

109. Preliminary Syntheses in the Morphine Series. Part II.* The Synthesis of 2-Arylcyclohex-2-enones.

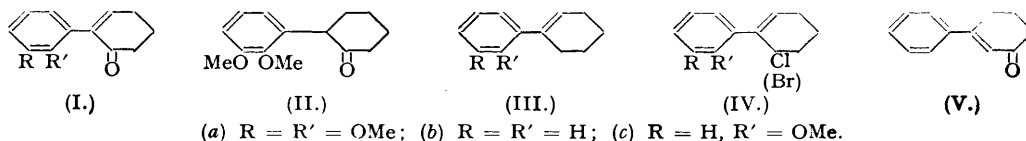
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2-Arylcyclohex-2-enones are synthesised by three routes, starting from 1-arylcyclohexenes : (i) allylic bromination with *N*-bromosuccinimide followed by hydrolysis to the carbinol and Oppenauer oxidation; (ii) allylic chlorination with *tert*.-butyl hypochlorite followed by analogous treatment; (iii) formation of the nitrosochloride, conversion into the oxime, and hydrolysis of the latter.

The action of *tert*.-butyl chromate on 1-phenylcyclohexene yields 3-phenylcyclohex-2-enone.

In the intended synthesis of compounds related to morphine, 2-(2 : 3-dimethoxyphenyl)cyclohex-2-enone (Ia) is a key intermediate. The present communication describes the synthesis of this substance and of the closely related 2-phenyl- (Ib) and 2-*o*-methoxyphenylcyclohex-2-enone (Ic).

The synthesis of (Ia) from the corresponding difficultly accessible saturated ketone (II) (Part I; * cf. Horning, Horning, and Platt, *J. Amer. Chem. Soc.*, 1947, **69**, 2929) was not fruitful. Bromination of this ketone in the 2-position, followed by dehydrobromination, gave poor results. (After this study had been completed, Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 339, reported satisfactory results with this method in the case of 2-phenylcyclohexanone.) Alternative methods were investigated, all using 1-arylcyclohexenes (III) as starting materials.



(a) Allylic bromination of 1-arylcyclohexenes (III) with *N*-bromosuccinimide yielded apparently only one of the possible brominated allylic compounds. Hydrolysis to the carbinol, followed by Oppenauer oxidation, yielded compounds of structure (I). The hydrolysis of the allylic halides (IV) may well involve allylic rearrangement (Young and Andrews, *ibid.*, 1944, **66**, 420) but inspection of formula (IV) will show that both direct hydrolysis, and rearrangement plus hydrolysis, will result in the same carbinol.

(b) Chlorination of type (III) compounds with *tert*.-butyl hypochlorite gave, presumably through addition of the reagent to the double bond and subsequent loss of *tert*.-butanol, the chlorinated allylic products (cf. Ritter and Ginsburg, *ibid.*, 1950, **72**, 2381; see, however, Teeter and Jackson, *J. Amer. Oil Chem. Soc.*, 1949, **26**, 535). As in method (a), the chloro-compounds were converted into the corresponding ketones (I).

(c) Treatment of compounds (III) with nitrosyl chloride (formed *in situ*) gave nitrosochlorides which were converted into the oximes, and these were hydrolysed to the $\alpha\beta$ -unsaturated ketones (I).

Methods (a) and (b) were less suited than (c) to the synthesis of compounds of type (I), because of the difficulty attending the production of $\alpha\beta$ -unsaturated alcohols from allylic halides (Young and Andrews, *loc. cit.*; Catchpole, Hughes, and Ingold, *J.*, 1948, 8), the formation of a hydrocarbon in addition to the alcohol, and the tediousness of the Oppenauer method of oxidation. Method (c) had none of these drawbacks and, in the case of the ketone (Ia) which was the most important for further work, overall yields of 40–50% were obtained from 1-(2 : 3-dimethoxyphenyl)cyclohexene (IIIa) *via* the nitrosochloride and the oxime.

