

345. Synthesis of Octahydrophenanthrene Derivatives.

By JAMES D. FULTON and ROBERT ROBINSON.

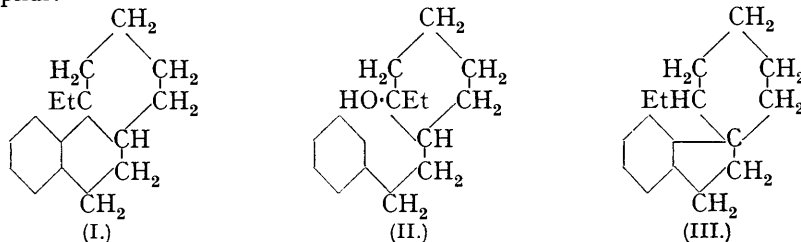
THE experiments described in this communication were carried out in 1927—28, and although the work is incomplete it is now necessary to place it on record in view of the anticipation of the general scheme of synthesis by Bardhan and Sengupta (J., 1932, 2520, 2798) and also because the method has an important bearing on current synthetical investigations in the sterol-oestrin group (compare R. D. Haworth and Mavin, this vol., p. 1012; Kon, *ibid.*, p. 1081).

The objective, six years ago, was the synthesis of the parent hydrocarbon of the morphine group of alkaloids, namely, 12-ethyloctahydrophenanthrene (I), and of its 5:6-dimethoxy-derivative, which it was hoped to obtain by degradation of codeine or thebaine.

The obvious starting point, 2- β -phenylethylcyclohexanone, was first obtained by Miss E. Gatewood in still earlier experiments on the condensation of β -phenylethyl bromide and ethyl cyclohexanone-2-carboxylate. The yields, both in the alkylation of the sodio-derivative of the ester and in its hydrolysis, were unfavourable,* and a much better process consisted in the formation of 2- β -phenylethylcyclohexanol by the action of β -phenylethylmagnesium bromide on cyclohexene oxide; the secondary alcohol could then be smoothly oxidised to the ketone by means of chromic acid.

2- β -Phenylethylcyclohexanol was directly dehydrated by heating with zinc chloride, but the product was largely unsaturated in contrast with Bardhan and Sengupta's observation that phosphoric oxide effects ring-closure. The latter stage in our experiments was carried out by replacing the hydroxyl group by a chlorine atom and then submitting the product to the action of aluminium chloride.

The octahydrophenanthrene so obtained was dehydrogenated to phenanthrene by heating with sulphur.



The action of ethylmagnesium bromide on 2- β -phenylethylcyclohexanone afforded the tertiary alcohol (II), and the corresponding chloride, treated with aluminium chloride, gave rise to a saturated hydrocarbon $C_{16}H_{22}$. This specimen gave some phenanthrene when it was heated with sulphur, but the yield was unsatisfactory and it is possible that the spirohydrindene (III) was one of the products of the reaction. On the other hand, the dehydrogenation of (I) may pursue an abnormal course.

By varying the method of ring-closure it is now hoped to obtain homogeneous products of type (I), and the series with methyl in place of ethyl is under examination.

In the following account we have avoided repetition of experimental details already published by Bardhan and Sengupta (*loc. cit.*).

EXPERIMENTAL.

cycloHexene.—The method described in "Organic Syntheses" (vol. V, p. 33) gave an 80% yield and was found to be convenient.

* Bardhan and Sengupta (*loc. cit.*) improved the yield in the alkylation by employing the potassio-derivative of the ester, and Kon (*loc. cit.*) adopted the device of full hydrolysis to a pimelic acid and subsequent cyclisation to the ketone. These methods may be suitable alternatives in some cases, but that described in the present paper is greatly to be preferred for the preparation of 2- β -phenylethylcyclohexanol.

