868. *Synthetical Studies relating to Colchicine. Part I. Some Derivatives of* 1 : 2-*Benzo*cyclo*hept*-1-*en*-4-*one.*

By T. A. Crabb and K. Schofield.

1 : 2-Benzo*cyclo*hepta-1 : 3-diene was converted into the epoxide and thence into 1 : 2-benzo*cyclo*hept-1-en-4-one. 3-Methyl-1 : 2-benzo*cyclo*hept-1-en-4-one was prepared similarly, but ethyl β-(1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-yl)propionate and methyl γ-(1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-yl)-butyrate gave hydroxy-lactones rather than epoxides or ketones when treated with perbenzoic acid. The mixture of ethyl 1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-ylacetate and its exocyclic isomer was epoxidised, and gave, after hydrolysis, some 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetic acid.

The last acid, its ethyl ester, ethyl β-(4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-yl)-propionate, and its nitrile were obtained from the pyrrolidine-enamine derived from 1 : 2-benzo*cyclo*hept-1-en-4-one.

A LARGE amount of work has been reported having as its aim either the synthesis of colchicine (I), or of compounds containing the colchicine skeleton. The most important studies in this field belong either to the " AC ⟶ ABC " or to the " AB ⟶ ABC " type, according to whether the starting materials contain rings A and C, or rings A and B substantially complete. This paper describes model experiments along the " AB ⟶ ABC " route, and corrects in two important respects a preliminary report.[1]

Previous workers using these lines have described the preparation of 1 : 2-benzo*cyclo*hept-1-en-4-one [2] (II; R = R′ = H), its trimethoxy-analogue [3] (II; R = OMe, R′ = H),

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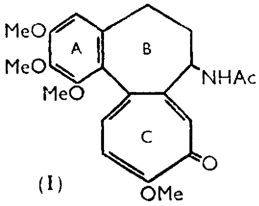
[1] Crabb and Schofield, *Chem. and Ind.*, 1958, 102.

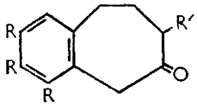
[2] Page and Tarbell, *J. Amer. Chem. Soc.*, 1953, **75**, 2053.

[3] Rapoport and Campion, *ibid.*, 1951, **73**, 2239; Eschenmoser and Rennhard, *Helv. Chim. Acta*, 1953, **36**, 290; Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 6699.

and the related acetamido-derivative[4] (II; R = OMe, R′ = NHAc). Several workers appear to share the aim of preparing compounds of type (III), for construction of ring C by cyclisation. Anderson and Greef[5] obtained an ester (III; R = Me, $m = 2$, $n = 1$) by well-known steps from 1 : 2-benzo*cyclo*hept-1-en-3-one, and Horton, Johnson, and Zollinger[6] prepared the analogue (III; R = Me, $m = n = 1$) by similar methods. Our own aim was initially similar to that of Anderson and Greef, having as its first target the discovery of a route to compounds of the type (VI; R = $[CH_2]_2 \cdot CO_2Et$).



(I)



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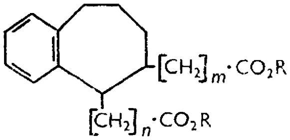

(III)

The original preparation[2] of the ketone (II; R = R′ = H) was inconvenient, and it seemed likely that this ketone might be more easily prepared from 1 : 2-benzo*cyclo*hepta-1 : 3-diene (IV; R = H), itself obtainable from the readily available 1 : 2-benzo*cyclo*hept-1-en-3-one by reduction to the alcohol and dehydration.[7] Treatment of the hydrocarbon (IV; R = H) with perbenzoic acid in chloroform provided the epoxide (V; R = H) in high yield. We stated earlier[1] that this epoxide was converted by magnesium bromide in ether into a mixture of ketones, (VI; R = H) and 1 : 2-benzo*cyclo*hept-1-en-3-one. This conclusion was based on bad experimentation. In fact, magnesium bromide converted the epoxide into the 4-ketone (VI; R = H) in high yield. This undirectional rearrangement of the epoxide was to be expected by analogy with the reactions of the oxides from indene, 1 : 2-dihydronaphthalene and related compounds, and the 3 : 4-epoxide[8] from 1 : 2-benzo*cyclo*octa-1 : 3-diene. In contrast, the use of the boron trifluoride–ether complex to isomerise the epoxide, whilst giving mainly 1 : 2-benzo*cyclo*hept-1-en-4-one, did produce a small amount of the isomeric 3-ketone, as was proved by isolation of the very characteristic red 2 : 4-dinitrophenylhydrazone of the latter. In addition, two other unidentified crystalline products were formed. This complex reaction was not examined further.

The epoxide could also be converted into the ketone (VI; R = H) through the intermediate crystalline 1 : 2-benzo*cyclo*hept-1-en-4-ol, formed by reduction with lithium aluminium hydride. The alcohol was oxidised with chromic acid in pyridine or acetic acid, though we did not find good conditions for avoiding over-oxidation on the one hand, or contamination of the product with unchanged alcohol on the other. Oppenauer oxidation of the alcohol was very satisfactory.