An attempt was made to obtain ketones of type (I) directly from the unsaturated hydrocarbons (III) by means of *tert*.-butyl chromate (Oppenauer and Oberrauch, *Anal. Assoc. Quim. Argentina*, 1949, **37**, 246). Oxidation took place exclusively in the alternative allylic position, and 3-phenylcyclohex-2-enone (V) was obtained in 22% yield. This reagent acts, therefore,

* The paper entitled "A Synthesis of 2-(2 : 3-Dimethoxyphenyl)cyclohexanone" (*J.*, 1950, 1369) is regarded as Part I of this series.

on 1-phenylcyclohexene similarly to chromic acid, which in the hands of Fieser and Szmuszkovicz (*J. Amer. Chem. Soc.*, 1948, **70**, 3352) gave small amounts of (V).

EXPERIMENTAL.

(M. p.s and b. p.s are uncorrected.)

1-*o*-Methoxyphenylcyclohexene (IIIc).—To the Grignard reagent, prepared from *o*-bromoanisole (486 g., 2.6 moles) and magnesium (63.1 g., 2.6 atoms) in ether (2.5 l.), under reflux (1 hour), was added cyclohexanone (255 g., 2.6 moles) in ether (250 ml.), with stirring, at 0–5°. A viscous mass formed, making further stirring difficult. The mixture was refluxed for 3 hours, kept overnight, and decomposed with saturated ammonium chloride solution. The ethereal layer was washed with water and dried and the product distilled at 0.05 mm. pressure. 1-*o*-Methoxyphenylcyclohexanol (398 g., 75%) crystallised spontaneously and melted at 54–55° (from light petroleum) (Found: C, 75.6; H, 8.7. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%).

The tertiary carbinol was dehydrated by azeotropic distillation with anhydrous oxalic acid and toluene (Part I, *loc. cit.*), in quantitative yield. 1-*o*-Methoxyphenylcyclohexene boiled at 105–110°/0.8 mm. It melted at 17.1° (Found: C, 83.6; H, 8.8. $C_{13}H_{16}O$ requires C, 83.0; H, 8.5%).

In the same manner, 1-phenylcyclohexene (IIIb) was prepared (cf. von Auwers and Treppmann, *Ber.*, 1915, **48**, 1216), b. p. 132–135°/17 mm., m. p. 0°. 1-(2:3-Dimethoxyphenyl)cyclohexanol was prepared as in Part I. The time required for the metalation of veratrole with butyl-lithium, according to Gilman, Swiss, and Cheney (*J. Amer. Chem. Soc.*, 1940, **62**, 1965), could be reduced from 24 to 3 hours without materially affecting the yield.

Preparation of 2-Arylcyclohex-2-enols.—(A) *Bromination with N-bromosuccinimide.* 1-Phenylcyclohexene (IIIb) (20 g.) and *N*-bromosuccinimide (22 g.) were refluxed in carbon tetrachloride (100 ml.) for 1 hour (a little hydrogen bromide was evolved). The succinimide was removed and the filtrate concentrated *in vacuo*. The residual oil was heated with potassium acetate (20 g.) in 75% acetic acid (500 ml.) for 8 hours at 60°. Most of the solvent was removed *in vacuo*, and the residue taken up in ether. After being washed with sodium carbonate solution, the ether was distilled off, and the residual oil dissolved in 10% methanolic potassium hydroxide (100 ml.) and boiled for one hour. Concentration *in vacuo*, addition of water, extraction with ether, and fractionation in a high vacuum yielded two fractions (and some polymeric material): (i) B. p. 80–110°/0.05 mm. (4 g.), chiefly phenylcyclohexadiene (contaminated with some starting material), which crystallised and melted at 55–58° (from light petroleum) (Found: C, 92.5; H, 7.7. $C_{12}H_{12}$ requires C, 92.3; H, 7.7%). Berlande (*Bull. Soc. chim.*, 1942, **9**, 642) has reported m. p. 66° for 1-phenylcyclohexa-1:3-diene. (ii) B. p. 110–125°/0.05 mm., 2-phenylcyclohex-2-enol (11 g., 50%), the phenylurethane of which melted at 152–153° (from methylcyclohexane) (Found: N, 4.7. $C_{19}H_{19}O_2N$ requires N, 4.8%).