Benzyl Δ¹-cycloHexenyl Ketone.—The condensation of *cyclohexene* and phenylacetyl chloride with the help of aluminium chloride did not proceed smoothly and after treatment of the product with diethylaniline the resulting oil, b. p. 155—165°/2 mm., would not crystallise.

cycloHexene (16.5 g.) was gradually added during 2½ hours to a mixture of stannic chloride (52 g.), phenylacetyl chloride (31 g.), and carbon disulphide (125 g.), cooled to -15°. After being kept for some hours at room temperature, the solvent was decanted from a dark oil, which was decomposed with ice. The product was isolated by means of ether, freed from acidic substances, and heated for 2 hours at 180° with diethylaniline (twice the theoretical amount), and after addition of an excess of dilute sulphuric acid the product was again collected by means of ether, freed from acidic and neutral substances, and distilled. The fraction (10.5 g.), b. p. 139—145°/1.5 mm., when cooled, partly crystallised and after draining on porous porcelain the substance crystallised from aqueous methyl alcohol in plates, m. p. 44.5° (Found : C, 83.8; H, 8.3. C₁₄H₁₆O requires C, 84.0; H, 8.0%). This *ketone* is easily soluble in most organic solvents; it is readily oxidised by potassium permanganate in acetone solution, and it forms a *semicarbazone* crystallising from methyl alcohol in colourless needles, m. p. 171—172° (Found : N, 16.0. C₁₅H₁₉ON₃ requires N, 16.3%).

The application of the above method to ethyl-Δ¹-*cyclohexene* had no satisfactory outcome.

1-β-Phenylethylcyclohexanol.—Purified *cyclohexanone* (9.8 g.) was gradually added to a Grignard reagent prepared from β-phenylethyl bromide (19.2 g.) and magnesium (2.7 g.) in ether (200 c.c.) and cooled to -15°. After some hours a semi-solid mixture (19.5 g.) of tertiary *alcohol* and unsaturated hydrocarbon was isolated in the usual manner. The former could be purified by draining and distillation in small quantities in one operation, followed by crystallisation from light petroleum; it had m. p. 56.5° and was readily soluble in most organic solvents (Found : C, 82.3; H, 10.0. C₁₄H₂₀O requires C, 82.4; H, 9.8%). The unsaturated hydrocarbon, probably *1-β-phenylethylcyclohexene*, was readily obtained from the foregoing tertiary alcohol by the action of zinc chloride, acetic anhydride, or phenyl isocyanate. It had b. p. 112—113°/2 mm., *n*_D²⁰ 1.5402, and possessed a characteristic odour (Found : C, 90.4; H, 9.6. C₁₄H₁₈ requires C, 90.3; H, 9.7%).

The *nitrosochloride*, prepared in the usual way at -10°, crystallised from acetone in prisms, m. p. 118—119° (Found : Cl, 14.3. C₁₄H₁₈ONCl requires Cl, 14.4%). The *nitropiperidide* separated from methyl alcohol in colourless needles, m. p. 117—118° (Found : N, 9.1. C₁₉H₂₈ON₂ requires N, 9.3%).

A by-product of reactions involving the formation of β-phenylethylmagnesium bromide was αδ-diphenylbutane, m. p. 53°.

2-β-Phenylethylcyclohexanol.—A solution of *cyclohexene oxide* (19.8 g.; compare "Organic Syntheses," V, p. 35) in ether was added to an ethereal solution of the reagent prepared from β-phenylethyl bromide (74 g.) and magnesium (9.75 g.). The ether was distilled from the steam-bath and, when but little of the solvent remained, a violent reaction set in and the large flask was almost completely filled with the frothing mass. After cooling and decomposition with ice-water, the product was collected by means of ether and distilled, b. p. 135—136°/1.5 mm. (yield, 37 g., and 37.3 g. in a second experiment, equivalent to 91.5% of the theoretical). The oil crystallised in a freezing mixture and a solution in light petroleum deposited long needles, m. p. 17—18°, when cooled to -15° (Found : C, 82.6; H, 9.7. Calc. for C₁₄H₂₀O : C, 82.4; H, 9.8%). The specimen obtained by Bardhan and Sengupta (*loc. cit.*) did not solidify in a freezing mixture, but, as the substance should occur in stereoisomeric forms, it is probable that the reduction of the related ketone gives either a mixture of *cis*- and *trans*-forms or a different modification from the process described above. Our product was apparently homogeneous.

