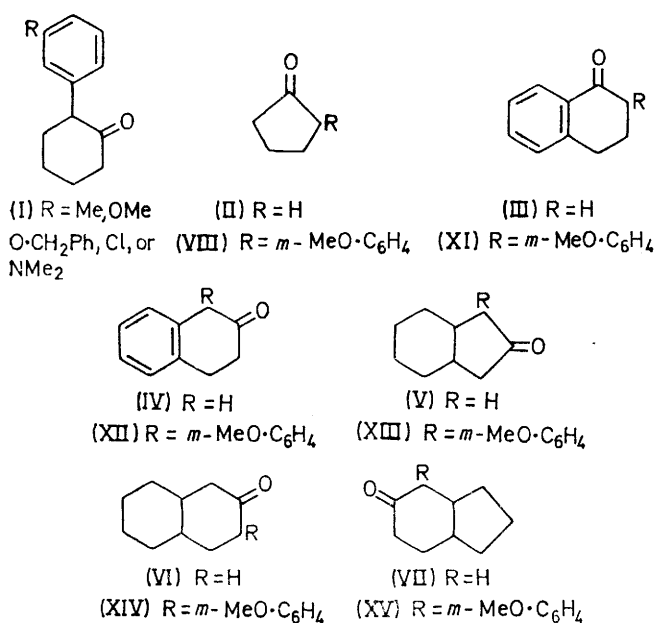


## Benzyne Reaction. Part XI.<sup>1</sup> Novel Syntheses of 2-(3-Substituted phenyl)cycloalkanones by the Benzyne Reaction †

By T. Kametani,\* K. Kigasawa, M. Hiiragi, T. Hayasaka, and O. Kusama, Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan, and Research Laboratories, Grelan Pharmaceutical Co. Ltd., Sakurashin-machi, Setagayaku, Tokyo, Japan

The benzyne reaction of *o*-halogenoanisole with cyclic carbonyl compounds (II)—(VII) gave 2-(3-substituted phenyl)cycloalkanones.

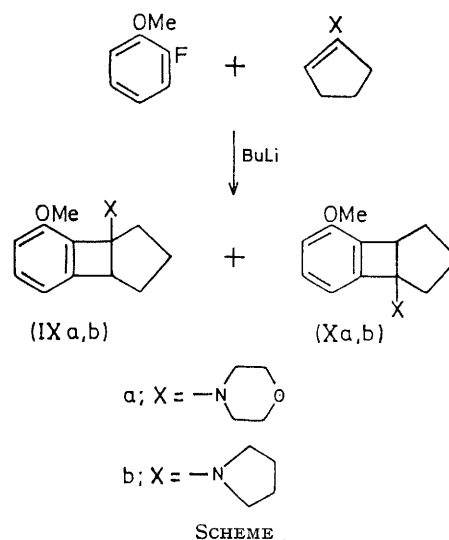
We have reported<sup>1</sup> that the benzyne reaction of *ortho*-substituted halogenobenzenes with cyclohexanone or its enamine derivatives in the presence of sodium amide gives 2-(3-substituted phenyl)cyclohexanone (I) in good yield. We have now studied the benzyne reaction of *ortho*-halogenoanisole with various other cyclic carbonyl compounds (II)—(VII).



The benzyne reactions of *o*-chloroanisole (1 mol.) with cyclopentanone (II),  $\alpha$ -tetralone (III),  $\beta$ -tetralone (IV), *cis*-hexahydroindan-2-one (V),<sup>2</sup> *cis*-octahydronaphthalen-2(1*H*)-one (VI),<sup>3</sup> and *cis*-tetrahydro-5(4*H*)-indanone (VII)<sup>2</sup> (each 2 mol.) in tetrahydrofuran in the presence of sodium amide (4 mol.) were carried out as in the reactions reported in the preceding paper.<sup>1</sup>