These experiments encouraged us to attempt the direct synthesis of compounds of the type (VI) in which R was an alkyl or ethoxycarbonylalkyl group, by using the same sequence of reactions with compounds (IV) already carrying the desired side-chain. For the simplest case, 3-methyl-1 : 2-benzo*cyclo*hepta-1 : 3-diene (IV; R = Me) was already known.[7] On ozonolysis it gave no detectable amount of 1 : 2-benzo*cyclo*hept-1-en-3-one; if the exocyclic analogue of (IV; R = Me) was present it must have been in small amount. Epoxidation of the diene gave the 4-ketone (VI; R = Me) directly and in good yield, the intermediate epoxide not being encountered. Evidence for the ketonic nature of the product came from the ready formation of a semicarbazone [the oxide (V; R = H)

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[4] Buchanan and Sutherland, *J.*, 1957, 2334.

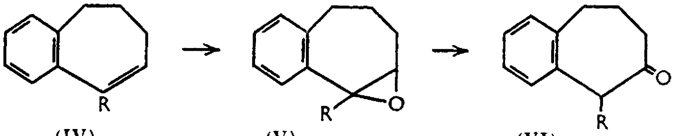
[5] Anderson and Greef, *J. Amer. Chem. Soc.*, 1952, **74**, 5203.

[6] Horton, Johnson, and Zollinger, *ibid.*, 1954, **76**, 4587.

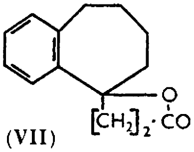
[7] Horn and Rapson, *J.*, 1949, 2421; Treibs and Klinkhammer, *Chem. Ber.*, 1950, **83**, 367.

[8] Tchoubar, *Compt. rend.*, 1942, **214**, 117; Kornfeld, Fornefeld, Kline, Mann, Morrison, Jones, and Woodward, *J. Amer. Chem. Soc.*, 1956, **78**, 3087; Huisgen, Rauenbusch, and Seidl, *Chem. Ber.*, 1957, **90**, 1958.

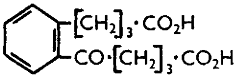
gave no derivatives with carbonyl reagents], and from the characteristic infrared band at 1707 cm.$^{-1}$ (for seven-membered ring ketones 1725—1705 cm.$^{-1}$ is reported [9]). With 2 : 4-dinitrophenylhydrazine the ketone, as obtained from epoxidation, gave a yellow derivative contaminated with traces of a red solid. The latter was difficult to eliminate (it was not 2 : 4-dinitrophenylhydrazine for it escaped from passage over a column of bentonite–kieselguhr), and to obtain the quite pure 2 : 4-dinitrophenylhydrazone it proved necessary to use a ketone obtained from hydrolysis of the semicarbazone. The direct isolation of ketones from epoxidations has been reported before.[10]



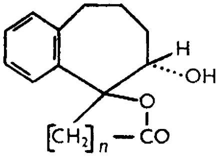
(IV) (V) (VI)



(VII)



(VIII)



(IX)

Next we turned to ethyl 1 : 2-benzo*cyclo*hepta-1 : 3-dienylacetate (IV; R = $\cdot CH_2\cdot CO_2Et$). This structure was assigned by Anderson and Wang [11] to the unsaturated ester obtained by dehydrating with formic acid the Reformatsky product from ethyl bromoacetate and 1 : 2-benzo*cyclo*hept-1-en-3-one. The position of the double-bond was assigned on the basis of the ultraviolet absorption maximum at 243 mμ. Accepting this assignment, we at first mistook the material formed by epoxidising the unsaturated ester for a homogeneous compound. Later, accumulated evidence showed that it could not be homogeneous, and, in fact, ozonisation of the unsaturated material from the Reformatsky–hydrogenation–dehydration sequence produced some 1 : 2-benzo*cyclo*hept-1-en-3-one. This, with what follows, proves the unsaturated material to be a mixture of the ester (IV; R = $\cdot CH_2\cdot CO_2Et$) and its exocyclic isomer. The product of epoxidation of this mixture was an oil which could not be fractionated by distillation. The infrared absorption spectrum of the oil indicated the presence of a ketone, and furthermore a yellow 2 : 4-dinitrophenylhydrazone, m. p. 106—107°, identical with that of authentic ethyl 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetate (VI; R = $\cdot CH_2\cdot CO_2Et$) (see below) could be obtained from the mixture. Alkaline hydrolysis of the epoxidation mixture gave 25% of 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetic acid, together with another acid. Whilst the epoxidation product from the mixed esters was thus proved to contain some ethyl 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetate, the other constituent, or constituents, of the epoxidation mixture have not been identified. We are examining this problem further.

