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METHODS OF SYNTHESIS AND TECHNOLOGY OF DRUG PRODUCTION

SYNTHESIS OF KETONES, KETOALDEHYDES, AND KETOACIDS FROM NITROESTERS*

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In an extension of work on the synthesis of nitrophenylalkylketones [2-5] and glyoxylic acids [6], the α-elimination of the nitroester group was of scientific and practical interest as a method for the synthesis of other aromatic ketones and also of difficultly-obtainable steroid ketoaldehydes and alkyl-aryl ketoacids.

Literature data on this problem is limited to examples of the preparation of phenylglyoxal from benzoylmethyl nitrate by the action of piperidine in ether [7] and 4,4′-dinitrobenzophenone (VI) from 4,4′-dinitrobenzhydryl nitrate (II) by oxidation with chromic anhydride in acetic acid or reduction by sodium sulfide in aqueous alcohol [8]. In the latter case, by analogy with the reduction of pentaerythrityl tetranitrate to pentaerythritol, the authors proposed to prepare 4,4′-dinitrobenzhydrol, but they unexpectedly isolated ketone VI. The authors did not explain the reason for the unusual course of the reaction of nitrate II under the action of sodium sulfide.

In our opinion, sodium sulfide in this reaction acts as a basic reagent which produces α-elimination in II with the formation of VI. Interest was therefore turned to this proposal: to study the reaction of II with basic reagents not showing reductive properties.

In order to obtain the starting nitroesters (I-III) we studied the nitration of 4-chlorophenylmethylcarbinol, mandelic acid and, more comprehensively than in [8], the nitration of benzhydrol. It was established that upon nitration of 4-chlorophenylmethylcarbinol with concentrated nitric acid, the main product of the reaction is 1-(3-nitro-4-chlorophenyl)ethylnitrate (I). The possible admixture of the 2-nitro isomer was not eliminated.

The nitration of mandelic acid with nitric acid also took place smoothly to form mixed nitrates of nitromandelic acid with the desired 4-nitroisomer (III) predominating.

The structures of the synthesized nitroesters I and III were established by oxidation with 30% nitric acid by the method of [3] to give 3-nitro-3-chlorobenzoic and 4-nitrobenzoic acids, respectively.

The nitration of benzhydrol took place with more difficulty. Upon nitration of this alcohol with concentrated nitric acid both we and [8] observed a yield of nitrate II of about 9%. The nitration of benzhydrol with a more aggressive nitrating mixture consisting of concentrated nitric and sulfuric acids allowed a threefold increase in yield of II.

17α-Hydroxy-21-nitroxypregn-4-en-3,20-dione (IV) was obtained by an exchange reaction of 17α-hydroxy-21-indopregn-4-en-3,20-dione with silver nitrate in acetonitrile.

A study of the α-elimination reaction of nitroesters I-IV showed that treatment of all of them with sodium hydroxide in alcohol, and, for nitroester III, in water, were transformed easily and in high yield into the corresponding carbonyl compounds (V-VIII); 3-nitro-4-chloroacetophenone (V); 4,4′-dinitrobenzophenone (VI), 4-nitrophenylglyoxylic acid (VII), and the hitherto unknown 17α-hydroxy-3,20-diketopregn-4-en-21-al (VIII).

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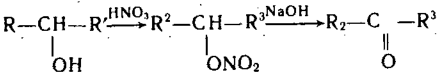
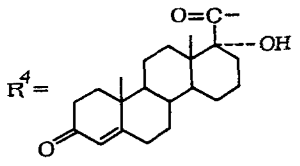


$$\underset{\displaystyle OH}{R-\overset{|}{C}H}-R^1 \xrightarrow{HNO_3} R^2-\underset{\displaystyle ONO_2}{\overset{|}{C}H}-R^3 \xrightarrow{NaOH} R_2-\underset{\displaystyle O}{\overset{\|}{C}}-R^3$$

I—III V—VII

R=Ph,4-ClC$_6$H$_4$; R^1=Me, Ph, COOH.
I,V:R^2=3-NO$_2$-4-ClC$_6$H$_3$, R^3=Me.
II, VI: R^2=R^3=4NO$_2$C$_6$H$_4$.
III, VII: R^2=4-NO$_2$C$_6$H$_4$, R^3=COOH.