Cyclopentanone (II) gave 2-(3-methoxyphenyl)cyclopentanone (VIII) in 41.2% yield. The same compound was obtained from the cyclopentanone morpholine enamine in 17.6% yield. The latter reaction also gave the cyclobutene derivative (IXa), m.p. 85–86°, in 40.4% yield. Keyton and his co-workers<sup>4</sup> have recently reported that the reaction of *o*-fluoroanisole with the

morpholine or pyrrolidine enamine of cyclopentanone in ether in the presence of butyl-lithium afforded the compound (VIII) by way of a benzyne intermediate; the benzocyclobutenes (IXa) and (Xa) were also formed, through a zwitterionic intermediate, in the ratio 1 : 7.



In our reaction only the head-to-head condensed compound (IXa) was obtained; n.m.r. spectroscopy showed no trace of the head-to-tail condensed compound (Xa). The chemical shifts of the methoxy-groups in structures (IXa) and (Xa) are reported<sup>4</sup> to be 3.75 (signal broadened in acid by the proximity of the nitrogen atom) and 3.82 p.p.m., respectively. Our sample showed a methoxy-singlet at 3.75 p.p.m., slightly broadened in acid.

The benzyne reactions of *o*-chloroanisole with  $\alpha$ -tetralone (III) and  $\beta$ -tetralone (IV) afforded 3,4-dihydro-2-(3-methoxyphenyl)naphthalen-1(2*H*)-one (XI) and 3,4-dihydro-1-(3-methoxyphenyl)naphthalen-2(1*H*)-one (XII), respectively. In the case of  $\beta$ -tetralone, the aryl group was introduced at C-1 rather than C-3 owing to the influence of the benzene nucleus; the structure of the product (XII) was verified by the n.m.r. singlet (methine proton) at  $\delta$  3.64 p.p.m. Similarly, *cis*-hexahydroindan-2-one (V) gave 1-(3-methoxyphenyl)hexahydroindan-2-one (XIII).

In the cases of *cis*-octahydronaphthalen-2(1*H*)-one (VI) and *cis*-tetrahydroindan-5(4*H*)-one (VII), each of

† This forms Part CCCLXXXVIII of Studies on the Syntheses of Heterocyclic Compounds. Part CCCLXXXVII, preceding paper.

<sup>1</sup> Part X, preceding paper.

<sup>2</sup> R. L. Augustine and A. O. Broom, *J. Org. Chem.*, 1960, **25**, 802.

<sup>3</sup> R. L. Augustine, *J. Org. Chem.*, 1963, **28**, 152.

<sup>4</sup> O. J. Keyton, G. W. Griffin, M. E. Kuehne, and C. E. Bayha, *Tetrahedron Letters*, 1969, 4163.

which has two reactive methylene groups, there are two possible products. Compound (VI) gave an oil, b.p. 180—185°/0.6 mm., which showed the methine proton n.m.r. signal as a broad triplet with  $J$  9.0 Hz, in agreement with the structure (XIV) of 3-(3-methoxyphenyl)octahydronaphthalen-2(1H)-one. The n.m.r. spectrum of the derived oxime showed a broad triplet due to the methine proton, at  $\delta$  3.35 p.p.m. ( $J$  10 Hz).

Compound (VII) gave an oil, b.p. 195—200°/0.9 mm., the n.m.r. spectrum of which showed a broad doublet at 3.45 p.p.m. for the methine proton, in agreement with the structure (XV) of 4-(3-methoxyphenyl)tetrahydroindan-5(4H)-one.

Thus, various arylcycloalkanones can be obtained simply in one step by application of the benzyne reaction.

## EXPERIMENTAL

N.m.r. spectra were measured with a JNM-NH-60 spectrometer, with tetramethylsilane as an internal standard.

