β-*Acetylacrylic* (4-*Oxopent-2-enoic*) *Acid in the Diels–Alder Reaction. Part I. Some Derivatives of the Adduct derived from* β-*Acetylacrylic Acid and Butadiene.*

By S. Dixon and L. F. Wiggins.

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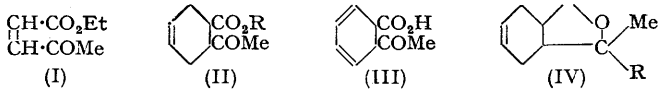
Ethyl β-acetylacrylate (4-oxopent-2-enoate), on being condensed with butadiene, furnished ethyl 2-acetyl*cyclo*hex-4-ene-1-carboxylate; the corresponding acid is obtained by hydrolysis of this ester, and from β-acetylacrylic acid and butadiene. When the ester was treated with hydrazine and the product subjected to bromination and dehydrobromination, 1 : 2-dihydro-4-methyl-1-oxophthalazine, identical with the product of condensation of acetophenone-*o*-carboxylic acid with hydrazine, was isolated. 2-Acetyl-*cyclo*hex-4-ene-1-carboxylic acid yielded, by treatment with Grignard reagents, 5 : 5-substituted derivatives of hydro-1-oxo*iso*benzofuran. Three such showed no anthelmintic activity, but two others were slightly active against liver fluke.

Interest has developed recently in the synthesis of heterocyclic systems from sucrose. Thus, sucrose has been converted into derivatives of pyridazine (Wiggins *et al.*, *J.*, 1947, 239, 549; 1948, 2191, 2195, 2199; 1949, 1248, 2066, 2546; 1950, 3236, 3500, 3505, 3508), thiazole (Gregory and Wiggins, *J.*, 1947, 590, 1400), furan (Haworth and Jones, *J.*, 1944, 667; Haworth, Jones, and Wiggins, *J.*, 1945, 1; Newth and Wiggins, *J.*, 1947, 396; 1948, 155), and glyoxaline (Albertson and Archer, *J. Amer. Chem. Soc.*, 1945, **67**, 308), all except the last by way of lævulic acid or 5-hydroxymethylfurfuraldehyde both of which can be obtained from sucrose (Haworth and Wiggins, B.P. 591,858/1944). The present work concerns application of the Diels–Alder reaction to a derivative of lævulic acid namely, β-acetylacrylic (4-oxopent-2-enoic) acid (I), for the preparation of other cyclic derivatives. Formation of the acrylic acid derivatives from lævulic acid is well known and involves conversion of the latter into β-bromolævulic acid (Conrad and Guthzeit, *Ber.*, 1886, **19**, 1981) and dehydrobromination of this with sodium acetate (Wolff, *Annalen*, 1891, **264**, 247). Ethyl β-acetylacrylate is prepared similarly. Consistently good yields of these substances have been obtained by the modified procedures outlined by Overend, Turton, and Wiggins (*J.*, 1950, 3500).

Ethyl β-acetylacrylate (I) and butadiene in benzene at 100° under pressure gave, smoothly and in good yield, ethyl 2-acetyl*cyclo*hex-4-ene-1-carboxylate (II; R = Et), a liquid characterised as its phenylhydrazone, thus providing a synthesis of a carbocyclic compound entirely from carbohydrate raw materials. Hydrolysis gave the corresponding crystalline acid (II; R = H) which was also prepared directly by addition of butadiene to β-acetylacrylic acid. In an attempt to obtain a *cyclo*hexadiene derivative, the acid (II; R = H) was converted into its dibromide and this was dehydrobrominated; however, only polymeric material was obtained in the latter reaction, and (III) could not be isolated.



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

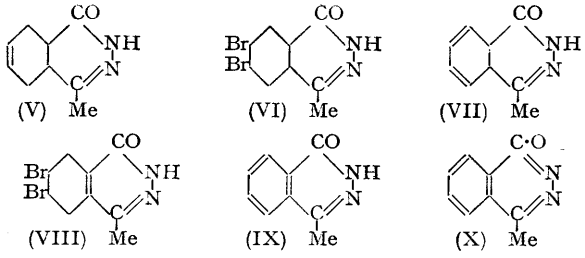
When 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid was heated above its melting point, water was evolved and after repeated distillation of the residue under atmospheric pressure a liquid, $C_9H_{10}O_2$, was isolated which will form the subject of a future communication.

