A Direct Transformation of cyclo*Hexanones into* bicyclo[5 : 3 : 0]*Dec-7-en-9-ones.*

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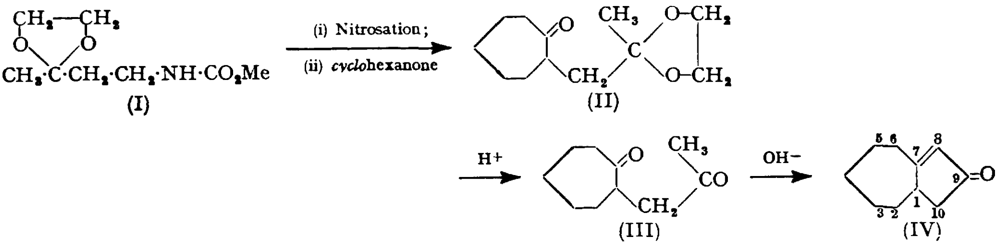
By reaction with 1-diazo-3 : 3-ethylenedioxybutane followed by acid hydrolysis and aldolisation, *cyclo*hexanones are converted into *bicyclo*-[5 : 3 : 0]dec-7-en-9-ones in a substantially one-step operation.

ALTHOUGH many routes have been used for the conversion of *cyclo*heptanone itself into *bicyclo*[5 : 3 : 0]decane derivatives the methods become both tedious and ambiguous when applied to the production of such derivatives with substituents in the seven-membered ring. To overcome these difficulties a method has now been evolved which entails the ring expansion of a *cyclo*hexanone with a diazo-compound of such a nature that the resulting *cyclo*heptanone possesses a side-chain capable of interaction with the ring carbonyl group to form the required five-membered ring.

The diazo-compound used was 1-diazo-3 : 3-ethylenedioxybutane. Addition of phthalimide to methyl vinyl ketone, followed by ketalisation of the resulting 4-phthalimidobutan-2-one with ethylene glycol, gave 3 : 3-ethylenedioxy-1-phthalimidobutane. This was converted by hydrazine into 1-amino-3 : 3-ethylenedioxybutane whence methyl chloroformate afforded the required urethane precursor (I). As these reactions were inconvenient on a large scale, ethyl lævulate was converted into its ethylene ketal which was then transformed into its hydrazide and azide in the usual fashion; treatment with methanol converted the last derivative into the urethane (I).



(I) (II) (III) (IV)

Treatment of the nitroso-derivative of urethane (I) with *cyclo*hexanone and potassium carbonate in methanol (the usual solvent for such ring expansions) caused vigorous evolution of the expected volume of nitrogen, but only unchanged *cyclo*hexanone was isolated. This was due to the immediate reaction of the diazo-compound formed with the solvent. When ethanol replaced methanol, ring expansion ensued, giving the *cyclo*heptanone (II). This seems to be one of the rare cases where the small difference in acidity between ethanol and methanol manifests itself (methanol, pK_a 16; ethanol, pK_a 18). Acid hydrolysis of the ketal (II) gave 2-acetonyl*cyclo*heptanone (III) which underwent a smooth base-catalysed internal aldol condensation to give *bicyclo*[5 : 3 : 0]dec-7-en-9-one (IV). On the preparative scale, isolation of the pure intermediates (II) and (III) is unnecessary.

Application of the method to 4-methyl- and 4-*iso*propyl-*cyclo*hexanone produced the 4-substituted *bicyclo*[5 : 3 : 0]dec-7-en-9-ones. Although these compounds contain two asymmetric centres, only one homogeneous product was obtained. This, however, is to be expected as the presence of a carbonyl group adjacent to one of the asymmetric centres in the intermediates corresponding to (II) and (III) ensures stereomutation to the more stable geometrical isomer. Unexpectedly, only one product was also obtained from 2-methyl*cyclo*hexanone, although in this case the incursion of position isomerism is possible, depending on which side of the carbonyl group the ring expansion takes place. It is suggested that the product is 6-methyl*bicyclo*[5 : 3 : 0]dec-7-en-9-one, the expansion ensuing at the less sterically hindered side of the carbonyl group. This is borne out by the finding that 2 : 6-dimethyl*cyclo*hexanone did not undergo ring expansion under the same conditions.

Catalytic reduction of *bicyclo*[5 : 3 : 0]dec-7-en-9-one (IV) gave a homogeneous ketone (semicarbazone, m. p. 198—199°), and lithium in liquid ammonia produced a stereoisomer (semicarbazone, m. p. 221—223°). The latter tallies with a known ketone of this structure but unspecified configuration (Plattner, Fürst, and Jirasek, *Helv. Chim. Acta*, 1946, **29**, 730, 740, report m. p. 222—223° for its semicarbazone). Although it can be said that this is the more thermodynamically stable isomer (Barton and Robinson, *J.*, 1954, 3045) it is difficult from purely conformational reasoning to determine its geometrical configuration. This assignment is being studied synthetically.

