Tetrahedron, 1965, Vol. 21, pp. 3273 to 3276. Pergamon Press Ltd. Printed in Northern Ireland

# BRIDGED RING SYSTEMS—VIII[1]

## A NOVEL RING EXPANSION REACTION

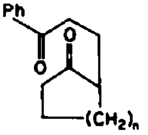
G. L. Buchanan, C. Maxwell and (in part) W. Henderson
Chemistry Department, Glasgow University

(*Received* 31 *May* 1965)

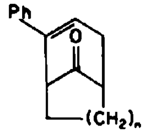
**Abstract**—Acid treatment of 2-(β-Benzoylethyl)-cyclopentanone (III) leads directly to a phenyl-cycloheptene carboxylic acid (VII) and the related lactone (XI), via a bicyclic intermediate.

Recent work on bridged bicyclic compounds includes a few cases in which the bridge has been broken, giving rise to medium-sized carbocycles.[2,3] The process is potentially valuable as a route to particularly substituted medium-sized rings, and a previous paper in this series has described its application to the synthesis of otherwise inaccessible cyclo-octenes and cyclononenes.[4] This communication describes a new route to cycloheptenes.

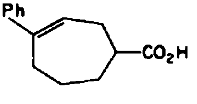
It has been shown, that the 1,5-diketone (I), which is readily prepared from cyclohexanone and the Mannich base of acetophenone, is cyclized under acid conditions to the bicyclo-(3,3,1)-nonenone (IV).[2] Under identical conditions, the cycloheptanone derivative (II) gave the corresponding bicyclo-(4,3,1)-decenone (V), ($\nu_{CO}^{CCl_4}$ 1718 cm$^{-1}$) whose NMR spectrum showed one vinyl proton (3·98τ) as a poorly resolved triplet (J 3 c/s); but the diketone (III) derived from cyclopentanone yielded an acid, $C_{14}H_{16}O_2$ together with a neutral by-product. The acid, which has been identified as VII, afforded a methyl ester, showed styrene absorption ($\lambda_{max}^{EtOH}$ 249 mμ; ε 10,000) and took up 1 molar equivalent of hydrogen, on catalytic reduction. Decarboxylation experiments were unrewarding, but similar treatment of the reduced acid afforded phenylcycloheptane which was identified by comparison with synthetic material prepared from cycloheptanone by an unambiguous, but exceptional route.[5] On ozonolysis, the unsaturated acid yielded a keto-acid ($\nu_{CO}^{Nujol}$ 1705, 1692 cm$^{-1}$) and on warming with acetyl chloride, the latter was converted smoothly to the anhydride (VIII) ($\nu_{CO}^{CCl_4}$ 1863



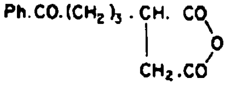
I; n=2
II; n=3
III; n=1



IV; n=2
V; n=3
VI; n=1



VII



$$\begin{array}{l} Ph.CO.(CH_2)_3.CH.CO \\ \qquad\qquad\qquad\;\; |\qquad\; O \\ \qquad\qquad\qquad CH_2.CO \end{array}$$

VIII

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[1] Part VII, E. W. Colvin and W. Parker, *J. Chem. Soc.* in press.

[2] A. C. Cope and E. C. Hermann, *J. Amer. Chem. Soc.* **72**, 3405 (1950).

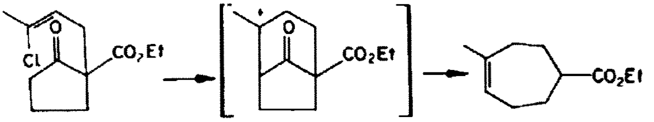
[3] G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.* **78**, 5129 (1956); C. D. Gutsche, T. D. Smith, M. F. Sloan, J. J. Quarles van Ufford and D. E. Jordan, *Ibid.* **80**, 4117 (1958); A. C. Cope, F. S. Fawcett and G. Munn, *Ibid.* **72**, 3399 (1950); A. C. Cope, E. J. Graham and D. J. Marshall, *Ibid.* **76**, 6159 (1954).

[4] G. L. Buchanan, A. McKillop and R. A. Raphael, *J. Chem. Soc.* 833 (1965).

[5] G. Baddeley, J. Chadwick and H. T. Taylor, *J. Chem. Soc.* 451 (1956) H. Pines, A. Edeleanu and V. N. Ipatieff, *J. Amer. Chem. Soc.* **67**, 2193 (1945).

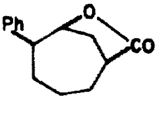
and 1794 cm$^{-1}$) showing the distinctive IR bands of a succinic anhydride.[6] The carboxyl function in VII is therefore located as shown.