The *p-nitrobenzoate*, prepared from the alcohol and *p*-nitrobenzoyl chloride in pyridine, crystallised from light petroleum in rosettes of fine needles, m. p. 73.5° (Found : N, 4.0. C₂₁H₂₃O₄N requires N, 4.0%), depressed to 45° on admixture with *p*-nitrobenzoyl chloride of about the same m. p.

2-Chloro-β-phenylethylcyclohexane.—This substance should contain Cl 15.9%, but, owing to the formation of a hydrocarbon, the chlorine content of the specimens prepared as described below did not exceed 13.0%; other methods gave inferior results.

Thionyl chloride (16 g.) was added to phenylethylcyclohexanol (20 g.) and dry pyridine (10.5 g.) in the course of 1 hour. The crystalline sulphinyl chloride that separated was decomposed by heating the mixture on the steam-bath until evolution of sulphur dioxide ceased (2—3 hours). The product was isolated in the customary manner and a fraction, b. p. 130—134°/5 mm., was collected. It is quite possible that the hydrocarbon contained in this material was octahydrophenanthrene.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydrophenanthrene.—A solution of the chlorophenylethylcyclohexane (13 g.; Cl, 13.0%) in light petroleum (40 c.c.) was added to powdered aluminium chloride (13 g.) covered with light petroleum (40 c.c.), and the reaction was completed by gentle heating on the steam-bath. The hydrocarbon was isolated in the usual manner, b. p. 135—137°/6.5 mm. (yield, 6.0 g.) (Found: C, 90.1; H, 10.2. $C_{14}H_{18}$ requires C, 90.3; H, 9.7%); it was halogen-free, saturated towards permanganate, and did not yield a picrate. As the oil crystallised when cooled to -11° to -12° , it is considered to differ stereochemically from the product of Bardhan and Sengupta (*loc. cit.*). On being heated with about two-thirds of its weight of sulphur, at first at 140° and later at 180° , hydrogen sulphide was continuously evolved, and after 24 hours, phenanthrene (identified by its m. p. and mixed m. p. with an authentic specimen and the same procedure with the picrate) and an unidentified hydrocarbon of higher melting point could be isolated.

2- β -Phenylethylcyclohexanone.—Phenylethylcyclohexanol (57 g.) was mixed with Beckmann's chromic acid solution (290 g.) at 30° , and the temperature raised to 55° in the course of 30 minutes. A dark-coloured double compound was formed, but this decomposed when heated to 65° and the ketone separated. Isolation followed standard practice; yield, 52 g., b. p. 135—136°/2 mm. (Found: C, 83.4; H, 9.0. Calc. for $C_{14}H_{18}O$: C, 83.2; H, 8.9%). The ketone has a distinctive odour; it forms a solid bisulphite compound which is decomposed by water. The oxime crystallised from methyl alcohol in colourless needles, m. p. $74-75^{\circ}$ (Found: N, 6.4. $C_{14}H_{18}ON$ requires N, 6.5%). The semicarbazone crystallised from alcohol in colourless needles, m. p. 157° (Found: N, 16.3. $C_{15}H_{21}ON_3$ requires N, 16.2%). Bardhan and Sengupta (*loc. cit.*) give $179-180^{\circ}$ (decomp.), a considerable discrepancy requiring further investigation.*

2- β -Phenylethyl-1-ethylcyclohexanol.—2- β -Phenylethylcyclohexanone (32.2 g.), dissolved in a little ether, was slowly added to a Grignard solution prepared from ethyl bromide (22.8 g.), magnesium (5.1 g.), and ether (150 c.c.) and cooled to -10° . The mixture was heated for 1 hour in the steam-bath, then decomposed by means of ice-water, and the product isolated and distilled, b. p. $147-148^{\circ}/3$ mm. (yield, 34.5 g.) (Found: C, 83.3; H, 10.2. $C_{16}H_{24}O$ requires C, 82.8; H, 10.4%). The high value for the carbon content is due to the presence of a small proportion of unsaturated hydrocarbon which is very easily produced from this tertiary alcohol; nevertheless the specimen solidified when cooled in a freezing mixture.