EXPERIMENTAL

4-Phthalimidobutan-2-one.—Phthalimide (18 g.), freshly distilled methyl vinyl ketone (8·7 g.), and benzyltrimethylammonium hydroxide (3 c.c.) in ethyl acetate (70 c.c.) were stirred at the b. p. for 30 min. Evaporation to dryness under reduced pressure gave the *ketone* (24 g., 90%) which crystallised from ethanol in rhombs, m. p. 112° (Found: C, 66·5; H, 5·25; N, 6·7. $C_{12}H_{11}O_3N$ requires C, 66·35; H, 5·05; N, 6·5%). The 2 : *4-dinitrophenylhydrazone* crystallised from ethyl acetate in orange prisms, m. p. 176° (Found: C, 54·6; H, 3·4; N, 17·75. $C_{18}H_{15}O_6N$ requires C, 54·45; H, 3·7; N, 17·65%).

3 : *3-Ethylenedioxy-1-phthalimidobutane* (*2-Methyl-2-3′-phthalimidopropyl-1 : 3-dioxolan*).—The above ketone (15 g.), ethylene glycol (6·5 g.), and toluene-*p*-sulphonic acid (0·2 g.) in dry benzene (300 c.c.) were heated under reflux for 3 hr. with automatic water separation. The cooled benzene solution was washed with sodium carbonate solution and water, and dried ($MgSO_4$), and the solvent removed. The solid residue of *1-phthalimido-compound* (15 g., 83%) crystallised from ethanol in prisms, m. p. 122°, depressed by 20° on admixture with the starting ketone (Found: C, 64·8; H, 5·7; N, 5·2. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·7; N, 5·3%). Treatment of the ketal with warm alcoholic 2 : 4-dinitrophenylhydrazine sulphate gave the 2 : 4-dinitrophenylhydrazone described above.

1-Amino-3 : 3-ethylenedioxybutane (*2-3′-Aminopropyl-2-methyl-1 : 3-dioxolan*).—The above ketal (15 g.) and hydrazine hydrate (100%; 3 g.) in water (250 c.c.) were heated under reflux until all the solid had dissolved (50 min.). 2N-Sodium hydroxide (25 c.c.) was added and the solution extracted continuously with ether for 3 days. Drying, evaporation, and distillation gave the *amine* (5·6 g., 79%), b. p. 121—122°/100 mm., n_D^{22} 1·4460 (Found: C, 54·6; H, 9·75; N, 10·3. $C_6H_{13}O_2N$ requires C, 54·95; H, 10·0; N, 10·7%). The 2 : *4-dinitrophenyl derivative* crystallised from ethanol in yellow prisms, m. p. 116—118° (Found: C, 48·65; H, 5·2; N, 14·2. $C_{12}H_{15}O_6N_3$ requires C, 48·5; H, 5·1; N, 14·1%).

3 : *3-Ethylenedioxybutanecarboxyhydrazide.*—A mixture of ethyl 3 : 3-ethylenedioxybutanecarboxylate (Kühn, *J. prakt. Chem.*, 1940, **156**, 103) and hydrazine hydrate (100%; 35 g.) was heated under reflux for 4 hr.; the mixture became homogeneous after 45 min. Distillation gave the *hydrazide* (80 g., 87%), b. p. 142°/0·4 mm., which solidified to extremely hygroscopic crystals, m. p. *ca.* 34° (Found: C, 46·65; H, 7·7; N, 16·3. $C_7H_{14}O_3N_2$ requires C, 48·2; H, 8·0; N, 16·1%). The *α-methylbenzylidene derivative*, prepared by heating the hydrazide with acetophenone, crystallised from ethanol in needles, m. p. 99—100° (Found: C, 65·35; H, 6·7; N, 10·35. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·2; N, 10·15%).

