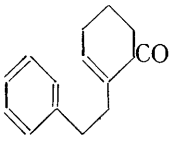
369. *Substituted Unsaturated Cyclic Ketones.*

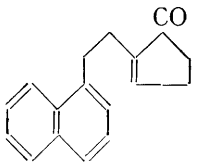
By A. Cohen and J. W. Cook.

Having seen an announcement of a communication on the synthesis of substituted *cyclo*hexenones (Rapson and Robinson, this vol., p. 1285), we wish to record the preparation of some compounds of this nature, carried out in the course of attempts to devise suitable methods for the synthesis of polycyclic hydroaromatic ketones related to the œstrogenic hormones.

The method used for the synthesis of our ketones has been much used in terpene chemistry, and consisted in the elimination of hydrogen chloride from nitrosochlorides, with hydrolysis of the resulting oximes. Pyridine was found more suitable for this elimination than the sodium acetate method which has been commonly employed. In this way 1-β-phenylethyl-Δ^1-*cyclo*hexene and 1-(β-1′-naphthylethyl)-Δ^1-*cyclo*pentene (Cook and Hewett, J., 1933, 1098) were converted into 2-β-*phenylethyl*-Δ^2-cyclo*hexenone* (I) and 2-(β-1′-*naphthylethyl*)-Δ^2-cyclo*pentenone* (II), respectively.

On account of the well-known suppression of anionoid reactivity of an ethylenic linkage by a conjugated carbonyl group, it was not anticipated that these ketones would undergo cyclisation to phenanthrene derivatives with the facility shown by the parent hydrocarbons. Nevertheless, the observations of Eaton, Black, and Fuson (*J. Amer. Chem. Soc.*, 1934, **56**,

(I.) 



(II.)

687) on the addition of aromatic hydrocarbons and their derivatives to chalkones gave grounds for hope that cyclisation would be effected under more drastic conditions. In spite of many attempts, however, this has not yet been achieved. We are continuing this line of work, and other possible routes to polycyclic ketones are also under investigation in this laboratory. For example, Dr. C. L. Hewett is studying the behaviour of arylethyldihydroresorcinols under conditions which lead to cyclisation of β-keto-esters of suitable structure.

The unsaturated ketone (II) gave no œstrous response when injected in 10 mg. doses into ovariectomised mice. We are indebted to Mr. F. Lloyd Warren for this observation.

Experimental.

(Except in the case of the two liquid ketones, the analyses are microanalyses by Dr. G. Weiler.)

1-β-*Phenylethyl*-Δ^1-cyclo*hexene Nitrosochloride*.—Dry hydrogen chloride was passed into a mixture of phenylethyl*cyclo*hexene (60 g.), glacial acetic acid (100 c.c.), anhydrous ether (100 c.c.), and amyl nitrite (70 g.), the temperature being kept below 0°. The nitrosochloride (28·5 g.) was collected, washed with ether, and recrystallised from benzene, forming colourless prisms, m. p. 139—140° (Found: C, 66·7; H, 7·1. Calc.: C, 66·8; H, 7·2%). Fulton and Robinson (J., 1933, 1464) give m. p. 118—119°.

2-β-*Phenylethyl*-Δ^2-cyclo*hexenoneoxime*.—A solution of the nitrosochloride (3 g.) in anhydrous pyridine (15 c.c.) was boiled for 2½ hours. The solution was poured into dilute hydrochloric acid and extracted with ether, and the extract washed with sodium bicarbonate solution. The residue remaining after removal of ether from the dried solution crystallised from alcohol in large, colourless, flat needles, m. p. 118—120° after sintering at 115° (Found: C, 78·1; H, 8·0; N, 6·6. $C_{14}H_{17}ON$ requires C, 78·1; H, 8·0; N, 6·5%).

2-β-*Phenylethyl*-Δ^2-cyclo*hexenone*.—A suspension of the aforesaid oxime (8 g.) in 6*N*-sulphuric acid (48 c.c.) was boiled for 1¼ hours. The resulting oil was extracted with ether, from which solution the *ketone* (I) was isolated by distillation, and formed an almost colourless, refractive liquid, b. p. 125—130°/0·7 mm. (Found: C, 83·65; H, 8·3. $C_{14}H_{16}O$ requires C, 83·95; H, 8·1%). This ketone gave an orange solution in concentrated sulphuric acid, and formed a *semicarbazone* which crystallised from alcohol in colourless needles, m. p. 188—190° (Found: N, 16·3. $C_{15}H_{19}ON_3$ requires N, 16·3%).

1-(β-1′-*Naphthylethyl*)-Δ^1-cyclo*pentene Nitrosochloride*.—A mixture of the *cyclo*pentene (19·6 g.), acetic acid (38 c.c.), ether (20 c.c.), and amyl nitrite (18 c.c.) was treated in the manner described with hydrogen chloride, and gave 17·1 g. of the nitrosochloride, a colourless microcrystalline powder, m. p. 108—110°, sparingly soluble in low-boiling media.