Ethyl β-(1 : 2-benzo*cyclo*hepta-1 : 3-dien-3-yl)propionate and the analogous butyrate (IV; R = $\cdot[CH_2]_2\cdot CO_2Et$ and $\cdot[CH_2]_3\cdot CO_2Et$ respectively), when submitted to similar treatment, gave interesting but not very useful results. The first of these esters was prepared by acid hydrolysis of the crude half-ester from the Stobbe condensation [12] of diethyl succinate with 1 : 2-benzo*cyclo*hept-1-en-3-one, followed by esterification. [The *spiro*-lactone (VII) was also formed in the hydrolysis.] Ozonolysis of the unsaturated ester showed the double bond to be endocyclic. The ester (IV; R = $\cdot[CH_2]_3\cdot CO_2Et$) resulted from hydrogenation and dehydration of the Reformatsky product from methyl γ-bromocrotonate and 1 : 2-benzo*cyclo*hept-1-en-3-one, the methods used being similar

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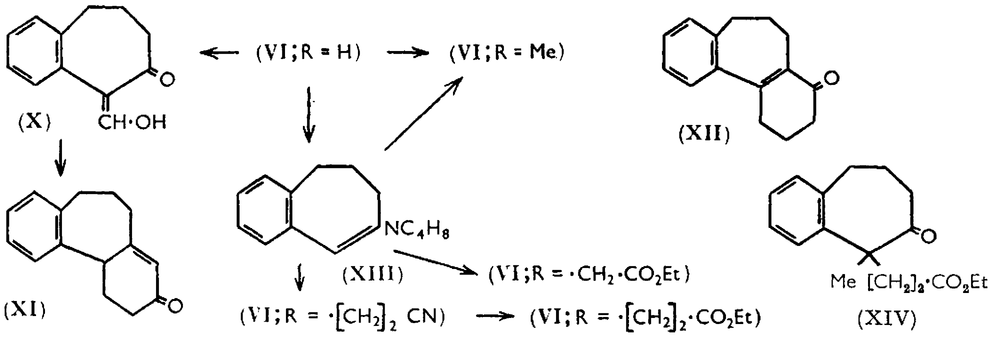
[9] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London 1954.
[10] English and Cavaglieri, *J. Amer. Chem. Soc.*, 1943, **65**, 1085; Mills and Schofield, *J.*, 1956, 4213.
[11] Anderson and Wang, *J. Org. Chem.*, 1954, **19**, 277.
[12] Cook, Philip, and Somerville, *J.*, 1948, 164.

to those described by Anderson and Greef.[13] Hydrogenation of the crude Reformatsky product was essential, for distillation of the intermediate hydroxy-ester caused dehydration. Again, ozonolysis of the unsaturated ester (IV; R = $\cdot[CH_2]_3\cdot CO_2Et$) proved the essential absence of the exocyclic isomer; no 1 : 2-benzo*cyclo*hept-1-en-3-one could be detected, but a crystalline acid, probably (VIII), resulted.

Epoxidation of the esters (IV; R = $\cdot[CH_2]\cdot CO_2Et$ and $\cdot[CH_2]_3\cdot CO_2Et$) in the usual way gave homogeneous products, in the first case a solid and in the second an oil, in good yield. These products showed no ketonic properties, nor could they be converted into ketones by acid treatment. The infrared absorption spectrum of the solid showed bands at 1755 and 3510 cm.$^{-1}$, appropriate to a γ-lactone and a hydroxyl group respectively.[9] The corresponding bands for the oil were at 1735 and 3480 cm.$^{-1}$. On this evidence the structures (IX; $n = 2$ and 3) are provisionally assigned to these compounds. A related case of lactone formation during oxidation of β-3-indenylpropionic acid was reported recently.[14]

These attempts to prepare derivatives of 1 : 2-benzo*cyclo*hept-1-en-4-one with ethoxycarbonylalkyl residues at the 3-position did not promise well. We therefore examined some reactions of the ketone (VI; R = H) itself. Methylation with methyl iodide–sodium methoxide, the most satisfactory of several reagents examined, gave a ketone (VI; R = Me) in moderate yield, characterised as its semicarbazone which was identical with that from the ketone obtained by epoxidising the hydrocarbon (IV; R = Me). Attempted reaction of the parent ketone (VI; R = H) with ethyl β-bromopropionate under a variety of conditions, or with diethyl carbonate in the presence of sodium hydride, failed. In contrast, the ketone reacted readily with ethyl formate and sodium ethoxide to give a product which, from the proved direction of the methylation just described as well as on general grounds, we take to be 3-hydroxymethylene-1 : 2-benzo*cyclo*hept-1-en-4-one (X). With methyl vinyl ketone this compound (X) reacted to give, after hydrolysis of the crude product, the tricyclic ketone (XI) (isolated as the 2 : 4-dinitrophenylhydrazone) isomeric with that (XII) formed by cyclising γ-(1 : 2-benzo*cyclo*hept-1 : 3-dien-3-yl)-butyric acid with zinc chloride in acetic anhydride–acetic acid. Most usefully, 1 : 2-benzo*cyclo*hept-1-en-4-one (VI; R = H) readily formed the enamine (XIII) with pyrrolidine. On treatment with methyl iodide in dioxan, followed by the usual hydrolysis,[15] the enamine was converted into 3-methyl-1 : 2-benzo*cyclo*hept-1-en-4-one. In the same way, use of ethyl bromoacetate gave the crystalline ester (VI; R = $\cdot CH_2\cdot CO_2Et$), hydrolysis of which produced the keto-acid, identical with one of the products of hydrolysis of the mixture of esters derived from the epoxidation already described. Our original aim was finally achieved by treating the enamine with acrylonitrile, the keto-nitrile (VI; R = $\cdot[CH_2]_2\cdot CN$) being formed in good yield. Acid-alcoholysis converted this into the



