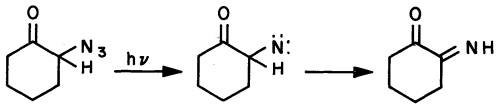
SOME REACTIONS OF ALICYCLIC α-AZIDOKETONES[1]

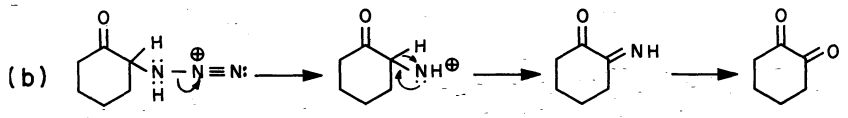
O. E. EDWARDS AND K. K. PURUSHOTHAMAN[2]

In connection with another problem we examined the preparation and reactions of two alicyclic α-azidoketones. Our initial object was a study of the photochemical decomposition of these compounds, but several factors forced a shift of emphasis to their acid- and base-catalyzed reactions.

The reaction of 2-chlorocyclohexanone and sodium azide in dimethylsulphoxide gave a good yield of yellow oil. This analyzed correctly for the 2-azidoketone and had intense absorption at 2110 cm^{-1} characteristic of an alkyl azide. However, it could not be distilled under reduced pressure without extensive decomposition and polymerization. Irradiation of a hexane solution of 2-azidocyclohexanone in a quartz vessel with ultraviolet light resulted in steady evolution of nitrogen. An oil deposited from the solution. This and the material remaining in the hexane after complete decomposition of the azide had absorption bands characteristic of an α-iminoketone (ν_{max} 3400 and 1670 cm^{-1}). However, the product could only partly be distilled under 15 mm pressure. It seemed that the expected (1) mode of reaction (equation *a*) was taking place, but that the iminoketone

(a) 

was undergoing rapid polymerization. It appeared probable that acid catalysis would bring about a similar decomposition, as indicated in equation *b*, with the sensitive iminoketone now being rapidly hydrolyzed to the α-diketone. This indeed proved to be a smooth reaction leading in good yield to 1,2-cyclohexanedione. This very convenient

(b) 

synthesis of the α-diketone is superior to the selenium dioxide oxidation or oximinoketone hydrolysis (2) methods for its preparation. A parallel acid-catalyzed conversion of cycloalkylazides to the corresponding ketones was described some time ago by Boyer and co-workers (3).

Attempts to prepare pure 2-azidocholestanone by the reaction of 2-α-bromocholestan-3-one with lithium azide in methanol or dimethylformamide or with sodium azide in dimethylsulphoxide were unsuccessful. A steady state concentration of the azidoketone was produced, as revealed by the infrared spectrum, but it was continuously being converted to a substance with ν_{max} 1655 cm^{-1}. After 1 hour at 50° in dimethylformamide containing excess lithium azide the bromoketone had been completely converted to the new compound. That this was the α-iminoketone I was shown by its hydrolysis to 2,3-cholestanedione, and by its reduction to a mixture rich in a 2-aminocholestan-3-ol which was characterized as its O,N-diacetate. The derived acetamido alcohol II was oxidized to 2-α-acetamidocholestane-3-one (III) (ν_{max} 1710 cm^{-1}, λ_{max} 279 mμ). Wolff-Kishner reduction of this gave a good yield of cholestane.[3]

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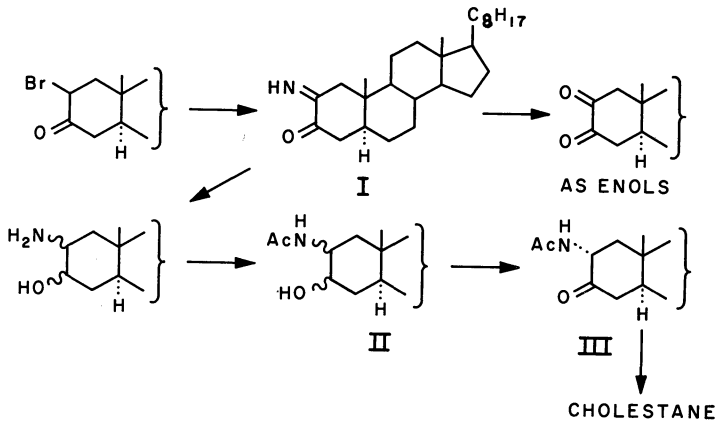
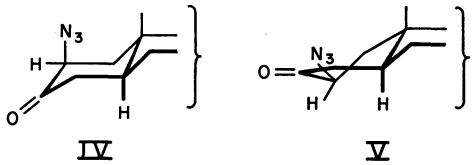
[2]*National Research Council of Canada Postdoctoral Fellow.*

