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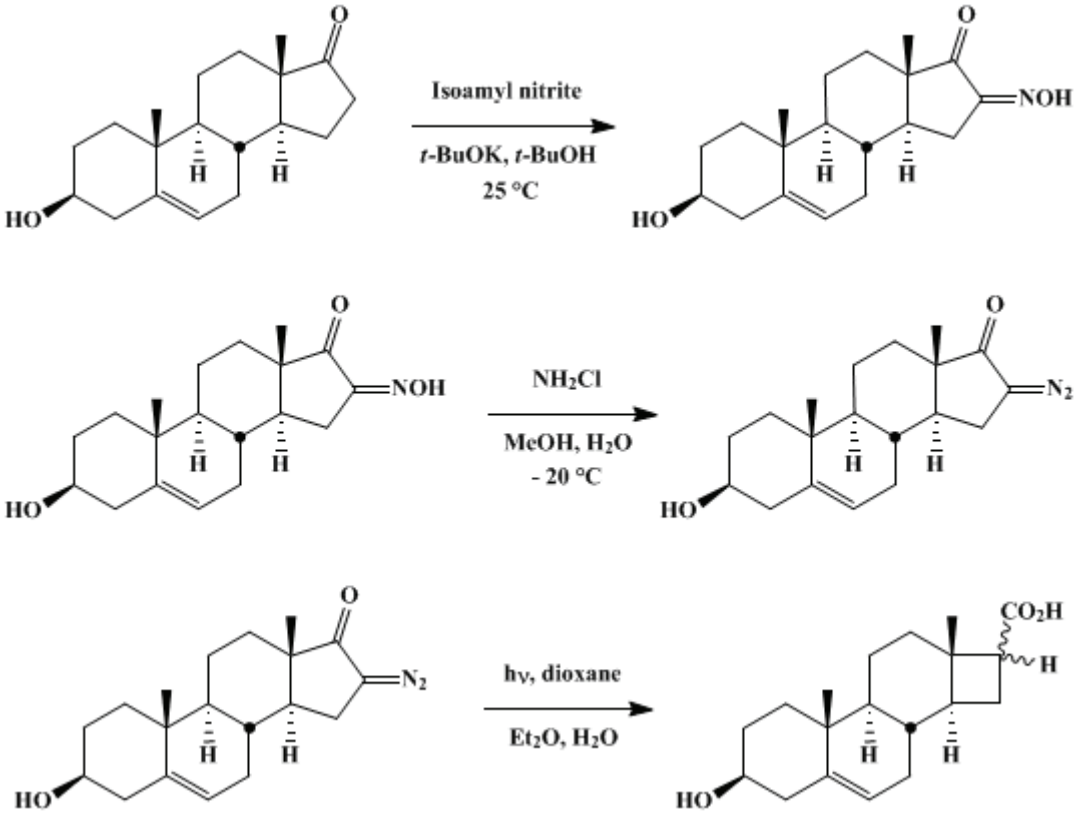
FORMATION AND PHOTOCHEMICAL WOLFF REARRANGEMENT OF CYCLIC α-DIAZO KETONES: D-NORANDROST-5-EN-3β-OL-16-CARBOXYLIC ACIDS

[D-Norandrost-5-ene-16-carboxylic acids, 3β-hydroxy-, (3β,16α) and (3β,16β)-]



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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *16-Oximinoandrost-5-en-3β-ol-17-one*. A 2-l., three-necked, round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a pressure-equalizing dropping funnel is charged with 750 ml. of anhydrous *tert*-butyl alcohol (Note 1). As the *tert*-butyl alcohol is slowly stirred, a stream of dry nitrogen is passed through the flask and 12.2 g. (0.312 g.-atom) of potassium metal is added cautiously. The flask is surrounded by a water bath maintained at 70° to assist in dissolving the potassium metal. After 1.5 hours the stirred mixture is homogeneous, the water bath is removed, and the reaction mixture is allowed to cool to room temperature. To the potassium *tert*-butoxide solution is slowly added 45.0 g. (0.156 mole) of dehydroisoandrosterone (Note 2), and stirring is continued for one hour until the gold-colored mixture is again homogeneous. To the reaction mixture is now added, dropwise, 36.5 g. (42.0 ml., 0.312 mole) of isoamyl nitrite (Note 3), and stirring is continued overnight at room temperature.

The deep-orange reaction mixture is diluted with an equal volume of water, poured into a 2-l.

separatory funnel, and acidified with 3 *M* hydrochloric acid. The addition of 400 ml. of diethyl ether assists in effecting the separation of the clear, yellow, aqueous, lower layer from the fluffy-white ethereal suspension that forms the upper layer. This suspension is filtered through a 250-ml. coarse sintered glass funnel, and the precipitate of oximino ketone is washed with ether several times. After drying overnight in a vacuum desiccator at −5°, 48.0–48.5 g. (79% (Note 5) and (Note 6)) of a white product, m.p. 245–247° (dec.), is obtained; its ^{1}H NMR spectrum (pyridine) shows it to be a 1:1 solvate of the oximino ketone with *tert*-butyl alcohol (Note 4). This product is used without further purification in the synthesis of the α-diazo ketone (Note 7).