$R^4-CH_2I \xrightarrow{AgNO_3} \underset{IV}{R^4-CH_2ONO_2} \xrightarrow{NaOH} \underset{VIII}{R^4-CHO}$



The inorganic products of the reactions of I-IV with sodium hydroxide were sodium nitrate and water.

It should be noted that ketoacid VII is easily soluble in water. Therefore it is most conveniently isolated from the reaction mixture as the barium salt (VIIa), difficultly-soluble in water. Subsequent passage of the solution through a column of Kationite KY-2 gives the free acid VII.

EXPERIMENTAL

The found values for the elemental analyses of I, III, IV, VII, VIIa, VIIb, and VIII corresponded with the calculated.

Nitration of 4-Chlorophenylmethyl Carbinol. To 60 ml of 98% nitric acid, heated to 40°C, was gradually added over 25-30 min in small portions with stirring 2.7 g of dry urea, maintaining the temperature of the flask between 40-43°C. Then the acid was stirred for 30 min at the same temperature, cooled to −12 to −10°C, and 14 g of 4-chlorophenylmethyl carbinol was added with stirring over 45 min, maintaining the temperature of the flask between −10 and −7°C. The reaction mass was stirred for 30 min at −10 to −7°C, added to ice-water (400 ml), the separated oily nitration product was extracted with chloroform (2 × 100 ml), the extract was washed with water, dried with sodium sulfate, and the solvent was removed under vacuum to give 16.4 g (79%) of crude 1-(3-nitro-4-chlorophenyl)ethylnitrate (I), which crystallized upon standing. Pure I had mp 35.5-36.5°C (from a mixture of petroleum ether−methanol, 3:1).

Nitration of Benzhydrol. To a mixture of 30 ml of concentrated sulfuric acid (specific gravity 1.84) and 20 ml of concentrated nitric acid (specific gravity 1.50) under cooling (0-10°C) and stirring was added 5.0 g of benzhydrol over 25-30 min. The nitration mixture was stirred for 2-2.5 h at the same temperature and poured into 500 ml of water with stirring and cooling. The precipitated mixed nitrates of dinitrobenzhydrol was filtered off, washed with water, methanol (10 ml) and crystallized from 10 ml of glacial acetic acid to give 2.4 g (27.6%) of 4,4′-dinitrobenzhydryl nitrate (II) with mp 156-159°C, suitable for the synthesis of ketone VI without another crystallization. A second recrystallization of II gave mp 160-162°C. Lit. [8], mp 160.5-162°C.

Nitration of mandelic acid was carried out analogously to the nitration of 4-chlorophenylmethyl carbinol. Yield of the mixture of isomeric nitrates was 80-88%, mp 93-96°C. For the isolation of pure nitrate of 4-nitromandelic acid (III), the isomer mixture was crystallized from a mixture of chloroform−ethanol (10:1) to give pale yellow crystals, mp 126.5-127°C (dec.).

17α-Hydroxy-21-nitrooxypregn-4-en-3,20-dione (IV). To a solution of 9.13 g (0.02 mole) of 17α-Hydroxy-21-iodopregn-4-en-3,20-dione in 100 ml of dry acetonitrile was added over 20 min a solution of 3.4 g (0.02 mole) of silver nitrate in 15 ml of acetonitrile, giving an immediate precipitate. The mixture was stored at room temperature for 24 h, the precipitate was filtered off, washed with acetonitrile (twice with 10 ml), and dried to give 4.65 g (~100%) of silver iodide. The combined filtrates were evaporated under vacuum to dryness and the residue was washed with water and dried to give 7.3 g (93.4%) of crude IV, mp 118-121°C. Pure IV has mp 123.5°C (from a mixture of chloroform–petroleum ether).