**2-(3-Methoxyphenyl)cyclopentanone (VIII).**—(a) To a stirred solution of sodium amide (29 g.) in dry tetrahydrofuran cyclopentanone (30 g.) was added drop by drop, followed by *o*-chloroanisole (25 g.). Stirring was continued under reflux for 6 hr. The excess of sodium amide was then decomposed with ammonium chloride solution, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic solutions were washed with 10% hydrochloric acid and water, dried ( $\text{MgSO}_4$ ), and evaporated to give an oil, which was distilled *in vacuo* to afford compound (VIII) (13.7 g.) as a pale yellow oil, b.p. 150—155°/0.9 mm.,  $\nu_{\text{max}}$  (liquid) 1745  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $\delta$  ( $\text{CCl}_4$ ) 3.05br (1H, t, ArCH) and 3.66 p.p.m. (3H, s, OMe); the oxime gave needles, m.p. 117—118° (from ethanol) (Found: C, 70.2; H, 7.2; N, 7.05.  $\text{C}_{12}\text{H}_{15}\text{NO}_2$  requires C, 70.2; H, 7.35; N, 6.8%).

(b) To a stirred solution of sodium amide (12 g.) in dry tetrahydrofuran, a mixture of *o*-chloroanisole (21 g.) and 1-morpholinocyclopentene (66 g.) was added drop by drop, and stirring was continued under reflux for 10 hr. The excess of sodium amide was then decomposed with ammonium chloride solution and the mixture was extracted with ether. The extract was washed with water, 15% hydrochloric acid, and water, dried ( $\text{MgSO}_4$ ), and evaporated to give an oil, which was distilled to give compound (VIII) (4.9 g., 17.6%) as a pale yellow oil, b.p. 130—135°/0.5 mm., identical (i.r. and n.m.r. spectra) with the samples prepared by method (a).

The acidic washings were basified with 30% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried ( $\text{MgSO}_4$ ), and evaporated. The oily residue was distilled *in vacuo* to yield an oil, b.p. 135—140°/0.5 mm., which crystallised overnight and afforded 2,3,3a,7b-tetrahydro-7-methoxy-7b-morpholino-1H-cyclopenta[3,4]cyclobuta[1,2]benzene (IXa) (15.4 g.) as prisms, m.p. 85—86° (from ethanol),  $\delta$  ( $\text{CDCl}_3$ ) 3.75 p.p.m. (3H, s, Me); the picrate gave needles, m.p. 179—180° (decomp.) (from ethanol) (Found: C, 53.85; H, 4.8; N, 11.4.  $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_6$  requires C, 54.1; H, 4.95; N, 11.4%).

**3,4-Dihydro-2-(3-methoxyphenyl)naphthalen-1(2H)-one (XI).**—To a stirred suspension of sodium amide (11 g.) in dry tetrahydrofuran was added  $\alpha$ -tetralone (20 g.), followed by *o*-chloroanisole (10 g.). Stirring was continued under

reflux for 12 hr. The excess of sodium amide was decomposed with ammonium chloride solution and the mixture was extracted with ether. The extract was washed with water, 10% hydrochloric acid, and water, dried ( $\text{MgSO}_4$ ), and evaporated. The oily residue was distilled *in vacuo* to give a pale yellow oil, b.p. 160—170°/0.8 mm., which solidified and yielded compound (XI) (10.6 g., 60%) as needles, m.p. 95—96° (from ethanol) (Found: C, 81.25; H, 6.4.  $\text{C}_{17}\text{H}_{16}\text{O}_2$  requires C, 80.9; H, 6.4%),  $\nu_{\text{max}}$  (KBr) 1690  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.58 (1H, t,  $J$  6 Hz, methine H) and 3.62 p.p.m. (3H, s, OMe).

**3,4-Dihydro-1-(3-methoxyphenyl)naphthalen-2(1H)-one (XII).**—Similar treatment of a suspension of sodium amide (8.3 g.) in dry tetrahydrofuran with  $\beta$ -tetralone (15 g.) and *o*-chloroanisole (7.5 g.), with 12 hr. stirring under reflux, gave a pale yellow oil, b.p. 160—170°/0.9 mm., which afforded compound (XII) (8.1 g., 61.5%) as needles, m.p. 106—107° (from ethanol) (Found: C, 81.0; H, 6.3.  $\text{C}_{17}\text{H}_{16}\text{O}_2$  requires C, 80.9; H, 6.4%),  $\nu_{\text{max}}$  (KBr) 1700  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.64 (1H, s, methine H) and 3.56 p.p.m. (3H, s, OMe).