[3]*The elimination of α-substituents in this reaction is well known (4). The olefin which is first produced is often reduced to the hydrocarbon by diimide formed from the hydrazine present (5).*

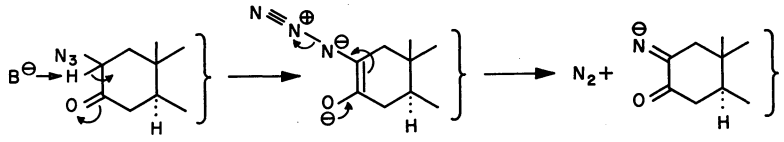


Boyer and Straw observed that thermal decomposition of phenacyl azides requires temperatures around 200° (6). The decomposition of liquid α-azidocyclohexanone began below 100°, but the compound was unchanged after several hours in boiling methanol or in dimethylformamide at 60° with or without added lithium bromide or lithium azide. Hence 2-azidocholestan-3-one is anomalously reactive. Investigation of its instability soon proved that it too was inert in methanol or dimethylformamide near 60°, or in these solvents containing lithium bromide. Clearly then, the observed decomposition during the preparative reaction is a lithium-azide-catalyzed process.

A conformational driving force for the accelerated decomposition of the azidocholestanone seems probable. Spectroscopic evidence (ν_{max}^{CO} 1720 cm^{-1} in chloroform) indicates that the parent bromoketone is 2-α-bromocholestane-3-one, with the bromine equatorial. Since the displacement of the bromine is probably a normal S_N2 reaction the azide should be 2-β-azidocholestane-3-one (IV). Since C-3 is trigonal, and the electrostatic repulsion between the carbonyl and azido groups seems low (2-azidocyclohexanone has an equatorial azido group) it is probable that the azido ketone adopts a ring A conformation closer to the half-boat V than the chair IV in order to help relieve the repulsive interaction of the azido group and the 10-methyl group.[4] This interaction seems the one factor which can



account for the rapid decomposition. We suggest that lithium azide acts as a generalized base aiding abstraction of the 2-hydrogen:



[4]*The azidoketone carbonyl appears as a shoulder on the low-wavelength side of the bromoketone carbonyl band in the infrared spectrum of a mixture of the two compounds. It is hence unlikely that the azidoketone has ring A as a boat with the azido group equatorial.*

The repulsive interaction between the 10-methyl group and the azide group will be relieved in the enolate anion, thus providing the driving force for enolization by the weak base. The enolate ion must rapidly lose nitrogen to give the anion corresponding to the product.

The above reactions of α-azidoketones may provide valuable alternative routes to steroidal α-diketones (7, 8) and α-amino alcohols (9).

EXPERIMENTAL

2-Azidocyclohexanone

A solution of 2.05 g of sodium azide in 45 ml of dimethylsulphoxide was added to 1.45 g of 2-chlorocyclohexanone. The mixture was stirred at room temperature for 80 minutes. Water containing crushed ice was added, then the product extracted by three 25 ml portions of *n*-pentane. The combined extracts were washed with ice-cold water, dried, and the solvent removed *in vacuo*. The residual yellow oil polymerized if distillation was attempted under water pump pressure. The oil had $\nu_{max}^{CHCl_3}$ 2110 (—N_3) and 1722 cm^{-1} (C=O). Found: N, 29.82. Calc. for $C_6H_9N_3O$: N, 30.20.

A solution of 50 mg of 2-azidocyclohexanone in 20 ml of dimethylformamide was heated at 65°. Aliquots were periodically removed, diluted with water, and extracted with *n*-pentane. The intensity of the azide peak in the infrared spectrum remained unchanged during 1½ hours heating. When the solution was heated above this temperature, however, slow decomposition resulted.

Photolysis of 2-Azidocyclohexanone

The photolysis cell was 1 cm thick and 6.5 cm in diameter with quartz windows equipped with a side reservoir with cooling coil and circulation device. A solution of 750 mg of the azidoketone in 165 ml of cyclohexane was irradiated under nitrogen with a 140 watt Hanovia lamp while the temperature was maintained below 40°. A steady evolution of nitrogen ensued. The azide band at 2110 cm^{-1} had disappeared after 12 hours. The photolysis was interrupted at intervals to remove an oil which collected on the walls of the cell. This oil was soluble in methylene chloride, but the solution deposited polymer on standing. Both the oil and cyclohexane solution had infrared absorption at 3400 and 1670 cm^{-1}.