2- β -Phenylethyl-1-ethyl- Δ^1 -cyclohexene.—The above-described tertiary alcohol could not be converted into acyl derivatives; it was conveniently dehydrated by gentle heating with zinc chloride. The product, obtained with but little loss, was distilled in steam and then over sodium; b. p. $113-114^{\circ}$, $n_{D}^{20} 1.5306$ (Found: C, 89.9; H, 10.3. $C_{16}H_{22}$ requires C, 89.7; H, 10.3%). This hydrocarbon had a pleasant terpene-like odour and rapidly absorbed bromine in chloroform solution, but it could not be converted into a nitrosochloride under the usual conditions.

12-Ethyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (I)?—2- β -Phenylethyl-1-ethylcyclohexanol was converted into a chloride as in the previous case and, again as before, the product was submitted to the action of aluminium chloride. A hydrocarbon, b. p. $130-140^{\circ}/1-2$ mm., was isolated and this was shaken with an excess of an alkaline solution of potassium permanganate during 2 hours in order to free it from an unsaturated by-product. Finally the hydrocarbon was distilled over sodium, b. p. $113-116^{\circ}/<1$ mm.; $n_{D}^{20} 1.5487$ (Found: C, 90.1; H, 10.3. $C_{16}H_{22}$ requires C, 89.7; H, 10.3%). This hydrocarbon is saturated in its behaviour towards bromine and potassium permanganate. When it was heated (1.5 g.) with sulphur (0.9 g.) at $170-180^{\circ}$ for 40 hours, hydrogen sulphide was evolved. After addition of sodium the mixture was distilled and phenanthrene was isolated from the distillate and identified by its melting point, $94-95^{\circ}$, and by that of its picrate ($138-139^{\circ}$) (both m. p.'s undepressed on admixture with authentic specimens). A second substance, m. p. 213° , was also isolated and this appears to be anthracene, since the m. p. was not depressed on admixture with an authentic specimen. The formation of both phenanthrene and anthracene in this experiment is difficult to interpret.

Ethyl 3 : 4-Dimethoxycinnamate and Stages to 3 : 4-Dimethoxyphenylacetylene.—3 : 4-Dimethoxyphenylacetylene has been prepared in order to study the behaviour of its organomagnesium bromide derivative towards ketones of the cyclohexane series. A mixture of 3 : 4-dimethoxycinnamic acid (13 g.), absolute alcohol (100 c.c.), and sulphuric acid (3 g.) was

* The specimen, m. p. 157° , had been preserved and has been re-analysed (Found: C, 69.4; H, 8.1; N, 16.3. $C_{15}H_{21}ON_3$ requires C, 69.5; H, 8.1; N, 16.2%) (October, 1933).

refluxed for 5 hours; yield, 14 g.; square plates, m. p. 56°, from light petroleum (Found: C, 66.0; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). A suspension of the *ester* in carbon disulphide cooled to 0° was treated slowly with bromine in 2% excess and in artificial light. There was no evolution of hydrogen bromide and after a few hours the slight excess of bromine remained; evidently the aromatic nucleus was not attacked. The addition may also be carried out in ethereal solution with the same results. The solvent was removed under diminished pressure; the *dibromide* crystallised from ether in needles, m. p. 107—108° (Found: Br, 40.5. $C_{13}H_{16}O_4Br_2$ requires Br, 40.4%).