3 : *3-Ethylenedioxy-1-methoxycarbonylaminobutane* (*2-3′-Methoxycarbonylaminopropyl-2-methyl-1 : 3-dioxolan*) (I).—(*a*) A solution of the hydrazide (60 g.) and sodium nitrite (60 g.) in water (150 c.c.) was covered with ether (120 c.c.) and cooled to −5°. An ice-cold solution of concentrated sulphuric acid (33 g.) in water (120 c.c.) was added, with shaking, at such a rate that the temperature remained between −5° and 0°. Then the ether layer was decanted and the aqueous layer washed twice with fresh ether. The combined extracts were dried (Na_2SO_4), methanol (100 c.c.) was added, and the ether was distilled off. The resulting methanolic

solution was heated under reflux for 2 hr. Removal of the solvent and distillation gave the water-soluble ***urethane*** (I) (33 g., 51%), b. p. 98—100°/0·4 mm., n_D^{18} 1·4555 (Found : C, 50·3; H, 7·6; N, 7·45. $C_8H_{15}O_4N$ requires C, 50·8; H, 7·9; N, 7·4%). A preparation on four times this scale gave a similar yield. The 2 : *4-dinitrophenylhydrazone* crystallised from methanol in light yellow needles, m. p. 121° (Found : C, 44·5; H, 4·8; N, 21·6. $C_{12}H_{15}O_6N_5$ requires C, 44·3; H, 4·6; N, 21·5%).

(*b*) To a stirred solution of 1-amino-3 : 3-ethylenedioxybutane (1·3 g.) in dry ether (15 c.c.) at 0° were added dropwise and simultaneously methyl chloroformate (1 g.) and a solution of sodium hydroxide (0·4 g.) in water (4 c.c.). After 15 min. the product was isolated with ether. Drying (K_2CO_3), evaporation, and distillation gave the above urethane (1·6 g., 84%), b. p. 148—150°/16 mm., n_D^{22} 1·4538, which gave a 2 : 4-dinitrophenylhydrazone identical with that described under (*a*).

A mixture of the urethane (10 g.), sodium nitrite (60 g.), crushed ice (10 g.), and water (80 c.c.) was covered with ether (30 c.c.) and cooled to 0°. A cold solution of concentrated nitric acid (20 c.c.) in water (30 c.c.) was run in slowly with occasional shaking from a dropping funnel, the end of which was immersed in the aqueous layer; the temperature was kept below 5°. The bluish-green ether layer was removed and the aqueous layer washed twice with fresh ether. The combined extracts were washed with chilled concentrated potassium hydrogen carbonate solution and dried (Na_2SO_4) at 0°. Removal of the ether at room temperature under reduced pressure gave the *N*-nitrosourethane as a pink viscous oil (10 g.) which decomposed on attempted distillation. This product was used as such for the following ring expansions.

2-(2 : *2-Ethylenedioxypropyl*)cyclo*heptanone* (*2-Methyl-*2-2′-*oxo*cyclo*heptyl-*1 : 3-*dioxolan*) (II).—The *N*-nitrosourethane (10 g.) was added dropwise to a stirred mixture of *cyclo*hexanone (6 g.), dry ethanol (20 c.c.), and freshly ignited, powdered potassium carbonate (3 g.) at such a rate that the temperature of the mixture did not exceed 28°. The colour deepened gradually to orange and 900 c.c. of nitrogen were collected after 5 hr. (theor., 1030 c.c.). After filtration and evaporation of the ethanol, water was added and the product was isolated with ether. Distillation gave the ketone (II) (6 g.), b. p. 94—96°/0·3 mm., $n_D^{20·5}$ 1·4747. The product tenaciously retained a small quantity of a nitrogen-containing impurity which resulted in inaccurate analytical figures.

2-*Acetonyl*cyclo*heptanone* (III).— A solution of the *cyclo*heptanone (II) (4 g.) in ethanol (20 c.c.) and 5% sulphuric acid (5 c.c.) was set aside overnight. Dilution with water and isolation by means of ether gave 2-*acetonyl*cyclo*heptanone* (2·5 g., 80%), b. p. 128°/12 mm., n_D^{19} 1·4700 (Found : C, 70·9; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%).

bicyclo[5 : 3 : 0]*Dec-7-en-9-one.*—A mixture of the diketone (III) (2 g.), aqueous potassium hydroxide (5%; 150 c.c.), and ethanol (10 c.c.) was heated under reflux for 3 hr. Steam-distillation and extraction of the distillate with ether gave the bicyclic *ketone* (1·3 g., 72%), b. p. 118—120°/16 mm., n_D^{19} 1·5212 (Found : C, 79·6; H, 8·9. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%). Light absorption in EtOH : max. at 233 (ε 12,600) and 289 mμ (ε 190). The 2 : 4-dinitrophenylhydrazone crystallised from ethanol–ethyl acetate in red needles, m. p. 184—185° (Lloyd and Rowe, *J.*, 1953, 3718, give m. p. 185°) (Found : C, 58·3; H, 5·5; N, 17·1. Calc. for $C_{16}H_{18}O_4N_4$: C, 58·2; H, 5·5; N, 17·0%). Light absorption in EtOH : max. at 388 mμ (ε 26,700). The *semicarbazone* crystallised from ethanol in plates, m. p. 220—222° (Found : N, 20·0. $C_{11}H_{17}ON_3$ requires N, 20·2%).