Acid-Catalyzed Decomposition of 2-Azidocyclohexanone

A mixture of 750 mg of 2-azidocyclohexanone and 15 ml of 10 *N* sulphuric acid was vigorously stirred a s the temperature was raised to 60°. Nitrogen evolution commenced. After 1 hour at 60–65° the oily drops of the azide had completely disappeared. The solution was cooled, saturated with sodium sulphate, and extracted three times with 50 ml portions of ether. The ether extracts were concentrated to 50 ml *in vacuo*, then extracted twice with 15 ml portions of ice-cold 10% potassium hydroxide solution. The aqueous layers were neutralized with cold 6 *N* hydrochloric acid and extracted thoroughly with ether. The dried ether solution was removed at 0° *in vacuo*, leaving 378 mg of 1,2-cyclohexanedione which crystallized from pentane; m.p. 38–40°, $\nu_{max}^{CHCl_3}$ 3500 cm^{-1} (OH), 1675 cm^{-1} (C=O), and 1650 cm^{-1} (C=C) corresponding to the enolic form; λ_{max} 266 mμ, ε 2460 shifted to 308 mμ in alkali. The dione formed a dioxime which melted at 187–188° after recrystallization from acetone. An aqueous solution of the dioxime gave a rose-red precipitate when a nickel sulphate solution was added.

Attempted Preparation of 2-Azidocholestanone

Numerous attempts were made to prepare pure 2-azidocholestanone by the action of alkali azides on 2-bromo(chloro)-cholestane-3-one, varying the solvent and temperature. Aliquots were removed from the reactions at intervals, the ether-extractable products isolated, and the infrared spectra examined. The azidoketone ($\nu_{max}^{CHCl_3}$ 2110 cm^{-1} and 1710 cm^{-1}) soon reached a steady state concentration while a second product steadily grew in concentration ($\nu_{max}^{CHCl_3}$ 1655 cm^{-1}). Of the three solvents used, dimethylformamide, dimethylsulphoxide, and methanol, the highest steady state concentration of azide was reached with the latter solvent, after 1 hour of refluxing. In a typical experiment 300 mg of 2-bromocholestan-3-one in 2 ml of chloroform was added to a solution of 300 mg of lithium azide in 25 ml of dry methanol. After 1 hour of refluxing the solvent was removed *in vacuo*, water added, and the products extracted into ether. After removal of the ether the extracted products were dissolved in benzene and the solution passed through a column of silica gel (20-fold ratio). The readily eluted material contained none of the by-product and had intense azide absorption. However, the product melted over a wide range and analysis for bromine indicated the presence of up to 50% of starting material. Attempts to further purify the azidoketone by chromatography on alumina were unsuccessful, hence this mixture was used to study the reactivity of the azidoketone.

The azide was not decomposed if a solution of 100 mg of the mixture in 10 ml of methanol or in 10 ml of methanol containing 100 mg of lithium bromide was refluxed for 1½ hours. It was also unchanged in a 3:7 mixture of chloroform and dimethylformamide after 2 hours at 50°.

2-Acetamidocholestan-3-ol Acetate

To a stirred solution of 3.8 g of 2-α-bromocholestan-3-one in 40 ml of dimethylformamide was added 3.8 g of lithium azide. The mixture was maintained at 50° for 1 hour then diluted with methanol and cooled to room temperature. Sodium borohydride (1.5 g) was added in small portions. After standing overnight the reaction mixture was diluted with water and thoroughly extracted with ether. The extracts were concentrated to 100 ml, then shaken with 3 *N* sulphuric acid. A sulphate which precipitated was collected by filtration and washed well with ether. It was then dissolved in 100 ml of hot ethanol, and the solution basified with alcoholic sodium hydroxide. The solvent was removed under reduced pressure, and the residue extracted with chloroform. The organic layer was washed with water and dried over anhydrous sodium sulphate. After removal of the solvent, 20 ml pyridine and 2 ml acetic anhydride were added and the contents left overnight. Pyridine was removed *in vacuo* and the residue taken up in ether. The fraction separated by the usual procedure was crystallized from alcohol to yield 2.6 g of 2-acetamidocholestanol acetate; m.p. 193–195°. $\nu_{max}^{CHCl_3}$ 3500 cm^{-1} (NH), 1722 cm^{-1} (ester), 1665 cm^{-1} (amide). Found: C, 76.74; H, 10.74; N, 2.94%. Calc. for $C_{31}H_{53}O_3N$: C, 76.33; H, 10.95; N, 2.87%.