The *cyclo*hexene keto-acid (II; R = H) might be expected to react with 3 mols. of methylmagnesium halide to yield a dialcohol. However, with 1 mol. or with an excess of the reagent, only the lactone (IV; R = Me) was obtained, in 67% and 69% yield, respectively. There seems no doubt that the starting material is an acid because of its analysis and since it behaves as an acid on titration and has pK 4·4; and the product must be (IV; R = Me) because of its analysis and titration as a lactone. Reaction with

1 mol. of Grignard reagent thus occurs preferentially (if not exclusively) with the keto-group rather than with the carboxyl group of the acid or the hydroxyl group of the intermediate alcoholic product; there appears to be no record of reaction of a keto-*acid* with a Grignard reagent and this merits further study. Formation of only the lactone, rather than the dialcohol, with an excess of methylmagnesium halide shows the preponderating influence of lactonisation in this reaction.

Although butyrolactone derivatives containing two alkyl, two aryl, or an alkyl and an aryl group at the carbon atom bearing the lactonic hydroxyl group show some activity as anthelmintics, three analogues of (IV; R = Me), *viz.*, (IV; R = Et, Ph, and *p*-MeO·C_6H_4), which were similarly prepared, had no useful activity; the 3 : 3-dimethyl (IV; R = Me) and the 3-methyl-3-phenyl compound (IV; R = Ph) in concentrations of 1 : 5000 reduced the activity of liver fluke, but not powerfully enough to counteract the stimulating effect of amphetamine.

2-Acetyl*cyclo*hex-4-ene-1-carboxylic acid or its ethyl ester readily condensed with hydrazine to form 1 : 2 : 5 : 8 : 9 : 10-hexahydro-4-methyl-1-oxophthalazine (V). This added one mol. of bromine in acetic acid, to form (VI), also obtained from 2-acetyl-4 : 5-dibromo*cyclo*hexane-1-carboxylic acid and hydrazine and converted by alkali into 1 : 2 : 9 : 10-tetrahydro-4-methyl-1-oxophthalazine (VII). When the dibromide (VI) was treated with a further mol. of bromine, dehydrogenation occurred with formation of (VIII) which was transformed by alkali into the aromatic benzo-derivative (IX or X); this was identical with the product of condensation of acetophenone-*o*-carboxylic acid with hydrazine.



Experimental

Condensation of Ethyl β-Acetylacrylate with Butadiene.—Ethyl β-acetylacrylate (4-oxopent-2-enoate) (5 g.) (Overend, Turton, and Wiggins, *J.*, 1950, 3500) was heated in a sealed tube at 100° for 4 hr. with a solution of butadiene (2 g.) in dry benzene (20 c.c.). Thereafter, the solvent was removed from the colourless solution, and the residual syrup (5·93 g.) fractionally distilled. After a small first fraction (b. p. 58—70°/0·02 mm.) which did not yield a crystalline phenylhydrazone, *ethyl 2-acetyl*cyclo*hex-4-ene-1-carboxylate* (4·0 g., 58%) distilled at 72°/0·02 mm. (Found: C, 67·4; H, 8·0. $C_{11}H_{16}O_3$ requires C, 67·4; H, 8·2%). The optimum yield (74%) was obtained by heating at 100° for 15 hr. The ester formed a crystalline *phenylhydrazone*, m. p. 107° (Found: C, 71·4; H, 7·8; N, 9·95. $C_{17}H_{22}O_2N_2$ requires C, 71·35; H, 7·7; N, 9·8%). It rapidly decolorized bromine in carbon tetrachloride with evolution of hydrogen bromide; after about 30 min. a solid was deposited, separation of which was completed by the addition of light petroleum. Recrystallized from alcohol–water, this furnished colourless needles of *ethyl 4 : 5-dibromo-2-bromoacetyl*cyclo*hexane-1-carboxylate*, m. p. 170—172° (Found: C, 29·9; H, 3·7. $C_{11}H_{15}O_3Br_3$ requires C, 30·3; H, 3·5%).

When the unsaturated ester (2 g.) was heated with 10% aqueous potassium hydroxide (25 c.c.) under reflux for 15 min. all the ester dissolved. The brown solution was allowed to cool, made slightly acid with dilute hydrochloric acid, and evaporated to dryness under reduced pressure. Extraction of the residue with boiling chloroform, evaporation, and recrystallization (charcoal) from alcohol–water or ether gave colourless prisms of *2-acetyl*cyclo*hex-4-ene-1-carboxylic acid* (1·45 g., 84·5%), m. p. 114—116° (Found: C, 64·3; H, 7·1. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%).

Condensation of β-Acetylacrylic Acid with Butadiene.—The acid (4·5 g.) (Overend, Turton, and Wiggins, *loc. cit.*) was heated in a sealed tube for 12 hr. at 100° with butadiene (3·5 g.) in dry benzene (20 c.c.) in the presence of quinol (0·5 g.). The light brown solution was then

concentrated to a syrup which rapidly crystallized. Crystallization from alcohol–water or ether gave colourless prisms of 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (4 g., 60·5%), m. p. 114—116°, identical with the product obtained as above. If the temperature was not allowed to exceed 100°, no polymerization inhibitor was needed, yields up to 83% being obtained.

