). Oxide formation can then occur (c) and then, as noted by Shoppee, if the oxide ring extends to the rear (c) migration of hydrogen from C_{20} results in inversion of the side-chain from the β- to the α-orientation. If the starting material is a 17-iso compound (e) and the oxide ring is β (f), then the rearrangement produces a ketone of the 17-normal series (g).



Experimental

Serini Reaction of Δ^5-Pregnene-3β,17α,20β-triol-3,20-diacetate (III) and 17-Iso-Δ^5-pregnene-3β,17β,20β-triol-3,20-diacetate (IV).—The two isomers were prepared according to Butenandt and co-workers.[3,9] Osmium tetroxide hydroxylation of 2 g. of 3β-acetoxy-$\Delta^{5,17}$-pregnadiene and fractional crystallization of triol diacetate mixture (1.9 g.) gave 1.13 g. of compound III, as long prisms, m. p. 151–152°, and 0.32 g. of compound IV, as small thin plates, m. p. 181°.

When the Serini reaction was conducted by refluxing the material with zinc dust in toluene for several hours according to Shoppee and Reichstein[10] only a small amount of reaction product was isolated (*e. g.*, 5–10 mg. from 200 mg. of III) and the recovered starting material had to be resubmitted to similar treatment several times. Substitution of xylene for toluene seemed to effect some improvement, but in our hands the procedure of sublimation from zinc seemed to be more convenient.

A mixture of 200 mg. of triol diacetate III with 4 g. of zinc dust was finely ground and heated slowly in an air-bath to 180° at 0.03 mm. pressure. The material that sublimed was extracted with chloroform and the product so collected on crystallization from dilute acetone gave 78 mg. (47.5%) of 17-iso-Δ^5-pregnene-3β-ol-20-one-3-acetate; on further crystallization from alcohol the substance melted at 159–164° and at 167–168°, $[\alpha]^{25}\text{D}$ −123° (C = 1% in alcohol). Admixture with pregnenolone acetate depressed the melting point to 129°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.17.

A mixture of 279 mg. of the isomer IV with 5 g. of zinc dust was heated in an air-bath as above. The partly crystalline sublimate on crystallization from alcohol gave 86 mg. of crude product, m. p. 115–120°. Repeated crystallization from dilute alcohol gave material melting at 146–147°, $[\alpha]^{25}\text{D}$ + 22° (C = 1% in alcohol).[11] The substance gave no depression when mixed with Δ^5-pregnene-3β-ol-20-one-3-acetate but depressed the melting point of the 17-iso compound.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.39; H, 9.32.

Saponification of the acetate with potassium carbonate in aqueous methanol gave pregnenolone, melting point and mixed melting point 189°.

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[8] Slotta and Niesser, *Ber.*, **71**, 2342 (1938).

[9] See also Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940).

[10] Shoppee and Reichstein, *ibid.*, **23**, 729 (1940).

[11] Butenandt and Fleischer, *Ber.*, **70**, 96 (1937), report $[\alpha]^{20}\text{D}$ +19.9°.

***cis-* and *trans*-$\Delta^{5,17}$-Pregnadiene-3β,20-diol Diacetates (VII, VIII).**—A solution of 4.4 g. of Δ^5-pregnene-3β-ol-20-one and 2.45 g. of *p*-toluenesulfonic acid in 500 cc. of acetic anhydride was boiled gently and the solvent allowed to distil. After about seven hours the residual dark solution (100–150 cc.) was poured into ice-water, and after a short interval the product was extracted with ether and the solution was washed with water, sodium carbonate solution, and again with water, dried and evaporated. The residue (5.06 g.) was dissolved in a small amount of benzene and the solution diluted with 150 cc. of petroleum ether (30–60°), chromatographed on alumina, and eluted with petroleum ether, benzene-petroleum ether (1:2 and 1:1) and with benzene. The initial crystalline fractions melting over the range 120–133° were combined and on repeated crystallization from methanol gave **enol acetate-A** as long prisms, m. p. 144–146° (1.84 g., 33%). A sample recrystallized again for analysis melted at 147°, $[\alpha]^{25}_{D}$ $-50.0°$ ($C = 2\%$ in chloroform).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.95; H, 9.06. Found: C, 74.82; H, 9.01.

Processing of later chromatographic fractions and of mother liquor material by further chromatography and recrystallization from methanol eventually afforded 0.22 g. of pure **enol acetate-B**, as plates, m. p. 171–172°, $[\alpha]^{25}_{D}$ $-52°$ ($C = 2\%$ in chloroform).

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.95; H, 9.06. Found: C, 74.58; H, 8.94.

