A Synthesis of Cyclohepta-2,4,6-trienones

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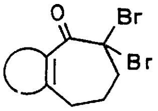
Dehydrobromination of 2,2,7-tribromocycloheptanones with lithium carbonate in boiling dimethylformamide gives cyclohepta-2,4,6-trienones.

2,2-DIBROMOCYCLOHEPTANONES with a fused ring (type A) are dehydrobrominated in high yield by lithium salts in boiling dimethylformamide (DMF) [1-3] giving, for example, benzocycloheptenones. Since the most probable mechanism for the dehydrobromination involves double-bond migration,[3] the synthesis should, in principle, be useful for monocyclic ketones, particularly since there is ample evidence for an equilibrium between cyclohept-2-enone and cyclohept-3-enone.[4] Representative cycloheptanones have been converted (*via* the 2,2,7-tribromo-derivatives) into cyclohepta-2,4,6-trienones to illustrate the scope of the method.



(A)

2,2,7-Tribromocycloheptanone (2) is the normal product [5] obtained from cycloheptanone (1) and an excess of bromine at low temperatures, in acetic acid as solvent. The yield of crude material is essentially quantitative, but it was found necessary to recrystallize the tribromo-derivative (2) once from methanol or the dehydro-

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[1] E. W. Collington and Gurnos Jones, *Tetrahedron Letters*, 1968, 1935.

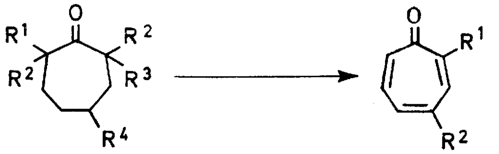
[2] E. W. Collington and Gurnos Jones, *J. Chem. Soc.* (*C*), 1969, 1029.

[3] E. W. Collington and Gurnos Jones, *J. Chem. Soc.* (*C*), 1969, 2656.

[4] For example see N. Heap and G. H. Whitham, *J. Chem. Soc.* (*B*), 1966, 166.

[5] W. v. E. Doering and A. A. Sayigh, *J. Amer. Chem. Soc.*, 1954, **76**, 39.

bromination stage gave mixtures. On a trial scale the dehydrobromination of compound (2) was shown to be 95% complete after 30 min. in boiling DMF with a three-fold excess of lithium carbonate (estimated from the intensity of the 314 nm. band in an accurately diluted solution). However on a preparative scale (0·25 mole) it was only possible to isolate 52% of distilled tropone (3); losses were probably due to the instability of tropone, and also to its high water solubility (no attempt was made to extract the aqueous work-up mixture on a continuous basis). However, the preparation is simple and rapid.



(1) $R^1 = R^2 = R^3 = R^4 = H$
(2) $R^1 = R^4 = H$; $R^2 = R^3 = Br$
(4) $R^1 = C_3H_5$; $R^2 = R^3 = R^4 = H$
(5) $R^1 = Pr^n$; $R^2 = R^3 = R^4 = H$
(6) $R^1 = Pr^n$; $R^2 = R^3 = Br$, $R^4 = H$
(7) $R^1 = Pr^n$; $R^2 = Br$; $R^3 = R^4 = H$
(9) $R^1 = R^2 = R^3 = H$; $R^4 = Pr^i$
(10) $R^1 = R^2 = R^3 = H$; $R^4 = Bu^t$
(11) $R^1 = H$; $R^2 = R^3 = Br$; $R^4 = Pr^i$
(13) $R^1 = R^2 = R^3 = Br$; $R^4 = Bu^t$