3-Nitro-4-chloroacetophenone (V). To a solution of 13.8 g (0.056 mole) of crude I in 50 ml of ethanol was added with stirring over 1 h a solution of 2.5 g (0.062 mole) of sodium hydroxide in 35 ml of ethanol. The temperature of the reaction mixture was maintained between 14-18°C by cooling the flask in ice water. After adding the alkali, the mixture was stirred for 3 h at 15-20°C, the excess base was neutralized with acid (acetic, hydrochloric, or sulfuric) to pH of about 5, 0.1 g of activated charcoal was added and the mixture was heated at 70-78°C, filtered, and the alcohol was almost completely distilled off. Water was added to the residue, the precipitate was filtered, washed on the filter with water until the sodium nitrite was absent from the wash water, then ethanol (the ethanolic mother liquor was collected separately). After drying, 5.4 g of V with mp 96-98°C was obtained, which was crystallized from water or aqueous ethanol to give pale yellow crystals, mp 98-101°C. Evaporation of the ethanolic mother liquor and crystallization of the residue from water or aqueous ethanol gave an additional 0.6-0.7 g of V with mp 97-101°C. Lit. [9], mp 99-101°C. Combined yield of V was 6.0-6.2 g (54-55%) based upon crude I. Use of pure I increased the yield of V to 80%.

4,4'-Dinitrobenzophenone (VI). To a hot solution of 3.2 g (0.01 mole) of II in 250 ml of methanol was added 1.1 g (0.011 mole) of 40% aqueous sodium hydroxide. The mixture was boiled for 40 min, the excess base was neutralized with acetic acid, the solution was warmed with charcoal, filtered, and the solvent was evaporated to a small volume. The resulting residue was filtered off, washed with water and methanol, and dried to give 2.1 g (77.7%) of crude VI, mp 185-188°C. Crystallization from alcohol gave mp 190-192°C. Lit. [8], mp 190.7-191.6°C.

4-Nitrophenylglyoxylic Acid (VII). To a suspension of 9 g of mixed nitroesters of nitromandelic acid in 20 ml of water was added over 10-15 min with stirring and cooling (15-18°C) 9.2 g of 33.6% aqueous sodium hydroxide. The solution was stirred for 3-4 h at 18-20°C, acidified with acetic acid, and a solution of 5.1 g of barium chloride dihydrate in 25 ml of water was added, giving heavy precipitate. The mixture was kept for 3-4 h at 0-5°C, the precipitate was filtered off, washed with water, and dried to give 8.2 g of crude barium salt of VII (VIIa) with mp 238-239°C (dec.). Crystallization from 70 ml of water with carbon treatment gave 5.2 g (36-41%, based upon mandelic acid) of pure VIIa, mp 245-246°C (dec.), yellow crystals, difficultly soluble in cold water. Use of pure III gave VIIa in 93% yield.

Acid VII was obtained by dissolution of 1.0 g of VIIa in 100 ml of distilled water by mild heating, then cooling to 18-20°C, and passage through a column of Kationite KY-2 (5 g per g of VIIa), the eluate (containing no barium ions) was evaporated under vacuum at a temperature less than 60°C, and traces of moisture were removed by azeotropic distillation with benzene. Crude VII was crystallized from benzene after treatment with charcoal to give a 90% yield of pure VII, yellow crystals with mp 105-106°C, easily soluble in water, alcohol, and most organic solvents, and difficultly soluble in benzene and petroleum ether. The semicarbazone of VII (VIIb) has mp 196-198°C (dec., from water). Lit. [10] VII mp 150°C, [10] VII mp 146°C. Lit. [12] VII mp 105-106°C, VIIb mp 234°C.

17α-Hydroxy-3,20-diketopregn-4-en-21-al (VIII) was obtained from IV analogously to V in 72% yield, mp 263-265°C (dec., darkens at 223°C, from alcohol).

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