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[13] Anderson and Greef, *J. Amer. Chem. Soc.*, 1952, **74**, 5124.
[14] Howell and Taylor, *J.*, 1957, 3011.
[15] Robinson, *J.*, 1916, 1038; Stork, *J. Amer. Chem. Soc.*, 1954, **76**, 2029.

desired keto-ester (VI; R = $\cdot[CH_2]_2\cdot CO_2Et$). The possibility of using this ester and the hydroxymethylene compound (X) in a closer approach to the colchicine skeleton, and the extension of these reactions to the trimethoxylated series, are being studied.

3-Methyl-1 : 2-benzo*cyclo*hept-1-en-4-one being readily available, we examined a few of its reactions. Although the reaction product was not purified, it was clear from the alkali-insolubility of the major portion of it that nitrosation of the ketone proceeded mainly at the 3-position, as was expected. In contrast to 1 : 2-benzo*cyclo*hept-1-en-4-one itself, the methylated ketone reacted with ethyl β-bromopropionate, giving (presumably) the keto-ester (XIV). With acrylonitrile in presence of benzyltrimethylammonium hydroxide the methylated ketone gave a mixture of mono- and di-substituted derivatives, as shown by their hydrolysis to a liquid mono- and a crystalline di-carboxylic acid.

EXPERIMENTAL

3 : 4-*Epoxy*-1 : 2-*benzo*cyclo*hept*-1-*ene*.—A cooled solution of the 1 : 3-diene[7] (35 g.) in chloroform (100 ml.) was stirred and treated with perbenzoic acid (40·6 g.) in chloroform (640 ml.) at such a rate that the temperature did not rise above 5°. The solution was then stirred at 0° for 8 hr., kept overnight at 5° (titration showed that 78% of the perbenzoic acid was consumed in 8 hr.), and then washed with sodium hydroxide solution and with water. Distillation of the dried (Na_2SO_4) solution gave the *epoxide* (32 g.), b. p. 80°/0·04 mm., n_D^{17} 1·5550 (Found: C, 82·2; H, 7·9. $C_{11}H_{12}O$ requires C, 82·5; H, 7·6%).

1 : 2-*Benzo*cyclo*hept*-1-*en*-4-*ol*.—The epoxide (16 g.) in dry ether (32 ml.) was added during 15 min. to a vigorously stirred suspension of lithium aluminium hydride (8 g.) in the same solvent (160 ml.), gentle refluxing being thus maintained. The mixture was heated under reflux for 1 hr., then decomposed with water. Isolation of the product in the usual way, and crystallisation from light petroleum (b. p. 40—60°) gave the *alcohol* (14 g.) as needles, m. p. 71° (Found: C, 81·2; H, 8·6. $C_{11}H_{14}O$ requires C, 81·4; H, 8·7%). The p-*nitrobenzoate* formed needles, m. p. 92—93° (Found: C 69·2; H, 5·7. $C_{18}H_{17}O_4N$ requires C, 69·4; H, 5·5%), from light petroleum (b. p. 40—60°).

1 : 2-*Benzo*cyclo*hept*-1-*en*-4-*one*.—(i) Rearrangement of the epoxide (8·4 g.) with magnesium bromide under the conditions used by Kornfeld *et al.*[8] gave the ketone (7·6 g.), b. p. 82°/0·2 mm., n_D^{20} 1·5552 [2 : 4-dinitrophenylhydrazone, m. p. 169·5° (reported[2] m. p. 169—170°) (Found: C, 59·6; H 4·9. Calc. for $C_{17}H_{16}O_4N_4$: C, 60·0; H, 4·7%)]. In a separate experiment the crude rearrangement product was treated with saturated sodium hydrogen sulphite solution. Decomposition of the resulting compound in the usual way and conversion of the total ketone into the 2 : 4-dinitrophenylhydrazone revealed no trace of the red derivative of 1 : 2-benzo*cyclo*hept-1-en-3-one.

(ii) Boron trifluoride–ether complex (7·2 g.) was added in one portion to a solution of the epoxide (6 g.) in dry ether (60 ml.). After the initial vigorous reaction the mixture was kept overnight and then washed with sodium hydroxide solution and water. Concentration of the dried solution gave a solid (0·35 g.) which formed needles, m. p. 190° (Found: C 82·8; H, 7·8. $C_{11}H_{12}O$ requires C, 82·5; H, 7·6%), from ethanol. It gave a semicarbazone m. p. 208—209°.

The residue left after removal of the solid, m. p. 190°, was distilled, giving a colourless liquid (2·3 g.), b. p. 80—90°/0·05 mm., and a product (3·2 g.), b. p. >160°/0·05 mm., which gave small white crystals, m. p. 145° (Found: C, 82·2; H, 7·6%), from ethanol. Treatment of the liquid with 2 : 4-dinitrophenylhydrazine in the usual way, and recrystallisation of the orange product from methanol, gave a mixture of fine yellow needles of 1 : 2-benzo*cyclo*hept-1-en-4-one 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 169—170°) and shorter red crystals of 1 : 2-benzo*cyclo*hept-1-en-3-one 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 205—206°), which were separated mechanically.