2-Acetamidocholestan-3-ol

A solution of 2-acetamidocholestanol acetate (2 g) in 40 ml of alcohol was heated on a steam bath and 4 ml of 10% sodium hydroxide solution added to it. The contents were refluxed for 1 hour. The mixture was then concentrated to 25 ml and 20 ml water added. The resulting precipitate was washed with water and recrystallized from ethanol; m.p. 256°. Found: C, 78.16; H, 11.35%. Calc. for $C_{29}H_{51}O_2N$: C, 78.14; H, 11.53%.

2-α-Acetamidocholestan-3-one

One gram of chromic acid was added in small portions to 10 ml of pyridine at 0° C with vigorous shaking. When the formation of the complex was complete 1.5 g of 2-acetamidocholestanol dissolved in 30 ml pyridine was added slowly. The mixture was shaken overnight at room temperature and extracted with 1:1 benzene–hexane mixture. The organic layer was washed with acid and alkali and finally with water. After drying over sodium sulphate the solvent was removed. A chloroform solution of the product was passed through a column of grade III alumina (weight ratio 20:1). The readily eluted material finally crystallized from ether to give 2-α-acetamidocholestane-3-one, m.p. 184–186°, $\nu_{max}^{CHCl_3}$ 3370 cm^{-1}(NH), 1710 cm^{-1} (), and 1665 (); λ_{max}^{EtOH} 279 mμ, ε 130. Found: C, 78.39; H, 11.09%. Calc. for $C_{29}H_{49}O_2N$: C, 78.5; H, 11.13%.

Wolff-Kishner Reduction

A mixture of 80 mg of 2-acetamidocholestan-3-one, 6 ml triethylene glycol, and 2 ml hydrazine was immersed in a bath at 110°. The temperature was gradually raised to 155–160° and maintained for 1 hour. Two grams of potassium hydroxide was now added and the water condenser replaced with an air condenser. The temperature was raised to 195–205° and kept at that temperature for 5 hours. The mixture was then cooled, diluted with water, and extracted with ether. The ether solution was washed with acid, with water, dried, and distilled. The 60 mg of residue was dissolved in pentane and the solution passed through a column of alumina (grade III). The eluate yielded 42 mg of a solid. Recrystallization from alcohol gave colorless plates, m.p. and mixed m.p. with cholestane 78–81.5°. Found: C, 86.81; H, 13.16. Calc. for $C_{27}H_{48}$: C, 87.02; H, 12.98%.

2,3-Secocholestan-2,3-dioic Acid

Four hundred milligrams of 2-α-bromo-5-α-cholestan-3-one was dissolved in 15 ml dimethyl formamide and 400 mg of lithium azide added. The mixture was heated at 50° for 1 hour, with shaking in nitrogen atmosphere. The contents were evaporated to dryness *in vacuo* and the residue taken up in 15 ml of 80% aqueous dioxane. Five milliliters of 1.5 *N* sulphuric acid was added and the mixture shaken at room temperature for 2 hours. The solution was concentrated to half its volume, diluted with water, extracted with ether. The residue (approx. 300 mg) obtained after the removal of the ether had $\lambda_{max}^{alcohol}$ 272 mμ which was shifted to 320 mμ in alkali (2).

Crude diketone (150 mg) was dissolved in 15 ml alcohol and a mixture of 1 ml hydrogen peroxide (30%) and 1 ml of 10% potassium hydroxide added. The mixture was heated on a steam bath. The same mixture of hydrogen peroxide and alkali was added twice more at 15 minute intervals. After 1 hour, the heating was stopped and the contents left overnight. After diluting with water the solution was extracted with ether to remove non-acidic materials. The clear aqueous layer was then acidified with 3 *N* sulphuric acid and ether-extracted. After washing with water the organic layer was dried over anhydrous sodium sulphate. Removal of solvent and crystallization of the residue from ethyl acetate gave 100 mg of the dicarboxylic acid, m.p. 193–194° (lit. m.p. 195° (2)). Found: C, 74.5; H, 10.29. Calc. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67%.

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DIVISION OF PURE CHEMISTRY,
NATIONAL RESEARCH COUNCIL,
OTTAWA, CANADA.