(3) $R^1 = R^2 = H$
(8) $R^1 = Pr^n$; $R^2 = H$
(12) $R^1 = H$; $R^2 = Pr^i$

2-Alkylcycloheptanones can be prepared in a variety of ways; notable are the ring expansion of cyclohexanone with diazoalkanes[6] and the alkylation of cycloheptanone enamines by reactive alkyl halides.[7] By the latter method 2-allylcycloheptanone (4) was prepared, and reduced to 2-n-propylcycloheptanone (5). It was expected that bromination of the 2-alkylcycloheptanones to the tribromo-stage would be difficult; however, by bromination of 2-n-propylcycloheptanone (5) with bromine in acetic acid at room temperature (7 days) a mixture was obtained and separated by preparative layer chromatography (p.l.c.) to give equal weights of a dibromo- and a tribromo-2-n-propylcycloheptanone. Since the n.m.r. spectrum of the tribromocycloheptanone showed no downfield protons, this compound is formulated as 2,2,7-tribromo-7-n-propylcycloheptanone (6). The dibromocycloheptanone showed a one-proton multiplet at δ 5·25 p.p.m., indicating the presence of a carbon atom bearing bromine adjacent to the carbonyl group; thus, it was identified as 2,7-dibromo-2-n-propylcycloheptanone (7). Dehydrobromination of the tribromo-derivative (6) gave a 75% yield of 2-n-propylcycloheptatrienone (8) identified by its spectra and characterized by exact mass measurement. As expected, the added alkyl group in the cycloheptatrienone decreases water solubility and facilitates extraction. Longer bromination times would probably lead to higher yields of the tribromocycloheptanone (6) and hence better overall conversion into the cycloheptatrienone (8).

With alkyl substituents in other than the 2-position in the cycloheptanone ambiguities can arise, as two tribromocycloheptanones will be possible. The 4-isopropylcycloheptane (9) has been prepared by reaction between diazomethane and 4-isopropylcycloheptanone;[6,8] 4-t-butylcycloheptanone[9] (10) was similarly prepared. Bromination of the 4-isopropylcycloheptanone under the conditions used for cycloheptanone gave a mixture; integration of the n.m.r. spectrum, with the methyl signals as standard, showed the mixture to be predominantly tribromocycloheptanone (11). The crude bromination mixture was treated with lithium carbonate in boiling DMF, and the 4-isopropylcycloheptatrienone (12) was isolated in 20—25% overall yield from the isopropylcycloheptanone (9); the spectral characteristics were identical with those reported for nezukone.[10] Attempts to brominate 4-t-butylcycloheptanone gave a mixture of products; four bands were obtained on p.l.c. of which only the fastest running (the most highly brominated) was obtained pure. Microanalysis and a comparison of the integrals of the t-butyl group with the remaining proton signals in the n.m.r. spectrum showed this to be the tetrabromocycloheptanone (13). In view of the complexity of the bromination mixture, no attempts were made at dehydrobromination to give 4-t-butylcycloheptatrienone.

EXPERIMENTAL

N.m.r. spectra were determined on a Perkin-Elmer R10 60 MHz spectrometer; values given are in δ (p.p.m.) from internal tetramethylsilane. Thick-layer separations were performed on Merck Kieselgel PF_{254} (40-cm. plates). DMF was dried over calcium oxide and distilled before use.

Cyclohepta-2,4,6-*trienone* (3).—A mixture of tribromocycloheptanone (88 g., prepared as described[5] and recrystallized once from methanol), lithium carbonate (35 g.), and dry DMF was boiled and stirred under a nitrogen atmosphere (45 min. to 1 hr.). The mixture was evaporated on a boiling water-bath at 15—20 mm., again under nitrogen. The solid residue was treated with saturated aqueous sodium hydrogen carbonate (50 ml.) and chloroform and the mixture was filtered through Hi-Flo Supercel. The Supercel was well washed with chloroform, and the combined chloroform solutions were dried. Solvent was evaporated off and the residue was distilled to give DMF (*ca.* 50 ml. b.p. 50—70°/15 mm.) and a fraction b.p. 120—125°/20 mm., which was shown by g.c. and the various spectra to be virtually pure cyclohepta-2,4,6-trien-1-one (13·55 g., 53%).

Bromination of 2-*n-Propylcycloheptanone*.—To a stirred solution of 2-n-propylcycloheptanone[7] (6 g.) in glacial acetic acid (10 ml.) was slowly added bromine (20 g.) in acetic acid (20 ml.). After 7 days at room temperature the mixture was diluted with ice-water and extracted with

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[6] E. Mueller and M. Bauer, *Annalen*, 1962, **654**, 92.

[7] G. Opitz and H. Mildenberger, *Annalen*, 1961, **649**, 47.

[8] J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, 1951, 695.

[9] T. Nozoe, H. Kishi, and A. Yoshikoshi, *Proc. Japan Acad.*, 1951, **27**, 149 (*Chem. Abs.*, 1951, **46**, 4523).