(iii) 1 : 2-Benzo*cyclo*hept-1-en-4-ol (3·35 g.), aluminium *iso*propoxide (10 g.), *cyclo*hexanone (83·8 ml.), and toluene (250 ml.) were heated together under reflux for 2 hr. The usual processing afforded a liquid (10 g.), b. p. 125—140°/15 mm., which was shaken with saturated sodium hydrogen sulphite solution for 2 hr. The precipitate was washed with ether and shaken with sodium carbonate solution. The ketone, isolated by ether-extraction, was a colourless liquid (3·1 g.), b. p. 128—132°/15 mm., which became pale yellow when kept.

An attempt to use acetone in benzene solution for the oxidation gave no ketone.

(iv) The alcohol (12 g.) in pyridine (120 ml.) was added to a slurry [16] of chromium trioxide (20·4 g.) in pyridine (204 ml.). The mixture was stirred overnight at room temperature, poured into water, and extracted with ether. Purification through the bisulphite compound gave the ketone (7 g.) and unchanged alcohol (4 g.).

Alternatively, the alcohol (18 g.) in acetic acid (20 ml.) was treated during 5 hr. with chromium trioxide (13·5 g.) in acetic acid (20 ml.) and water (10 ml.), the temperature being kept below 5°. After being stirred for 12 hr. at room temperature the solution was diluted with water and extracted with ether. Distillation gave the ketone (13·5 g.), b. p. 82°/0·2 mm.

3-*Methyl*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one*.—(i) An ice-cooled mixture of 1 : 2-benzo*cyclo*hept-1-en-4-one (2 g.), dry methanol (2·2 ml.), and methyl iodide (1·1 ml.) was stirred under nitrogen during the addition (1 hr.) of a solution of sodium (0·28 g.) in methanol (4·4 ml.). The solution was stirred for 2 hr. more, boiled for 2 min., treated with dilute sulphuric acid, and extracted with ether. Distillation gave an oil (1·4 g.), b. p. 134°/15 mm. This (0·3 g.) gave the *semicarbazone* (0·2 g.) which from ethanol formed small needles, m. p. and mixed m. p. with the specimen described below, 208° (Found: C, 67·5; H, 7·5; N, 18·2. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·4; N, 18·2%). The yield of the methylated ketone, estimated by semicarbazone formation, was 42%. Corresponding yields for methylations carried out with potassium–benzene and with sodium *iso*propoxide–propan-2-ol were 16% and 26%, respectively.

(ii) 3-Methyl-1 : 2-benzo*cyclo*hept-1-en-3-ol (prepared from 1 : 2-benzo*cyclo*hept-1-en-3-one in 74% yield by the method of Treibs and Klinkhammer [7]) gave on dehydration 68% of 3-methyl-1 : 2-benzo*cyclo*hepta-1 : 3-diene ($\lambda_{max.}$ 244 mμ, $\log_{10} \varepsilon$ 3·98). Treatment of this compound (1·5 g.) in ethyl acetate (20 ml.) with ozone, followed by hydrogenation of the solution in presence of platinum oxide (0·1 g.), gave an acid fraction (1·4 g.) and a neutral yellow oil (0·1 g.). From neither of these could a pure 2 : 4-dinitrophenylhydrazone be obtained.

3-Methyl-1 : 2-benzo*cyclo*hepta-1 : 3-diene (6 g.) in chloroform (25 ml.) was treated with perbenzoic acid (6·3 g.) in chloroform (150 ml.) at 0—5°, and the solution was then stirred at this temperature for 10 hr. and kept overnight. Working up gave 3-*methyl*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one* (5·1 g.), b. p. 120°/1·5 mm., $n_D^{15.5}$ 1·5621 (Found: C, 82·6; H, 8·0. $C_{12}H_{14}O$ requires C, 82·7; H, 8·1%). The semicarbazone, m. p. 208°, was identical with that described above. The pure semicarbazone (0·22 g.) was heated at 95° for 10 min. with 6N-hydrochloric acid (50 ml.). The ketone, recovered by ether-extraction, gave in the usual way the yellow 2 : 4-*dinitrophenylhydrazone* which formed platelets, m. p. 150—151° (Found: C, 60·7; H, 5·0. $C_{18}H_{18}O_4N_4$ requires C, 61·0; H, 5·1%), from methanol.

Experiments with the Mixture of Ethyl 1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*ylacetate and* 1 : 2-*Benzo*cyclo*hept*-3-*ylidenacetate*.—The mixture was obtained in 62% yield by Anderson and Wang's method.[11]

Ozonisation of the mixture (1·4 g.) in the usual way gave a viscous, oily acid (1·4 g.) (of which the tarry 2 : 4-dinitrophenylhydrazone could not be purified) and a yellow neutral oil (0·5 g.). The latter provided 0·45 g. of pure 1 : 2-benzo*cyclo*hept-1-en-3-one 2 : 4-dinitrophenylhydrazone as fine red-bronze needles, m. p. and mixed m. p. 206° (from methanol–chloroform) (Found: C, 59·7; H, 4·7. Calc. for $C_{17}H_{16}O_4N_4$: C, 60·0; H, 4·7%).