The methanol mother liquors afforded 1.2 g. of a mixture of A and B, m. p. 115–117°, that showed no depression when mixed with either isomer.

Bromination of Enol Acetate-A (m. p. 147°).—A solution of 0.08 g. of bromine in chloroform was added dropwise at room temperature to a solution of 0.1 g. of A in 5 cc. of chloroform. Removal of the solvent in vacuum and crystallization from acetone-ligroin (70–90°) gave 90 mg. (60%) of bromo product melting at 162°, dec. Recrystallization from the same solvent gave pure material in the form of plates, m. p. 166–168°, dec. Plattner and coworkers[7] have reported the preparation of **3β-acetoxy-20-keto-5,6,17-tribromopregnane** (IX) by bromination of pregnenolone acetate, but they report merely the melting point 149–151° and give no analysis. We prepared the tribromo compound according to their procedure and on repeated recrystallization from acetone-ligroin formed plates, m. p. 167–168°, dec., that gave no depression when mixed with the substance from enol acetate-A.

Anal. Calcd. for $C_{23}H_{33}O_3Br_3$: C, 46.25; H, 5.56. Found: C, 46.26; H, 5.38.

The bromination of isomer-A was conducted more conveniently in acetic acid; dilution with water precipitated the product and one crystallization from acetone-ligroin gave plates, m. p. 161–162° in 71% yield. The fully purified sample melted at 166–167° dec., and gave no depression with either of the above samples.

Bromination of Enol Acetate-B (M. p. 171°).—Bromination in acetic acid as above gave plates, m. p., and mixed m. p. with the product from A, 167–168°, dec.

Anal. Calcd. for $C_{23}H_{33}O_3Br_3$: C, 46.26; H, 5.56. Found: C, 46.19; H, 5.31.

Saponification of the Enol Acetates.—A solution of 0.1 g. of isomer A or B in 10 cc. of methanol was treated with a solution of 0.1 g. of potassium carbonate in 1 cc. each of water and methanol and let stand at room temperature for five hours. The product, precipitated by water, on crystallization from dilute alcohol gave plates identified by crystal form, m. p. and mixed m. p. (189–190°) as Δ^5-pregnene-3β-ol-20-one; yield, 60 mg. (76%) from A, 58 mg. (73%) from B.

Saponification of 30 mg. of A or B in 4 cc. of methanol was also conducted by adding a solution of 30 mg. of potassium bicarbonate in a few drops of water and 2 cc. of methanol. After forty-eight hours at room temperature, processing as above gave crude pregnenolone, m. p. 184–188°: 19.5 mg. (82%) from A, and 19.0 mg. (80%) from B. The recrystallized samples had the m. p. and mixed m. p. 189–190°.

Summary

A statement in the literature indicating that the Serini reaction in one instance proceeds without inversion at C_{17} has been shown to be in error.

A pair of *cis–trans*-Δ^{17}-enol-20-acetates prepared from pregnenolone both yield pregnenolone and not 17-isopregnenolone on saponification. Such substances therefore cannot be intermediates in the Serini reaction, and this probably proceeds through the oxide.

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A New Method of Preparing the High Explosive RDX[1]

BY W. E. BACHMANN AND JOHN C. SHEEHAN[2]

Cyclotrimethylenetrinitramine (also called cyclonite and more recently RDX)[3] was first prepared in 1899 from nitric acid and the dinitrate of hexamethylenetetramine by Henning,[4] who gave few details and offered no structure for the product. Herz[5] proposed the correct structure for the compound and recognized its explosive properties, and Hale[6] reported improved directions for its preparation. In 1940 we learned that Ross and Schiessler[7] had obtained RDX from formaldehyde, ammonium nitrate and acetic anhydride in the absence of nitric acid, but no details of their experiments were available to us.

In the conventional process for making RDX, hexamethylenetetramine is treated with 98–100% nitric acid. The reaction has been formulated by Hale[6] as shown in Equation 1.

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(1) This investigation was carried out in 1941 under a contract recommended by the NDRC between the OSRD and the Regents of the University of Michigan.

(2) Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.

(3) According to various reports RDX played a critical role in World War II as one of the most powerful high explosives. For an excellent popular discussion of the development and large scale production of RDX and its importance to the war effort see James Phinney Baxter 3rd, "Scientists Against Time," Little, Brown and Company, Boston, 1946, pp. 256–259.

(4) Henning, German Patent 104,280 (1899).

(5) Herz, Swiss Patent 88,759 (1920); *Chem. Zentr.*, **92**, IV, 926 (1921).

(6) Hale, THIS JOURNAL, **47**, 2754 (1925).

(7) Ross and Schiessler, McGill University, unpublished results.