B. 16-*Diazoandrost*-5-*en*-3β-*ol*-17-*one*. A 1-l., three-necked, round-bottomed flask is fitted with a mechanical stirrer, a 50-ml., pressure-equalizing dropping funnel, and a thermometer. As stirring is initiated, 375 ml. of methanol and 72 ml. of 5.0 *M* aqueous sodium hydroxide (0.36 mole) is added to the flask, followed by 18.0 g. (0.0460 mole) of the 1:1 solvate of 16-oximinoandrost-5-en-3β-ol-17-one with *tert*-butyl alcohol. The oximino ketone readily dissolves, giving a yellow solution. To the reaction mixture is added 28.3 ml. of concentrated aqueous ammonia (0.425 mole), and the flask is surrounded by an ice bath, maintaining the reaction temperature at 20°. Through the dropping funnel 133 ml. of 3.0 *M* aqueous sodium hypochlorite (0.40 mole) is added dropwise. The sodium hypochlorite solution should be kept near 0°; 25-ml. portions should be added to the addition funnel and the remaining solution should be kept in an ice bath (Note 8). It is important that the rate of addition of the sodium hypochlorite, and the position of the ice bath be adjusted so as to maintain the temperature of the reaction mixture at 20° ± 1° (Note 9). As soon as all of the sodium hypochlorite has been added, the ice bath is removed, and the reaction mixture is allowed to warm to room temperature and stirred for 6 hours.

The reaction mixture is diluted with an equal volume of water and extracted with 400-ml. and 200-ml. portions of dichloromethane. The combined dichloromethane extracts are washed with three 250-ml. portions of 20% aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated, leaving a yellow solid. Recrystallization from acetone gives 8.0–9.3 g. (55–64%) of crystalline α-diazo ketone, m.p. 200–202° (dec.) (Note 10).

C. D-*Norandrost*-5-*en*-3β-*ol*-16α- *and* 16β-*carboxylic acids*. In a solution of 500 ml. of 1,4-dioxane, 1250 ml. of ether, and 250 ml. of water contained in a 3-l. three-necked, round-bottomed flask is dissolved 7.50 g. (0.0239 mole) of 16-diazoandrost-5-en-3β-ol-17-one. The flask is fitted with a reflux condenser, a quartz immersion well, and a nitrogen inlet. After the reaction vessel has been flushed with nitrogen, the diazo ketone solution is irradiated for 48 hours with a 450-watt Hanovia lamp with a Corex filter (Note 11). The photolysis mixture is decanted in portions into a 2-l. separatory funnel, washed three times with 500-ml. portions of water, removing the dioxane, and dried over magnesium sulfate. The ether is evaporated, leaving a pale-yellow residue. The residue is digested with 125 ml. of boiling dichloromethane under reflux for 30 minutes. The dichloromethane solution is allowed to cool to room temperature and filtered, separating about 1.4 g. of the crude α-isomer as a white powder. This solid is recrystallized by dissolving it in a large volume of methanol (125 ml.) and concentrating the solution to a small volume (25 ml.), yielding 1.2 g. (17%) of D-norandrost-5-en-3β-ol-16α-carboxylic acid as a white solid, m.p. 271–274° (Note 12). The β-isomer is most readily obtained by concentrating the dichloromethane mother liquor and dissolving the residue in a mixture of 75 ml. of methanol and 25 ml. of ether. This solution is treated with an excess of diazomethane in ether at room temperature. After one hour at room temperature, the excess diazomethane is removed with a stream of nitrogen, the solvent is evaporated, and the solid residue is chromatographed on 175 g. of Woelm neutral alumina Activity Grade II. Elution with a 3:1 (v/v) benzene–ether mixture gives 3.9 g. of a white solid, which is recrystallized from ether-heptane, giving 3.0–3.1 g. (39–41%) of white, crystalline methyl D-norandrost-5-en-3β-ol-16β-carboxylate, m.p. 161–163° (Note 13) and (Note 14).