The mixed esters (33 g.) in chloroform (50 ml.) were oxidised in the usual way with perbenzoic acid (24 g.) in chloroform (560 ml.). The product was a colourless liquid (25 g.), b. p. 136°/0·8 mm., n_D^{20} 1·5298 (Found: C, 73·5; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%), $\nu_{max.}$ 1735 and 1710 cm.$^{-1}$. With 2 : 4-dinitrophenylhydrazine this liquid (1 g.) gave a mixture of yellow and red crystals (0·32 g.). These could not be separated by crystallisation, but on passing a solution of the mixture (0·2 g.) in chloroform over a column of bentonite–kieselguhr the yellow 2 : 4-dinitrophenylhydrazone (0·17 g.) was obtained. From ethanol it formed silky yellow needles, m. p. 106—107°, identical with ethyl 4-oxo-1 : 2-benzo*cyclo*hept-1-en-3-ylacetate 2 : 4-dinitrophenylhydrazone (see below).

The epoxidation product (11 g.) was boiled for 10 hr. with potassium hydroxide (30 g.) in aqueous ethanol (200 ml.). The mixture was acidified and the product was isolated with ether. Concentration of the extract gave 4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*ylacetic acid* (2·5 g.), m. p. 132—133° after crystallisation from tetrahydrofuran–light petroleum (b. p. 40—60°) (Found: C, 70·8; H, 6·7. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%); distillation of the residue from the

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[16] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

extract gave a very viscous *acid* (5·4 g.), b. p. 128°/0·06 mm., n_D^{14} 1·5776 (Found: C, 76·7; H, 7·2. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

Ethyl β-(1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*yl*)*propionate.*—The crude half ester (13 g.) resulting from the reaction between diethyl succinate and 1 : 2-benzo*cyclo*hept-1-en-3-one,[12] was boiled with acetic acid (91 ml.), concentrated hydrochloric acid (45·5 ml.), and water (65 ml.) under nitrogen for 4 hr. The mixture was concentrated under reduced pressure and extracted with ether. The ether solution was extracted with sodium hydrogen carbonate solution. Acidification of the alkaline solution, followed by ether-extraction, gave the crude acid as a viscous brown oil (7 g.). Concentration of the neutral ether extract gave the spiro-*lactone* (VII) (3 g.) which formed needles, m. p. 134° (Found: C, 77·2; H, 7·2. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·4%), from ether.

The crude acid (14 g.) was boiled for 12 hr. with absolute ethanol (40 ml.) and concentrated sulphuric acid (1 ml.). Working up gave the *ester* (11·5 g.), b. p. 120°/0·1 mm., $n_D^{18.5}$ 1·5327 (Found: C, 79·2; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·3%) ($\lambda_{max.}$ 241 mμ, $\log_{10} \varepsilon$ 3·93). Ozonolysis of the ester (0·5 g.) in the usual way gave an acid fraction (0·5 g.), and a neutral oil (0·05 g.) from which a 2 : 4-dinitrophenylhydrazone could not be prepared.

The Lactone (IX; $n = 2$).—The above ester (3·9 g.) in chloroform (30 ml.) was treated with perbenzoic acid (2·7 g.) in chloroform (40 ml.) as described above. The *lactone* (3 g.) formed plates, m. p. 138—139° (Found: C, 72·5; H, 7·0. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%), from ethanol.

Methyl γ-(1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*yl*)*crotonate.*—1 : 2-Benzo*cyclo*hept-1-en-3-one (20 g.), amalgamated zinc (25 g.), methyl γ-bromocrotonate (22·5 g.), dry ether (50 ml.), dry benzene (50 ml.), and a crystal of iodine were heated under reflux. Three additions of zinc (12·5 g.) and methyl bromocrotonate (7·5 g.) were made at hourly intervals, and after the last addition the mixture was boiled for 2 hr. more. It was then poured into iced dilute acetic acid, and the product was extracted with ether. The extract was washed with 1% ammonia solution, water, and saturated brine, and then dried (Na_2SO_4). Distillation gave the *ester* as a golden-yellow oil (12 g.), b. p. 122°/0·05 mm., $n_D^{17.3}$ 1·5820 (Found: C, 78·8; H, 7·4. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%).

Methyl γ-(1 : 2-*Benzo*cyclo*hept*-1-*en*-3-*yl*)*butyrate.*—The unsaturated ester (2 g.) was shaken with hydrogen in the presence of ethanol (8 ml.) and Raney nickel (1 g.). Filtration and distillation gave the *ester* (1·2 g.), b. p. 120°/2 mm., n_D^{17} 1·5309 (Found: C, 79·0; H, 8·6. $C_{16}H_{22}O_2$ requires C, 78·0; H, 9·0%).