Dry Distillation of 2-*Acetyl*cyclo*hex-4-ene-1-carboxylic Acid.*—The acid (1·0 g.) was heated in a distilling flask until distillation occurred, with dehydration (formation of water in the receiver). The colourless distillate was redistilled twice, dried ($MgSO_4$), and distilled once again, under reduced pressure. The *product* (0·7 g., 78%) was a mobile liquid, b. p. 168—170°/15 mm., n_D^{19} 1·5147 (Found: C, 71·5; H, 6·5. $C_9H_{12}O_2$ requires C, 71·9; H, 6·7%). A small amount of the product was dissolved in carbon tetrachloride and bromine added dropwise. Decolorization occurred and an oil separated. This solidified after several weeks and recrystallized from alcohol–water as colourless needles, m. p. 90°. It was a *dibromide* (Found: C, 34·9; H, 3·4. $C_9H_{10}O_2Br_2$ requires C, 34·9; H, 3·2%).

Addition of Bromine to 2-*Acetyl*cyclo*hex-4-ene-1-carboxylic Acid.*—(a) *At room temperature.* To the acid (1 g.) in dry ether (30 c.c.) bromine (1 g.) was added dropwise. Decolorization occurred and hydrogen bromide was eliminated. The precipitated solid 2-*acetyl*-4 : 5-*dibromo*-cyclo*hexane*-1-*carboxylic acid* crystallized from alcohol–water as needles (0·1 g., 5·1%), m. p. 170° (Found: C, 32·9; H, 3·8. $C_9H_{12}O_3Br_2$ requires C, 32·9; H, 3·7%). The filtrate, on evaporation under reduced pressure yielded a decomposed tar.

(b) On similar reaction at 0°, with continuous stirring, very little hydrogen bromide was evolved. Crystalline dibromide (0·85 g., 44%), m. p. 170° (from alcohol–water), separated when the solution was set aside.

Action of Alcoholic Potassium Hydroxide on 2-*Acetyl*-4 : 5-*dibromo*cyclo*hexane*-1-*carboxylic Acid.*—The dibromide (1·0 g.) was heated with potassium hydroxide (1·0 g.) in dry methyl alcohol (40 c.c.) on a water-bath for 3 hr. and then allowed to cool. No solid separated. After being made slightly acid with hydrochloric acid, the solution was evaporated to dryness and the residue extracted with chloroform. Evaporation of the extract yielded a viscid syrup (0·6 g.) which failed to crystallize, could not be distilled, and appeared to be polymeric. The same result was obtained when 1 mol. of potassium hydroxide was used.

Treatment of 2-*Acetyl*-4 : 5-*dibromo*cyclo*hexane*-1-*carboxylic Acid with Hydrazine Hydrate.*—The dibromide (0·5 g.) was heated with hydrazine hydrate (0·16 c.c., 50% aqueous solution) in methyl alcohol (15 c.c.) under reflux for 2 hr., concentrated to 5 c.c., and cooled. The solid which separated crystallized from alcohol–water as colourless plates (0·09 g., 18%), m. p. 194° (decomp.) alone or in admixture with 6 : 7-dibromo-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-octahydro-4-methyl-1-oxophthalazine (see below).

Action of Methylmagnesium Iodide on 2-*Acetyl*cyclo*hex-4-ene-1-carboxylic Acid.*—To the Grignard reagent prepared from methyl iodide (0·7 g.) and magnesium turnings (0·12 g.) in ether (2 c.c.) 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (0·75 g.) in ether (20 c.c.) was added dropwise. When the initial vigorous reaction had subsided, the mixture was heated under reflux on a water-bath for 3 hr. After being cooled, the ether was decanted from the complex and evaporated, yielding a negligible residue. The Grignard complex was decomposed with ice and dilute sulphuric acid. The precipitated solid 1 : 2 : 4 : 7 : 8 : 9-*hexahydro*-3 : 3-*dimethyl*-1-*oxo*iso*benzofuran* was separated and, recrystallized from alcohol–water, formed colourless plates (0·5 g., 67%), m. p. 114° (mixed m. p. with 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid, 72—80°) (Found: C, 72·3; H, 8·1. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%). Reaction with 4 mols. of Grignard reagent gave the same product, m. p. 114° in 69·5% yield.

Action of Other Grignard Reagents on 2-*Acetyl*cyclo*hex-4-ene-1-carboxylic Acid.*—To ethylmagnesium iodide (from ethyl iodide, 5·57 g. in ether), 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (1·5 g.) in dry ether (30 c.c.) was added. Heating for 2 hr. after the initial vigorous reaction, cooling, addition of dilute sulphuric acid, extraction of the aqueous layer several times with ether, drying ($MgSO_4$) and evaporation of the combined extracts yielded 3-*ethyl*-1 : 2 : 4 : 7 : 8 : 9-*hexahydro*-3-*methyl*-1-*oxo*iso*benzofuran* as a light brown oil (0·75 g.). This distilled as a colourless liquid, b. p. 175°/15 mm., n_D^{18} 1·4898 (Found: C, 73·1; H, 8·8. $C_{11}H_{16}O_2$ requires C, 73·4; H, 8·9%).