2. Notes

1. Anhydrous *tert*-butyl alcohol may be conveniently prepared by distilling it from calcium hydride into a receiver containing Type 4A molecular sieves.
2. Dehydroisoandrosterone is available from Searle Chemicals, Inc.
3. Isoamyl nitrite of sufficient purity may be prepared by the method in *Org. Synth.*, **Coll. Vol. 2**, 108

(1943). The isoamyl nitrite is stored over anhydrous magnesium sulfate until used.
4. The ^{1}H NMR spectrum (pyridine) included signals at δ 0.97 (s, 3H), 1.03 (s, 3H), 1.42 (s, 9H) and 5.37 (m, 1H).
5. The submitters, working on twice the scale described, obtained 90.0 g. (74%) of the solvate, m.p. 245–247°.
6. This oximino ketone has been previously prepared by a somewhat different procedure[2] and recrystallized from 2-propanol, m.p. 247–248°.
7. Other oximino ketones may be too soluble in ether to permit utilization of this isolation procedure. In this case, the submitters, working on twice the scale described, utilized the following procedure. After acidification of the reaction mixture, the oximino ketone is extracted into 1000 ml. of ether, and the ethereal extract is washed with four 100-ml. portions of saturated aqueous sodium hydrogen carbonate and exhaustively extracted with 0.5 *M* aqueous potassium hydroxide in 250-ml. portions until acidification of the basic extract gives no oximino ketone. A stream of nitrogen is bubbled through the combined basic extracts, removing any dissolved ether before the solution is cooled in an ice bath and acidified with 3 *M* hydrochloric acid. The precipitate is collected by suction filtration and dried in a vacuum desiccator.
8. A procedure for preparing concentrated sodium hypochlorite solution is given by Coleman and Johnson.[3] Common bleach solution, such as Clorox, may also be used, although the volume of the solution is considerably increased.
9. If the temperature of the reaction mixture is maintained below 20°, an appreciable amount of colorless α-dichloro ketone is obtained.[4] If the temperature rises above 20°, the chloramine decomposes before it has time to react with the oximino ketone. The generation of chloramine *in situ* is quite exothermic, and care must be taken to maintain the temperature at 20°.
10. The submitters, working on twice the scale described, obtained 21.6 g. (74%) of product, m.p. 201–202° (dec.).
11. A Pyrex filter has been used; however, the photolysis appears to proceed more cleanly through Corex. The photolysis is considered complete when the IR spectrum of a sample shows no diazo absorption at 2065 cm^{-1}.
12. Utilizing a somewhat different procedure, Mateos and Pozas have also obtained the α-carboxylic acid, m.p. 272–275°.[5]
13. The reported melting point of the β-methyl ester is 163–164°.[5]
14. The submitters, working on twice the scale described, obtained 2.8 g. (19%) of the α-acid, m.p. 272–275°, and 9.2 g. (61%) of the methyl ester of the β-acid, m.p. 161–163°.

3. Discussion

The earliest methods for preparing cyclic α-diazo ketones involved the oxidation of the monohydrazones prepared from α-diketones, generally using mercury(II) oxide.[6,7] Recent modifications of this procedure include the use of calcium hypochlorite in aqueous sodium hydroxide or "activated" manganese dioxide as oxidants.[8] The latter reagent, especially, seems preferable to mercury(II) oxide. The base-catalyzed decomposition of the monotosylhydrazones of α-diketones has been used to prepare α-diazo ketones. Such reactions have been performed in aqueous sodium hydroxide,[9,10] with basic aluminum oxide in dichloromethane,[11] and with a variety of other bases. A promising and novel approach to cyclic α-diazo ketones involves the reaction of α-hydroxymethylene ketones with diethylamine and tosyl azide, giving high yields of the α-diazo ketone.[12]

The present procedure for the synthesis of an α-diazo ketone is a modification of the Forster reaction,[13] which has been recently exploited by numerous workers.[10,14,15,16,17,18] The synthesis is convenient, generally applicable to cyclic ketones, and offers moderate yields (60–70%) of pure α-diazo ketones.

The photochemical Wolff rearrangement represents a generally useful ring contraction technique.[19,20]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

alumina

D-Norandrost-5-ene-16-carboxylic acids, 3β-hydroxy-, (3β,16α) and (3β,16β)-

dehydroisoandrosterone

D-norandrost-5-en-3β-ol-16α-carboxylic acid

methyl D-norandrost-5-en-3β-ol-16β-carboxylate

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium hydrogen carbonate (144-55-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

2-propanol (67-63-0)

manganese dioxide (1313-13-9)

potassium (7440-09-7)

diethylamine (109-89-7)

sodium hypochlorite (7681-52-9)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

Isoamyl nitrite (110-46-3)

Diazomethane (334-88-3)

aluminum oxide (1344-28-1)

calcium hypochlorite (7778-54-3)

heptane (142-82-5)

chloramine (10599-90-3)

tert-butyl alcohol (75-65-0)

calcium hydride (7789-78-8)

1,4-dioxane (123-91-1)

16-oximinoandrost-5-en-3-ol-17-one (21242-37-5)

16-Diazoandrost-5-en-3β-ol-17-one (26003-42-9)

tosyl azide (941-55-9)

potassium tert-butoxide (865-47-4)