Methyl γ-(3-*Hydroxy*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*yl*)*butyrate.*—The Reformatsky reaction was repeated as described above, but at the end of the reaction the solvent was removed under reduced pressure and the crude product was shaken with ethanol (500 ml.) and Raney nickel (15 g.) under hydrogen. Filtration and distillation gave the *hydroxy-ester* (12 g.), b. p. 136°/0·05 mm., n_D^{18} 1·5426 (Found: C, 73·6; H, 8·1. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

Methyl γ-(1 : 2-*Benzo*cyclo*hepta*-1 : 3-*dien*-3-*yl*)*butyrate.*—The hydroxy-ester (12 g.) and 98% formic acid (90 ml.) were heated on the water-bath for 30 min. The diluted solution was extracted with benzene, and the extract was washed with sodium carbonate solution and dried. Distillation gave the ester as a colourless liquid (8·6 g.), b. p. 110°/0·05 mm., n_D^{17} 1·5439 (Found: C, 79·2; H, 8·4. Calc. for $C_{16}H_{20}O_2$: C, 78·7; H, 8·3%), which became pale yellow when kept. From 1 : 2-benzo*cyclo*hept-1-en-3-one (20 g.), without purification of the hydroxy-ester, this method gave the unsaturated ester in 30·5% overall yield.

The unsaturated ester (0·9 g.) in ethyl acetate (20 ml.) was ozonised in the usual way. After hydrogenation the solution was filtered, diluted with ether, and extracted with N-sodium hydroxide. The ether retained a neutral yellow oil (0·44 g.) which contained no 1 : 2-benzo*cyclo*hept-1-en-3-one. The alkaline extract was acidified and extracted with ether. Removal of the ether and recrystallisation of the residue from this solvent gave needles of an *acid*, m. p. 116—117° (Found: C, 64·2; H, 6·5. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

The Lactone (IX; $n = 3$).—The preceding unsaturated ester (9·25 g.) in chloroform (50 ml.) was treated in the usual way at 0—5° with perbenzoic acid (6·5 g.) in chloroform (125 ml.). (Titration showed that after 8 hr. 84% of the perbenzoic acid had been consumed.) After 15 hr. more at 5° the solution was processed as before. Distillation gave the *lactone* (7·2 g.), b. p. 145°/0·01 mm. (Found: C, 74·0; H, 7·2. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%).

γ-(1 : 2-*Benzo*cyclo*hept*-1-*en*-3-*yl*)*butyric Acid.*—The ester (IV; $R = \cdot[CH_2]_3\cdot CO_2Me$) (9 g.), sodium hydroxide (7 g.), and 50% aqueous ethanol (30 ml.) were boiled together for 10 hr.

Acidification and extraction with ether isolated the *acid* (7 g.), b. p. 154—156°/0·1 mm., n_D^{16} 1·5588 (Found: C, 78·3; H, 8·0. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9%), which became yellow when kept.

1′ : 2′ : 3′ : 4′-*Tetrahydro*-1 : 2-3 : 4-*dibenzo*cyclo*hepta*-1 : 3-*dien*-1′-*one* (XII).—The acid (6 g.), acetic anhydride (96 ml.), acetic acid (5 ml.), and a solution (5 ml.) of zinc chloride in acetic acid (20 mg./ml.) were kept together under nitrogen for 20 hr. The solution was then boiled for 2½ hr., concentrated under reduced pressure, diluted with water and extracted with ether. The washed (sodium hydrogen carbonate, water) and dried (Na_2SO_4) extract was distilled, giving the *ketone* as a yellow oil (4 g.), b. p. 122°/0·07 mm., n_D^{18} 1·6038 (Found: C, 83·8; H, 7·8. $C_{15}H_{16}O$ requires C, 84·9; H, 7·6%).

The 2 : 4-*dinitrophenylhydrazone*, m. p. 242° (Found: C, 64·3; H, 5·4. $C_{21}H_{20}O_4N_4$ requires C, 64·3; H, 5·1%), formed small red crystals from benzene.

3-*Hydroxymethylene*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one*.—Ethyl formate (4·4 g.) in dry benzene (47·5 ml.) was added under nitrogen to powdered sodium methoxide (from 1·43 g. of sodium) which had previously been baked at 200° for 2 hr. under reduced pressure. The mixture was cooled in ice and treated with 1 : 2-benzo*cyclo*hept-1-en-4-one (4·8 g.) in benzene (50 ml.). The whole was allowed to reach room temperature and then heated at 95° for 2 hr. Water was added and the benzene layer was extracted with N-sodium hydroxide. Acidification of the alkaline solution, extraction with ether, and distillation gave the *hydroxymethylene compound* (4 g.), b. p. 92°/0·05 mm., n_D^{20} 1·5960 (Found: C, 76·0; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

2 : 1′ : 2′ : 3′-*Tetrahydro*-1 : 2-3 : 4-*dibenzo*cyclo*hepta*-1 : 3-*dien*-3′-*one* (XI).—The hydroxymethylene compound (2 g.), methyl vinyl ketone (1·4 g.), potassium hydroxide (40 mg.), and anhydrous methanol (10 ml.) were boiled together for 6 hr. After concentration the mixture was diluted with water and extracted with ether. The ether contained a brown oil (2 g.) which was boiled for 2 hr. with acetic acid (25 ml.), hydrochloric acid (15 ml.), and water (7·5 ml.) under nitrogen. The solution was diluted with water and extracted with ether, and the extract was washed with sodium hydrogen carbonate solution. Distillation gave a colourless oil, b. p. 140—150°/0·1 mm., which provided a 2 : 4-*dinitrophenylhydrazone* as scarlet crystals, m. p. 209—210° (Found: C, 64·1; H, 5·2. $C_{21}H_{20}O_4N_4$ requires C, 64·3; H, 5·1%), from ethanol.