2-(β-1′-*Naphthylethyl*)-Δ^2-cyclo*pentenone*.—A solution of the foregoing nitrosochloride (3·4 g.) in pyridine (15 c.c.) was boiled for 5 minutes. This sufficed to complete the reaction; longer boiling led to decomposition. The *oxime* (2·1 g.) of (II), isolated in the usual way, formed colourless rhombic tablets, m. p. 106·5—107·5° (Found: C, 81·1; H, 6·75; N, 6·05. $C_{17}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%). For hydrolysis to the ketone, the oxime (10 g.) was boiled with 6*N*-sulphuric acid (60 c.c.) for 1¼ hours. The oxime formed a crystalline sulphate, which was transformed into a yellow oil as hydrolysis proceeded. The unsaturated *ketone* (II) formed a yellowish liquid, b. p. 165—167°/0·3 mm., which gave a red colour with acetic acid containing sulphuric acid (Found: C, 86·4; H, 7·0. $C_{17}H_{16}O$ requires C, 86·1; H, 7·0%). This ketone gave a sparingly soluble *semicarbazone*, m. p. 226—227° (Found: C, 73·3; H, 6·5; N, 14·5. $C_{18}H_{19}ON_3$ requires C, 73·7; H, 6·5; N, 14·3%).

Cyclisation Attempts.—(I) 2-β-*Phenylethyl*-Δ^2-cyclo*hexenone*. (a) A solution of the ketone

(1·3 g.) in concentrated sulphuric acid (3 c.c.) was kept at 0—3° for 2 days. The orange solution was poured on ice, and the oil extracted with ether and distilled, giving 0·8 g. of unchanged ketone. (b) A solution of the ketone (2 g.) in sulphuric acid (55% by weight; 12 c.c.) was boiled for 24 hours. The ketone was almost entirely converted into non-volatile resinous material. (c) Aluminium chloride (1·5 g.) was added to an ice-cold solution of 2-β-phenylethyl*cyclo*hexenoneoxime (1·2 g.) in carbon disulphide (6 c.c.). The aluminium chloride was soon replaced by a brownish heavy oil. After being kept over-night at 0—3°, the product was decomposed with ice and hydrochloric acid. The oxime was recovered entirely unchanged, being identified by the method of mixed m. p.'s.

(II) 2-(β-1′-*Naphthylethyl*)-Δ^2-cyclo*pentenone*. (a) Dry hydrogen chloride was passed for 6 hours into a water-cooled mixture of the ketone (II) (1·6 g.) and anhydrous aluminium chloride (1·8 g.) in benzene (15 c.c.). The yellow hydrochloride which was at first precipitated gradually became transformed into a dark red aluminium chloride complex. The mixture was kept overnight and then decomposed with ice and hydrochloric acid. Unchanged ketone (0·8 g.) was recovered by distillation, and identified by conversion into the semicarbazone, m. p. 226°, alone or mixed with an authentic specimen. (b) A similar experiment was performed, using nitrobenzene as the solvent. The unsaturated ketone was recovered completely unchanged.

(*Note added on September 24th.*) The structure assigned to the ketone (I) is based on the assumption that the hydrocarbon resulting from dehydration of 1-β-phenylethyl*cyclo*hexanol is 1-β-phenylethyl-Δ^1-*cyclo*hexene, and not the alternative phenylethylidene-*cyclo*hexane. This assumption seems justified, for the reactions herein described would lead, if the latter structure were correct, to phenylacetyl-Δ^1-*cyclo*hexene (m. p. 46—48°; Cook and Hewett, *loc. cit.*; semicarbazone, m. p. 171—172°, Fulton and Robinson), whereas the ketone which we actually obtained was a liquid (semicarbazone, m. p. 188—190°).

Nenitzescu and Gavăt (*Annalen*, 1935, **519**, 260) have recently taken exception to the suggestion of Cook and Hewett (*loc. cit.*) that their failure to cyclise phenylacetyl*cyclo*hexene to hexahydrophenanthrone was due to the inhibiting influence of the conjugated carbonyl group on the activity of the ethylenic bond. On the basis of the remarkable migrations which they have discovered the former authors attribute this cyclisation failure to a migration of chlorine away from the carbonyl group in a hypothetical chloro-compound formed by the action of aluminium chloride on the unsaturated ketone. If this explanation were correct, it would be necessary further to postulate a *reversible* migration to account for the isolation of unchanged ketone after treatment with aluminium chloride, and a similar reversible migration of hydroxyl or sulphate would be required to account for the inactivity of sulphuric acid towards phenylacetyl*cyclo*hexene. In the absence of any evidence of these reversible changes we still consider that the original suggestion of Cook and Hewett provides the most satisfactory explanation of the stability towards cyclising agents of phenylacetyl*cyclo*hexene and the ketones (I and II) now described.

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The Research Institute of The Cancer Hospital (Free),
London, S.W. 3.

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