(B) *Chlorination with tert.-butyl hypochlorite.* To 1-phenylcyclohexene (IIIb) (111 g., 0.7 mole) in boiling carbon tetrachloride (225 ml.), *tert.*-butyl hypochlorite (80 g.) was added during 30 minutes. Heating was continued for 1 hour and the solvent and *tert.*-butanol were removed *in vacuo*. The crude residue (110 g.) was heated under reflux for 8 hours with potassium acetate (73 g.), acetic acid (550 ml.), and water (180 ml.). Further treatment as described under (A) yielded fractions, (i) b. p. 90–110°/0.05 mm. (25 g.), (ii) b. p. 110–130°/0.05 mm., 2-phenylcyclohex-2-enol (51 g.), and (iii) polymeric material.

1-*o*-Methoxyphenylcyclohexene (IIIc) (132 g., 0.7 mole) with *tert.*-butyl hypochlorite (80 g.) in carbon tetrachloride (265 ml.) similarly yielded fractions, (i) b. p. 80–90°/0.05 mm. (21 g.), consisting largely of mono- and di-olefin, (ii) b. p. 90–115°/0.05 mm., 2-*o*-methoxyphenylcyclohex-2-enol (48 g.), and (iii) polymeric material. The phenylurethane from (ii) melted at 135° (crystallised from methylcyclohexane) (Found: N, 4.3. $C_{20}H_{21}O_3N$ requires N, 4.3%).

Treatment of the allylic chloro-compounds with silver nitrate did not increase the yields of $\alpha\beta$ -unsaturated alcohols.

Preparation of 2-Arylcyclohex-2-enones.—A. *Oppenauer oxidation of 2-arylcyclohex-2-enols.* A mixture of 2-phenylcyclohex-2-enol (17.8 g.), aluminium *tert.*-butoxide (40 g.), acetone (400 ml.), and dry benzene (1600 ml.) was heated under reflux for 17 hours, and worked up in the usual manner. After removal of mesityl oxide (a by-product) *in vacuo*, the product solidified. It consisted of unchanged 2-phenylcyclohex-2-enol (4 g.; identified as the phenylurethane) and 2-phenylcyclohex-2-enone (Ib), m. p. 96–97° (11 g.) (Found: C, 83.7; H, 7.3. Calc. for $C_{12}H_{12}O$: C, 83.6; H, 7.0%). Bachmann and Wick (*loc. cit.*) report m. p. 95–95.5°. The oxime melted at 151° (from ethanol) (Found: C, 76.7; H, 7.0; N, 7.8. $C_{12}H_{13}ON$ requires C, 77.0; H, 6.95; N, 7.5%). The 2:4-dinitrophenylhydrazone formed orange-red crystals (from chloroform-ethanol), m. p. 165–166°, λ_{max} . 3800 Å., ϵ_{max} . = 25,800 (in anhydrous ethanol) (Found: C, 61.5; H, 4.5; N, 16.2. $C_{18}H_{16}O_4N_4$ requires C, 61.4; H, 4.5; N, 15.9%).

2-*o*-Methoxyphenylcyclohex-2-enol was oxidised similarly. The resulting 2-*o*-methoxyphenylcyclohex-2-enone (Ic) crystallised from the reaction mixture (40% yield) only after seeding, and after recrystallisation from hexane, melted at 53°.

Proof of structure of 2-arylcyclohex-2-enones (I). (i) *Dehydrogenation.* 2-Phenylcyclohex-2-enone (Ib) (1 g.) in *p*-cymene (10 ml.) was heated under reflux for 2 hours with 5% palladium-charcoal (2 g.) in a current of carbon dioxide. The catalyst was removed by filtration and washed with benzene, the filtrate extracted with 10% aqueous sodium hydroxide, and the extract saturated with carbon dioxide. A pinkish-white precipitate (0.8 g.) was obtained which, recrystallised from light petroleum, had m. p. 57° alone or on admixture with authentic 2-hydroxydiphenyl (Hückel *et al.*, *Annalen*, 1930, **477**, 123, report m. p. 58°). For such hydrogenations compare Horning, Horning, and Walker, *J. Amer. Chem. Soc.*, 1949, **71**, 169; Horning and Horning, *ibid.*, 1947, **69**, 1359.