Reactions of 4-*Pyrrolidino*-1 : 2-*benzo*cyclo*hepta*-1 : 3-*diene* (XIII).—(i) *With methyl iodide.* 1 : 2-Benzo*cyclo*hept-1-en-4-one (1 g.), pyrrolidine (0·5 g.), and benzene (20 ml.) were heated under reflux in an apparatus provided with a water-separator. The reaction was complete in 30 min.; boiling was carried on for 1 hr. in all. The oil left when benzene was removed was heated with dioxan (10 ml.) and methyl iodide (8 ml.) at 95° for 30 hr.; a dark oil separated during the reaction. The mixture was left overnight with water, then extracted with ether. Removal of the ether and conversion of the residue into the semicarbazone, m. p. and mixed m. p. 207—208°, showed that 3-methyl-1 : 2-benzo*cyclo*hept-1-en-4-one had been formed in about 40% yield.

(ii) *With ethyl bromoacetate.* The enamine (XIII) (from 4 g. of ketone), ethyl bromoacetate (6·4 g.), and dioxan (40 ml.) were boiled together for 2 days. Working up as before gave *ethyl* 4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*ylacetate* (2·4 g.), b. p. 146°/0·2 mm., n_D^{16} 1·5321, plates [from light petroleum (b. p. 40—60°)], m. p. 64° (Found: C, 73·9; H, 7·7. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as silky yellow needles, m. p. 106° (Found: C, 58·9; H, 5·9; N, 13·1. $C_{21}H_{22}O_6N_4$ requires C, 59·1; H, 5·2; N, 13·1%), identical with the compound already described. Boiled for 12 hr. with potassium hydroxide (3 g.) in 50% aqueous ethanol (20 ml.), the ester (1 g.) gave the acid (0·8 g.) as white crystals (m. p. and mixed m. p. with the compound described above, 132°) from ether–light petroleum (b. p. 40—60°).

(iii) *With acrylonitrile.* The enamine (from 3·5 g. of ketone), acrylonitrile (4 g.), and dioxan (20 ml.), boiled together for 2 days and worked up as before, gave 3-2′-*cyanoethyl*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one* (2·8 g.) as white needles, m. p. 76—77° (Found: C, 78·8; H, 7·3; N, 6·5. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1; N, 6·6%), from ether–light petroleum (b. p. 40—60°).

The keto-nitrile (2·8 g.) and ethanol (50 ml.) which had been saturated at 0° with hydrogen chloride were boiled together for 12 hr. Filtration, dilution with water, extraction with ether, and distillation gave *ethyl* β-(4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*yl*)*propionate* (2 g.), b. p. 136—138°/0·08 mm., n_D^{17} 1·5278 (Found: C, 73·3; H, 7·3. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* formed fine yellow needles, m. p. 101° (Found: C, 60·5; H, 5·5. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5%), from methanol.

Ethyl β-(3-*Methyl*-4-*oxo*-1 : 2-*benzo*cyclo*hept*-1-*en*-3-*yl*)*propionate*.—The methylated ketone (4·35 g.), powdered potassium (0·97 g.), and benzene (50 ml.) were stirred together overnight. Ethyl β-bromopropionate (5 g.) was added, and the mixture was set aside for 24 hr., and then boiled for 4 hr. The usual processes gave the *propionate* (0·7 g.), b. p. 122°/0·05 mm., n_D^{18} 1·5380 (Found: C, 75·4; H, 8·5. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·1%).

Reaction of 3-*Methyl*-1 : 2-*benzo*cyclo*hept*-1-*en*-4-*one with Acrylonitrile*.—The ketone (1 g.) in dioxan (7·5 ml.) was cooled and shaken during the addition first of 40% benzyltrimethylammonium hydroxide solution (1 c.c.) and then of acrylonitrile (0·5 g.). The mixture was shaken at room temperature for 48 hr., acidified, and concentrated under reduced pressure. The residual oil, isolated with ether, was boiled with 20% potassium hydroxide solution (30 ml.) for 20 hr. The usual methods isolated a dibasic *acid* (0·3 g.), which formed white crystals, m. p. 174° (Found: C, 67·5; H, 6·7. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·9%), from ethanol, and a pale yellow viscous liquid (0·3 g.), b. p. 190—206°/0·1 mm. The latter gave a 2 : 4-*dinitrophenylhydrazone* which separated from methanol as orange needles, m. p. 127—128° (Found: C, 60·3; H, 5·3. $C_{21}H_{22}O_6N_4$ requires C, 59·2; H, 5·2%).

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