The *ester dibromide* (1 mol.) was refluxed with ethyl-alcoholic potassium hydroxide (3 mols.) for 7 hours, and the solvent evaporated. The residue was taken up in water, heated with animal charcoal, and the solution filtered, cooled, and acidified with dilute sulphuric acid. The precipitated 3:4-dimethoxyphenylpropionic acid (12.6 g.) crystallised from water in radiating needles, m. p. 154° (Found: C, 63.7; H, 5.0. $C_{11}H_{10}O_4$ requires C, 64.1; H, 4.9%). This acid (38.6 g.), mixed with diethylaniline (80—90 c.c.), was heated at 150—160° until carbon dioxide was no longer evolved (about 35 minutes). The solution was added to excess of dilute hydrochloric acid, and the dimethoxyphenylacetylene collected by means of ether (yield, 15.6 g.). This material was purified by steam distillation and crystallised from not too much alcohol and from light petroleum in hexagonal plates, m. p. 73—74° (Found: C, 73.9; H, 6.3. $C_{10}H_{10}O_2$ requires C, 74.1; H, 6.2%), readily soluble in most organic solvents. It was treated with ethylmagnesium bromide, but there was no satisfactory outcome of an attempt to bring about the interaction of the organo-magnesium derivative with cyclohexene oxide. Similar experiments with phenylacetylene led only to the formation of a hydrocarbon, m. p. 48—49° after crystallisation from methyl alcohol (Found: C, 85.1; H, 14.7%).

β -3:4-Dimethoxyphenylethyl Alcohol.—A mixture of homoveratric acid (40 g.), absolute alcohol (300 c.c.), and sulphuric acid (5 c.c.) was refluxed for 5 hours. The yield of ethyl homovertrate, a colourless odourless oil, b. p. 159—160°/4 mm., was 38 g. (84%) (134 g. of acid gave 137 g. of ester; 90%) (Found: C, 64.4; H, 7.4. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%). In contact with concentrated aqueous ammonia the ester was gradually transformed into the *amide*, which crystallised from alcohol in colourless prisms, m. p. 139° (Found: C, 61.5; H, 6.5; N, 7.5. $C_{10}H_{13}O_3N$ requires C, 61.5; H, 6.7; N, 7.2%). The derivative may also be crystallised from hot water; it is sparingly soluble in ether or benzene. Ethyl homovertrate, dissolved in three times its weight of anhydrous alcohol, was reduced by means of three-fifths of its weight of sodium under the usual conditions for the Bouveault reaction. That is, the solution was added to all the sodium heated in an oil-bath at 140—150° as quickly as possible; finally the heating was continued until almost all the metal had disappeared. The yield from 10 g. of the ester was 33%; from 22.4 g. it was 44%; and by using 108 g. of the ester the yield was 54%. On the larger scale it is more easy to exclude traces of water, which greatly diminish the yield out of all proportion to their stoichiometric amount. The reaction mixture was steam-distilled, and the residual oil collected by means of ether and distilled, b. p. 168—170°/8 mm.; the β -3:4-dimethoxyphenylethyl alcohol then crystallised from light petroleum, containing a little benzene, in rectangular plates, m. p. 47—48° (Found: C, 65.8; H, 7.7. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%). The phenylurethane crystallised from ether in radiating clusters of needles, m. p. 99° (Found: N, 4.8. $C_{17}H_{19}O_4N$ requires N, 4.7%). The *p*-nitrobenzoate, prepared by adding a solution of *p*-nitrobenzoyl chloride in chloroform to one of the dimethoxyphenylethyl alcohol in pyridine, separated from benzene-light petroleum in fern-like crystals, m. p. 85° with previous softening (Found: N, 4.4. $C_{17}H_{17}O_6N$ requires N, 4.2%).

In connexion with other experiments in this group, 3:4-dimethoxymandelonitrile was crystallised from ether, forming colourless clusters of rods, m. p. 104—105° (Found: N, 6.9. $C_{10}H_{11}O_3N$ requires N, 7.3%), and then converted by the usual process into the hydrochloride of the related imino ethyl ester, colourless lustrous plates, m. p. 139—140° after washing with ether (Found: Cl, 13.2. $C_{12}H_{18}O_4NCl$ requires Cl, 12.9%).