The reaction described above constitutes a novel synthesis of the seven membered ring from a cyclopentanone, *in one operation*, and its scope and application are being studied. The mechanism of the reaction is also of interest, and although the details are still obscure, it appears likely that an unstable intermediate bicyclo-(3,2,1)-octenone (VI) is involved. There are indications that this bicyclic system is strained,[7] and an analogous transformation has been postulated to explain the formation of a nonconjugated ester from IX under acid conditions. The yield was below 3% and the structure of the product (X) was not established, but in view of the present work, it seems highly probable. All our attempts to isolate an intermediate (VI) were unsuccessful until conditions were defined, which removed even the water formed in the initial aldol reaction (III → VI). Thus prepared, the bicyclic-enone showed evidence of ring strain[7b] ($\nu_{CO}^{CCl_4}$ 1756 cm$^{-1}$) and its NMR spectrum showed the expected 1 × H triplet at 4·1τ (J 3·7 c/s). It readily rearranged to the acid (VII) under mild acid conditions. Similar treatment of the bicyclic ketones (IV and V) gave no acidic product, and the driving force for the reaction thus appears to be the release of strain in the bicyclo-octenone system. However, the low yield recorded in the transformation (IX → X) suggests that other factors are of importance, and this question will be discussed in a future publication.

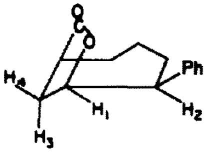


IX X

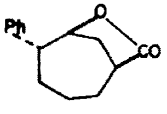
The neutral by-product, which was found to be isomeric with the acid (VII), showed ($\nu_{CO}^{CCl_4}$ 1780 cm$^{-1}$). It was unaffected by sodium borohydride; indeed it was conveniently freed from contaminating traces of the diketone (III) by borohydride reduction, followed by chromatography. It could be formed directly from VII by treatment with hot sulphuric acid, and is accordingly the γ-lactone (XI). This formulation was confirmed by the NMR spectrum, which showed the —CO—O—C—H proton as a doublet at 5·1τ (J = 6·9 c/s) with barely discernible sub-splitting. It can be seen from models that XI, as represented in the most probable conformation (XII) would give rise to just such a signal, since the dihedral angles $H_1H_2$, $H_1H_3$ and $H_1H_4$ are close to 90°, 90° and 30° respectively. The observed coupling constant is of the correct order.[8] An alternative, epimeric, structure (XIII) which also satisfies the NMR data, can be



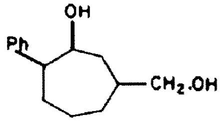
XI



XII



XIII



XIV

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[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* p. 128. Methuen, London (1958).

[7a] W. G. Dauben and J. W. McFarland, *J. Amer. Chem. Soc.* **82**, 4245 (1960);

[b] N. A. Le Bel and L. A. Spurlock, *Tetrahedron* **20**, 215 (1964);

[c] C. A. Grob, *Helv. Chim. Acta* **46**, 2212 (1963).

[8] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

discounted, since it would require the lactonization to proceed by a *cis*-addition mechanism.[9] On reduction with LAH, the lactone afforded a diol (XIV) whose NMR spectrum ($CDCl_3$) showed a poorly resolved multiplet (1 × H) centred at 5·98τ (>CHO—) and a doublet (2 × H) at 6·54τ (J 5 c/s)(—O—$CH_2$—CH<). In dimethyl sulphoxide[10] the secondary and primary OH protons were observed respectively as a doublet (5·78τ; J 4·8 c/s) and a triplet (5·5τ; J 4·8 c/s) each with the weight of 1 × H, and the expected chemical shift.[10]

## EXPERIMENTAL

The UV and IR Spectra were measured on Unicam S.P. 500 and S.P. 100 spectrophotometers respectively; NMR spectra were determined in $CDCl_3$ on a Perkin–Elemer 60 mc instrument by Mr. J. Gall: micro-analyses were carried out by Mr. J. M. L. Cameron, B.Sc., and his staff.

### 2-(*β-Benzoylethyl*)-*cycloheptanone* (II)

*β*-Dimethylaminopropiophenone[11] (69 g) and cycloheptanone (124 g) were boiled under reflux for 1 hr, cooled and neutralized with acetic acid and extracted with ether. The ether solution was washed with water, dried and distilled, affording 58 g crude diketone as a viscous oil (b.p. 163–168/0·35 mm) which slowly solidified, m.p. 27° (light petroleum). (Found: C, 78·4; H, 7·9. $C_{16}H_{20}O_2$ requires: C, 78·65; H, 8·25%.) $\nu_{CO}^{CCl_4}$ 1702 and 1693 cm$^{-1}$.