(ii) *Reduction.* 2-(2 : 3-Dimethoxyphenyl)cyclohex-2-enone (Ia) (1 g.) in 95% ethanol (11 ml.) was hydrogenated in presence of 5% palladium-charcoal (0.5 g.), at room temperature and 60 lbs./sq. in pressure. One mole of hydrogen was taken up. The catalyst was removed by filtration and the solvent evaporated. Recrystallisation of the solid residue from light petroleum gave pure 2-(2 : 3-dimethoxyphenyl)cyclohexanone (II), m. p. 71° alone or on admixture with an authentic sample (Part I, *loc. cit.*).

(iii) The ultra-violet absorptions of the 2 : 4-dinitrophenylhydrazones agree with those reported by Braude and Jones (*J.*, 1945, 497) for derivatives of $\alpha\beta$ -unsaturated ketones.

Further proof of the position of the double bond will be offered in a subsequent communication.

B. *Through nitrosochlorides of 1-arylcyclohexenes (III).* *Formation of nitrosochlorides.* The example given refers to 1-(2 : 3-dimethoxyphenyl)cyclohexene (IIIa) but the procedure is general. To a mixture of the cyclohexene (0.1 mole, 21.3 g.), amyl nitrite (0.12 mole, 13.8 g.), and acetic acid (25 ml.), 30% hydrochloric acid (12 ml.) was added dropwise with stirring. The temperature during the addition, which required 30 minutes, was kept at -10° , and the mixture stirred for a further 3 hours at -10° . The colour, initially brown, soon became green. The white microcrystalline nitrosochloride was filtered off with suction and washed thoroughly with ice-cold ethanol. The yields were 60–70% of 1-phenylcyclohexene nitrosochloride, m. p. 110° (decomp.), 1-*o*-methoxyphenylcyclohexene nitrosochloride, m. p. 106° (decomp.), and 1-(2 : 3-dimethoxyphenyl)cyclohexene nitrosochloride, m. p. 125° (decomp.). The nitrosochlorides are insoluble in most organic solvents. They are soluble in chloroform, but decompose in solution. They also decompose on storage. For this reason, they were not recrystallised, but were used immediately for the next step.

Conversion of the nitrosochlorides into 2-arylcyclohex-2-enone oximes. The dry nitrosochloride (0.1 mole) was suspended in pyridine (30 ml.), and the mixture heated to 60–70°, an exothermic reaction then setting in, which often caused boiling and dissolution.

In the case of 1-phenylcyclohexene nitrosochloride, a slight excess of 20% aqueous potassium hydroxide (0.11 mole) was added and the mixture swirled for a few minutes. Sufficient acetic acid was added to neutralise the pyridine and potassium hydroxide present, and then water (200 ml.) 2-Phenylcyclohex-2-enone oxime crystallised from the mixture. It was filtered off, washed with water, and recrystallised from ethanol, and had m. p. 151° (yield, 70–80%). It was identical with the oxime prepared by the other methods described above.

In the case of 1-(2 : 3-dimethoxyphenyl)cyclohexene nitrosochloride, the reaction mixture was diluted with ether, and the ethereal solution washed with a small volume of 10% aqueous potassium hydroxide and extracted with excess of Claisen alkali solution. The alkaline layer was diluted fivefold with water and acidified with acetic acid. 2-(2 : 3-Dimethoxyphenyl)cyclohex-2-enone oxime was precipitated; recrystallised from ethanol, it had m. p. 130° (Found : C, 67.9; H, 6.9; N, 5.7. $C_{14}H_{17}O_3N$ requires C, 68.0; H, 6.9; N, 5.7%). 1-*o*-Methoxyphenylcyclohexene nitrosochloride, treated analogously, gave 2-*o*-methoxyphenylcyclohex-2-enone oxime, m. p. 150° (Found : C, 71.7; H, 6.8; N, 6.6. $C_{13}H_{15}O_3N$ requires C, 71.9; H, 6.9; N, 6.4%).

The yields varied from 70 to 80%.