[10] Y. Hirose, B. Tomita, T. Nakatsuka, *Tetrahedron Letters*, 1966, 5875; A. J. Birch and R. Keeton, *J. Chem. Soc.* (*C*), 1968, 109.

chloroform. The dried chloroform extracts were evaporated to dryness; the residue showed two well separated spots on t.l.c. Preparative-layer separation of the residue (10·8 g.) (multiple runs, with light petroleum as eluant) gave two bands. The material from the first band extracted by methanol weighed 4·9 g.; a small sample was distilled in a bulb tube to give 2,2,7-*tribromo*-7-*n-propylcycloheptanone* (6), b.p. 115°/0·1 mm. (Found: C, 30·3; H, 3·7. $C_{10}H_{15}Br_3O$ requires C, 30·7; H, 3·85%); n.m.r. ($CDCl_3$) δ 3·4—3·0 (2H, m, CH_2CBr_2), 2·6—1·7 (10H, m), and 0·95 p.p.m. (3H, t). The second band, eluted with methanol, gave 2,7-*dibromo*-2-*n-propylcycloheptanone* (7) b.p. 95°/0·1 mm. (4·8 g.) (Found: C, 38·8; H, 4·95. $C_{10}H_{16}Br_2O$ requires C, 38·45; H, 5·15%); n.m.r. ($CDCl_3$) δ 5·25 (1H, d of d, CHBr·CO) 2·8—1·4 (12H, m) and 1·0 p.p.m. (3H, t, CH_2CH_3).

2-*n-Propylcyclohepta*-2,4,6-*trienone* (8).—The tribromocycloheptanone (6) (4·8 g.) with lithium carbonate and DMF as described before, gave 2-*n-propylcyclohepta*-2,4,6-*trienone*, b.p. 72°/0·1 mm. (1·36 g., 75%), M^+, 148·0887 ($C_{10}H_{12}O$ requires M^+, 148·0888); $\nu_{max.}$ (film) 1625, 1570br cm.$^{-1}$; $\lambda_{max.}$ (EtOH) 235, 313 nm. ($\log_{10} \varepsilon$ 4·18, 3·81); n.m.r. δ (CCl_4) 7·2—6·6 (5H, m) 2·5 (2H, t, CH_2CH_2) 1·8—1·2 (2H, m, $CH_2CH_2CH_3$) and 0·9 p.p.m. (3H, t, CH_2CH_3).

4-*Isopropylcyclohepta*-2,4,6-*trienone* (*Nezukone*) (12).—4-Isopropylcycloheptanone (7 g.)[8] was brominated as described for cycloheptanone by Doering;[5] the crude bromination product was a mixture (g.c.). Treatment of the crude mixture (9 g.) with lithium carbonate in DMF gave, after work up, 4-isopropylcyclohepta-2,4,6-trienone (12), b.p. 90—95°/0·7 mm. (1 g., 22% overall); $\nu_{max.}$ (film) 1635, 1580, 1235 cm.$^{-1}$ (lit.,[10] 1635, 1580, 1237 cm.$^{-1}$); $\lambda_{max.}$ (EtOH) 230, 314 nm. ($\log_{10} \varepsilon$ 4·25, 3·90) [lit.,[10] 230, 310—315 nm. ($\log_{10} \varepsilon$ 4·32, 3·90)]; n.m.r. δ (CCl_4) 7·2—6·5 (5H, m), 2·8 [1H, m, $CH(CH_3)_2$] and 1·25 p.p.m. [6H, d, $CH(CH_3)_2$] [lit.,[10] δ 7·2—6·5 (5H, m), 2·7 (1H, m) and 1·21 (6H, d) p.p.m.].

Bromination of 4-*t-Butylcycloheptanone* (10).—Bromination of 4-t-butylcycloheptanone[9] (7·5 g.) with bromine (29 g.) in glacial acetic acid (20 hr., 2—5°) with work-up as previously described gave the crude product. T.l.c showed at least four products. A preparative-layer separation gave only one clean band; extraction of this with methanol gave after evaporation of the solvent a solid which was recrystallized from methanol to give 2,2,7,7-*tetrabromo*-4-*t-butylcycloheptanone* (13) m.p. 75—77° (Found: C, 28·0; H, 3·35. $C_{11}H_{16}Br_4O$ requires C, 27·3; H, 3·35%); n.m.r. δ (CCl_4) 3·4—2·5 (4H, m, CH_2CBr_2) 2·2—1·4 (3H, m) 0·95 p.p.m. [9H, s, $C(CH_3)_3$]. Examination of other bands from the preparative plate showed mixtures and no further attempts at purification were made.

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