### 2-*Phenylbicyclo* (4,3,1)*dec*-2-*en*-10-*one* (V)

(a) The above diketone (3 g) and an equal weight of toluene-*p*-sulphonic acid in 125 ml dry benzene, were boiled under reflux in an apparatus fitted with a Dean and Stark water separator[12] until no more water was removed. The solution was treated with excess dry $K_2CO_3$ and then evaporated to a brown oil (2·2 g). Chromatography in light petroleum on silica (40 g) gave the *bicyclic ketone* m.p. 78–80° (light petroleum). (Found: C, 85·2; H, 7·8. $C_{16}H_{18}O$ requires: C, 84·9; H, 8·0%) NMR 1 × H, 3·98τ (mult) assigned to $H_3$, and 1 × H, 6·45τ (mult) assigned to $H_6$. $\nu_{CO}^{CCl}$ 1718 cm$^{-1}$.

(b) A solution of II (3 g) in 25 ml acetic acid and 6 ml conc. HCl was boiled under reflux for 6 hr, concentrated *in vacuo* and flooded with water. The brown oil which precipitated was taken up in ether, and this solution was washed with 6 N NaOH, dried and evaporated; the semi-solid residue (2·12 g) was identified as V, by comparison of IR spectra and by TLC, with the product from (a) above. Acidification of the alkali washing yielded a trace of oil.

### 4-*Phenylcyclohept*-3-*ene carboxylic acid* (VIII) *and lactone* (XI)

The diketone (III[13]; 37 g) in acetic acid (300 ml) was treated with 74 ml conc. HCl and boiled under reflux for 8 hr. Thereafter, the solution was concentrated at 100° under vacuum, diluted with water and extracted with ether. The ethereal solution was re-extracted with 6 N NaOH and on acidification the extract yielded the *acid* as a viscous oil b.p. 150–154°/0·15 mm. (Found: C, 77·7; H, 7·55. $C_{14}H_{16}O_2$ requires: C, 77·75; H, 7·5%.) Yield 27·6 g, $\nu_{CO}^{CCl_4}$ 1756 cm$^{-1}$ (ε 194; $\Delta\nu\frac{1}{2}$ 17 cm$^{-1}$) and 1707 cm$^{-1}$ (ε 563; $\Delta\gamma\frac{1}{2}$ 14 cm$^{-1}$) corresponding to monomeric and dimeric $CO_2H$.

The ether layer was washed with brine, dried and evaporated, yielding the crude lactone (XI) contaminated with starting diketone. Purification was effected by reduction with $NaBH_4$ followed by chromatography in light petroleum on silica. This procedure afforded pure *lactone* m.p. 122° (light petroleum). (Found: C, 78·0; H, 7·7. $C_{14}H_{16}O_2$ requires: C, 77·75; H, 7·5%.) Yield 4·45 g, $\nu_{CO}^{CCl_4}$ 1780 cm$^{-1}$, (ε 90; $\Delta\nu\frac{1}{2}$ 12·5 cm$^{-1}$).

Prolonged reflux (e.g. 48 hr) increased the proportion of lactone in the mixture.

*Ester*. The unsaturated acid (VII; 4·15 g) in 50 ml anhydrous MeOH and 0·5 ml conc. $H_2SO_4$ was allowed to stand at room temp for 36 hr, and then boiled under reflux for 6 hr. Some of the solvent was distilled off, and the residue was flooded with water and extracted with ether. The ethereal

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[9] M. F. Ansell and M. H. Palmer, *Quart. Rev.* **18**, 211 (1964).

[10] O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.* **86**, 1256 (1964).

[11] *Organic Syntheses*, Coll. Vol. 3, 305.

[12] A. I. Vogel, *A Textbook of Practical Organic Chemistry* p. 429. Longmans Green, London (1956).

[13] N. S. Gill, K. B. James, F. Lions and K. T. Potts, *J. Amer. Chem. Soc.* **74**, 4923 (1952).

solution was washed with 6 N $NaHCO_3$, dried and evaporated, yielding the *methyl ester* (4 g) b.p. 134°/1 mm. (Found: C, 78·6; H, 8·1. $C_{15}H_{18}O_2$ requires: C, 78·2; H, 7·9%.)

*Reduction and decarboxylation.* The unsaturated acid (0·3 g) in ethyl acetate (25 ml) was hydrogenated at 1 atm in presence of 5% Pd–C (50 mg). Uptake ceased after 1 molar equiv. $H_2$ had been consumed, and removal of catalyst and solvent afforded the *saturated acid* m.p. 57–59° (light petroleum). (Found: C, 76·7; H, 7·8. $C_{14}H_{18}O_2$ requires: C, 77·0; H, 8·3%.)