Conversion of the oximes into the ketones (I). The oxime (0.5 mole), concentrated sulphuric acid (200 g.), and water (2 l.) were refluxed for 1 hour. The mixture was cooled, and the $\alpha\beta$ -unsaturated ketone filtered off, washed with water until neutral, dried, and distilled in a high vacuum. Thus were obtained 2-phenylcyclohex-2-enone (Ib), m. p. 96° (from methylcyclohexane), identical with the product described above, 2-*o*-methoxyphenylcyclohex-2-enone (Ic), m. p. 53° (Found : C, 77.5; H, 7.1. $C_{13}H_{14}O_2$ requires C, 77.2; H, 6.9%) [2 : 4-dinitrophenylhydrazone, orange, m. p. 179–180°, λ_{max} , 3820 Å., ϵ_{max} , = 24,400 (in anhydrous ethanol) (Found : C, 59.8; H, 4.8; N, 14.7. $C_{19}H_{18}O_8N_4$ requires C, 59.7; H, 4.7; N, 14.7%)]; and 2-(2 : 3-dimethoxyphenyl)cyclohex-2-enone (Ia), m. p. 96° (from butanol) (Found : C, 72.4; H, 6.9. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%) [2 : 4-dinitrophenylphenylhydrazone, red, m. p. 141° (from ethanol), λ_{max} , 3810 Å., ϵ_{max} , = 25,200 (in anhydrous ethanol) (Found : C, 57.7; H, 4.65; N, 13.9. $C_{20}H_{20}O_6N_4$ requires C, 58.3; H, 4.9; N, 13.6%); semicarbazone, m. p. 190.5–191.5° (from ethanol) (Found : C, 62.5; H, 6.5; N, 14.5. $C_{15}H_{19}O_3N_3$ requires C, 62.3; H, 6.6; N, 14.5%)].

The yields from the crude oximes were 90–95%, and the overall yields from the 1-arylcyclohexenes (without purification of intermediates) were 40–50%.

Oxidation of 1-Phenylcyclohexene (IIIb) with tert.-Butyl Chromate (Oppenauer and Oberrauch, *loc. cit.*).—Chromic anhydride (0.8 mole, 80 g.) was added with stirring during 10 minutes to *tert.*-butanol (200 ml.) with external cooling (to $<20^\circ$). To the dark-red solution was added carbon tetrachloride (680 ml.), and vigorous stirring was continued for 10 minutes after addition of anhydrous sodium sulphate. The solution was filtered, the solid washed with a small volume of carbon tetrachloride, and the filtrate concentrated *in vacuo* (water pump; internal temp. $<30^\circ$) to a volume of 200 ml. (solution A).

To a solution of 1-phenylcyclohexene (IIIb) (20 g.) in carbon tetrachloride (560 ml.), were added glacial acetic acid (80 ml.), acetic anhydride (4 ml.), and solution A (200 ml.). During the first hour the temperature was allowed to rise to 40°. Then the mixture was kept at room temperature for 4 days and added in portions with stirring and cooling to a suspension of oxalic acid (200 g.) in water (1 l.) in a large vessel (foaming!). Stirring was continued for 3 hours. The upper aqueous layer was extracted with carbon tetrachloride (200 ml.), and the combined organic extracts were washed with two portions of 10% potassium hydroxide solution. The carbon tetrachloride was removed by distillation at atmospheric pressure and the residue distilled *in vacuo*. The distillate (17 g.) partly crystallised on cooling, and consisted of 3-phenylcyclohex-2-enone (V) and some unchanged 1-phenylcyclohexene. Recrystallisation from hexane yielded pure 3-phenylcyclohex-2-enone (5 g.), m. p. 64° (Abdullah, *J. Indian Chem. Soc.*, 1935, 12, 62, reports m. p. 64°; Downes, Gill, and Lions, *J. Amer. Chem. Soc.*, 1950, 72,

3464, report m. p. 64·5°). The ketone is quite soluble in 1-phenylcyclohexene. No attempt was made to improve the yield.

The 2:4-dinitrophenylhydrazone melted at 220—221° (Downes, Gill, and Lions, *loc. cit.*, report m. p. 221°), and had λ_{\max} . 3950 μ ., ϵ_{\max} . = 51,000 (in anhydrous ethanol).

The ultra-violet absorption data reported in this paper were determined by Dr. Y. Hirshberg of this Institute. This paper represents part of a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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