Combined Ring Expansion and Cyclisation Procedure.—The *N*-nitrosourethane (10 g.) was added to a stirred mixture of the relevant *cyclo*hexanone (6 g.), dry ethanol (20 c.c.), and ignited potassium carbonate (3 g.) at such a rate that the mixture remained between 20° and 30°. After 5 hr. the potassium carbonate was filtered off, 5% sulphuric acid (10 c.c.) added, and the mixture set aside overnight. Saturated ammonium sulphate solution was then added and the organic layer isolated with ether. After removal of the solvent the product was heated under reduced pressure to remove any unchanged *cyclo*hexanone. The residue was treated with potassium hydroxide solution as described above and the resulting bicyclic ketone isolated in the same way.

Applied to *cyclo*hexanone itself this process gave a very reproducible yield of *bicyclo-*[5 : 3 : 0]dec-7-en-9-one (28% based on *N*-nitrosourethane). 4-Methyl*cyclo*hexanone gave the *4-methyl homologue* (32%), b. p. 124°/16 mm. (Found : C, 80·4; H, 9·4. $C_{11}H_{16}O$ requires C, 80·5; H, 9·7%). The chromatographically homogenous 2 : *4-dinitrophenylhydrazone* crystallised from ethanol–ethyl acetate in red needles, m. p. 155—157° (Found : C, 59·1; H, 6·1; N, 16·3. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·8; N, 16·3%); light absorption in EtOH : max. at 388 mμ (ε 28,900). The *semicarbazone* formed plates, m. p. 222—224°, from ethanol (Found : N, 18·85. $C_{12}H_{19}ON_3$ requires N, 19·0%). Similarly, 4-*iso*propyl*cyclo*hexanone gave the bicyclic

4-iso*propyl homologue* (28%), b. p. 136—139°/18 mm., n_D^{21} 1·5085 (Found : C, 80·9; H, 10·5. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%); its 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 142—144°, from ethanol–ethyl acetate (Found : C, 61·45; H, 6·55; N, 14·9. $C_{19}H_{24}O_4N_4$ requires C, 61·3; H, 6·5; N, 15·0%); light absorption in EtOH : max. at 388 mμ (ε 29,000). 2-Methyl*cyclo*hexanone gave a small yield (9%) of homogeneous bicyclic product, whose 2 : 4-*dinitrophenylhydrazone*, red needles, had m. p. 128—130° (from ethanol–ethyl acetate) (Found : C, 59·5; H, 6·0; N, 16·2. $C_{17}H_{20}O_4N_4$ requires C, 59·3; H, 5·8; N, 16·3%) and absorption max. in EtOH 388 mμ (ε 27,900).

Reduction of bicyclo[5 : 3 : 0]*Dec-7-en-9-one*.—(*a*) The unsaturated ketone (90 mg.) in methanol (30 c.c.) was hydrogenated at a palladium–charcoal catalyst (5%; 5 mg.); 14·5 c.c. of hydrogen were taken up in 15 min. at 21°/760 mm. (theor., 14·3 c.c.). The filtered solution was treated with methanolic semicarbazide acetate; the resulting *semicarbazone* crystallised from methanol in needles, m. p. 198—199° (Found : N, 20·0. $C_{11}H_{19}ON_3$ requires N, 20·1%). Heating this semicarbazone with ethanolic 2 : 4-dinitrophenylhydrazine sulphate gave the corresponding 2 : 4-*dinitrophenylhydrazone*, orange-yellow needles, m. p. 125—126°, from ethanol (Found : C, 58·1; H, 6·2; N, 17·0. $C_{16}H_{20}O_4N_4$ requires C, 57·85; H, 6·0; N, 16·85%).

(*b*) A solution of the unsaturated ketone (150 mg.) in ether (5 c.c.) was added to a stirred solution of lithium (100 mg.) in liquid ammonia (50 c.c.). After 30 min. ammonium chloride was added and the ammonia evaporated off. Extraction with ether yielded the saturated ketone, which was converted directly into the semicarbazone, plates, m. p. 221—223° (from ethanol) (Found : N, 19·8%). Treatment of this as described above gave the corresponding 2 : 4-*dinitrophenylhydrazone* which crystallised from ethanol in red sheaves of needles on slow crystallisation or yellow plates on rapid cooling. Both forms partially melted at 129—130°, then rapidly resolidified to a mass of yellow needles which melted sharply at 138° (Found: C, 58·3; H, 6·0; N, 17·0%).

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