The saturated acid (8 g) and 2 g Cu dust in 28 g redistilled quinoline was boiled under reflux for 72 hr, then filtered. The filtrate, dissolved in ether, was washed with 6 N HCl, and with 6 N NaOH, dried and evaporated under vacuum. The dark-coloured oily product was chromatographed in light petroleum on alumina; the first product eluted was phenylcycloheptane (200 mg, b.p. 110–112°/10 mm) which was identical (IR spectrum) with a synthetic[3] sample. Trace impurities in the decarboxylation product gave rise to two small extraneous peaks, and this was equally true of the NMR and mass spectra, but all of the genuine peaks were present.

*Ozonolysis.* The unsaturated acid (VII; 5·0 g) in 60 ml $CH_2Cl_2$ was treated (at $-70°$) with $O_3$ until the solution developed a blue colour. The cooling was removed, and when the solution had reach room temp it was added dropwise over 30 min, to 50 ml warm $H_2O_2$ (30%). A vigorous reaction took place, and the temp was maintained below 60° by cooling. The mixture was then stirred overnight, heated under reflux for 1 hr and finally heated *in vacuo* to remove $CH_2Cl_2$. The organic material was then extracted into ether and washed successively with $FeSO_4$aq and $NaHCO_3$aq. These operations produced, respectively, a curdy precipitate and an alkaline extract, and on acidification, each furnished the same crude acid, m.p. ca. 155–170°, which resisted purification.

The crude acid (64 mg) was warmed for 3 hr, with 5 ml acetyl chloride. Excess acetyl chloride was removed *in vacuo* and the residue was dissolved in ether and washed with $NaHCO_3$aq and dried. Evaporation yielded the *ketoanhydride* m.p. 100–101° (benzene–light petroleum). (Found: C, 68·5; H, 5·6. $C_{14}H_{14}O_4$ requires: C, 68·3; H, 5·7%.) Yield 52 mg (87·5%), $\nu_{CO}^{CCl_4}$ 1863, 1794 and 1692 $cm^{-1}$.

### 2-*Phenylbicyclo*(3,2,1)*Oct-2-en-8-one* VI

Benzene (400 ml) containing toluene-*p*-sulphonic acid (12 g) was boiled under reflux in an apparatus fitted with a Dean and Stark water separator, until all water had been removed. Thereafter, III (12 g) was added and boiling was continued for a further 2·5 hr. Anhydrous $K_2CO_3$ was added in excess, and after filtration, the benzene was removed in vacuum, and the residual oil (11 g) was chromatographed in light petroleum on silica (230 g). Elution with light petroleum removed by-products (ca. 100 mg); further elution with light petroleum—10% ethyl acetate afforded the *bicyclic ketone* (5·8 g) m.p. 90–93° (benzene—light petroleum). (Found: C, 85·1; H, 7·1. $C_{14}H_{14}O$ requires: C, 84·8; H, 7·1%), $\nu_{CO}^{CCl_4}$ 1758 $cm^{-1}$ ($\varepsilon$548).

A solution of VI (60 mg) in 10 ml acetic acid containing 0·1 ml conc HCl was boiled for 2·5 hr, concentrated *in vacuo* to remove acetic acid, and dissolved in ether. The ethereal solution was extracted with $Na_2CO_3$aq, and on acidification the extract yielded ca. 20 mg VII.

*Lactonization.* The unsaturated acid (2 g) in 30 ml acetic acid and 15 ml $H_2SO_4$aq (50% by volume) was boiled for 8 hr, concentrated *in vacuo*, flooded with water and extracted with ether. The etheral solution was washed with $Na_2CO_3$aq, dried and evaporated, affording 0·2 g crude lactone m.p. 115–120°. After purification, it was identified by mixed m.p. and by comparison of IR spectra.

On acidification, the base washings gave ca. 1·7 g unchanged acid.

*Hydride reduction.* A solution of the lactone (6 g) in 75 ml anhydrous tetrahydrofuran was added over 2 hr, to a stirred suspension of LAH (1 g) in 50 ml, of the same solvent, and heated under reflux for 7 hr. Excess hydride was destroyed with ethyl acetate, and sufficient 6 N HCl was added to dissolve the inorganic salts. Thereafter, most of the solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate, affording the *diol* (XIV), which was recrystallized with difficulty from water, m.p. 80–85°. (Found: C, 75·2; H, 8·45. $C_{14}H_{20}O_2$ requires: C, 76·3; H, 9·15%.)