**1-(3-Methoxyphenyl)hexahydroindan-2-one (XIII).**—A stirred suspension of sodium amide (1.1 g.) in dry tetrahydrofuran (10 ml.) was treated with *o*-chloroanisole (1.0 g.) and *cis*-hexahydroindan-2-one (1.5 g.), and stirring was continued under reflux for 10 hr. Work-up as usual, followed by distillation, gave an oil, b.p. 170—175°/1 mm., which yielded compound (XIII) (1.2 g., 70.5%) as needles, m.p. 118—119° (from ethanol) (Found: C, 78.35; H, 8.35.  $\text{C}_{16}\text{H}_{20}\text{O}_2$  requires C, 78.65; H, 8.25%),  $\nu_{\text{max}}$  (KBr) 1700  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.71 (1H, d,  $J$  9.0 Hz, methine H) and 3.69 p.p.m. (3H, s, OMe).

**3-(3-Methoxyphenyl)octahydronaphthalen-2(1H)-one (XIV).**—A mixture of sodium amide (8 g.), dry tetrahydrofuran (100 ml.), *o*-chloroanisole (7 g.), and *cis*-octahydronaphthalen-2(1H)-one (10 g.) was heated for 10 hr. and treated as before to give compound (XIV) (6.4 g., 50.4%) as a pale yellow oil, b.p. 180—185°/0.6 mm.,  $\nu_{\text{max}}$  (liquid) 1710  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.65br (1H, t,  $J$  9.0 Hz, methine H) and 3.70 p.p.m. (3H, s, OMe). The oxime afforded needles, m.p. 177—178° (from ethanol) (Found: C, 74.7; H, 8.05; N, 5.35.  $\text{C}_{17}\text{H}_{23}\text{NO}_2$  requires C, 74.7; H, 8.5; N, 5.1%),  $\nu_{\text{max}}$  (KBr) 3300 (OH) and 1660  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.35br (1H, t,  $J$  10 Hz, methine H), 3.90 (3H, s, OMe), and 8.60br p.p.m. (1H, s, OH).

**4-(3-Methoxyphenyl)tetrahydroindan-5(4H)-one (XV).**—A mixture of sodium amide (3.5 g.), dry tetrahydrofuran (50 ml.), *o*-chloroanisole (3.4 g.), and *cis*-tetrahydroindan-5(4H)-one (5 g.) was treated as before (12 hr.) to give compound (XV) (2.4 g., 41.4%) as a pale yellow oil, b.p. 195—200°/0.9 mm.,  $\nu_{\text{max}}$  (liquid) 1700  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.45br (1H, d,  $J$  10.5 Hz, methine H) and 3.76 p.p.m. (3H, s, OMe). The oxime gave needles, m.p. 128—129° (from ethanol) (Found: C, 74.35; H, 8.0; N, 5.5.  $\text{C}_{16}\text{H}_{21}\text{NO}_2$  requires C, 74.1; H, 8.15; N, 5.4%),  $\nu_{\text{max}}$  (KBr) 3300 (OH) and 1655  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ),  $\delta$  ( $\text{CDCl}_3$ ) 3.24br (1H, d,  $J$  10 Hz, methine H), 3.70 (3H, s, OMe), and 8.40br p.p.m. (1H, s, OH).

We thank A. Yanagisawa (President) and O. Takagi (Director), Grelan Pharmaceutical Co. Ltd., for their encouragement, and Miss A. Kawakami and Miss C. Yoshida, Pharmaceutical Institute, Tohoku University, for microanalyses.

[0/884 Received, May 27th, 1970]