The Grignard reagent from bromobenzene (2·4 c.c.) and magnesium turnings (0·5 g.) in ether (8 c.c.), with 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (1·5 g.) in ether (30 c.c.), similarly gave the 3-*methyl*-3-*phenyl* compound as a dark brown oil which solidified during several days. Recrystallized from alcohol–water, it formed a colourless microcrystalline solid (0·65 g., 32%), m. p. 85° (Found: C, 78·8; H, 6·9. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·0%).

The Grignard reagent from *p*-methoxyphenyl bromide (6·8 g.) and magnesium turnings

(0·9 g.), with the acid (1·5 g.) in ether, similarly gave the 3-p-*methoxyphenyl*-3-*methyl* compound as needles (0·6 g., 26%; from alcohol–water), m. p. 145—147° (Found: C, 74·1; H, 7·1. $C_{16}H_{18}O_3$ requires C, 74·5; H, 7·0%).

Condensation of Ethyl 2-Acetylcyclohex-4-ene-1-carboxylate with Hydrazine.—The ester (6·0 g.) was mixed with 50% aqueous hydrazine solution (3·6 c.c.) and alcohol added until the mixture was homogeneous. The solution was then heated under reflux on a water-bath. After 15 min. a white crystalline solid began to separate, but heating was continued for 1 hr. After cooling, the solid was collected and, recrystallized from hot alcohol, formed long colourless needles of 1 : 2 : 5 : 8 : 9 : 10-*hexahydro-4-methyl-1-oxophthalazine* (4·8 g. 95·5%), m. p. 225—226° (Found: C, 65·7; H, 7·6; N, 17·1. $C_9H_{12}ON_2$ requires C, 68·85; H, 7·3; N, 17·1%).

Condensation of 2-Acetylcyclohex-4-ene-1-carboxylic Acid with Hydrazine.—The acid (7 g.) was dissolved in N-sodium hydroxide (42 c.c.) and cooled in ice. A cold solution of hydrazine sulphate (5·5 g.) in N-sodium hydroxide (42 c.c.) was carefully added and the mixture heated under reflux. After 10 min. crystals appeared. After being heated for 1 hr. the solution was allowed to cool, and the 1 : 2 : 5 : 8 : 9 : 10-hexahydro-4-methyl-1-oxophthalazine was collected, washed with water, and recrystallized from alcohol in long colourless needles (6·2 g., 88·5%), m. p. 225—226°, identical with the product described above.

Treatment of 1 : 2 : 5 : 8 : 9 : 10-*Hexahydro-4-methyl-1-oxophthalazine with Bromine.*—The oxophthalazine (4·0 g.), in hot glacial acetic acid (15 c.c.), decolorised bromine (4·0 g.; added dropwise) rapidly without elimination of hydrogen bromide. After about 10 min. a solid separated. After cooling, this was collected. It recrystallized from alcohol–water as colourless plates (0·8 g.), m. p. 194° (decomp.). The filtrate from the reaction mixture was concentrated under reduced pressure to a syrup which solidified on trituration with water. Recrystallized from alcohol–water, it formed colourless plates (3·9 g.), m. p. 194° (decomp.). The total yield of 6 : 7-*dibromo*-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-*octahydro-4-methyl-1-oxophthalazine* was 4·7 g. (59·5%) (Found: C, 33·4; H, 4·0; N, 8·8. $C_9H_{12}ON_2Br_2$ requires C, 33·4; H, 3·7; N, 8·7%).

Action of Alcoholic Potassium Hydroxide on 6 : 7-*Dibromo*-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-*octahydro-4-methyl-1-oxophthalazine.*—The bromo-derivative (2·0 g.) was heated with potassium hydroxide (0·75 g.) in absolute alcohol (25 c.c.) under reflux for 5 hr. and the precipitated potassium bromide separated from the hot mixture. On being allowed to cool, the filtrate deposited crystalline 1 : 2 : 9 : 10-*tetrahydro-4-methyl-1-oxophthalazine* and a further crop was obtained from the mother liquor on concentration. It recrystallized from alcohol in long colourless needles (0·82 g., 82%), m. p. 223—224° (Found: C, 66·8; H, 6·3; N, 17·1. $C_9H_{10}ON_2$ requires C, 66·7; H, 6·2; N, 17·3%).

Dehydrogenation of 6 : 7-*Dibromo*-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-*octahydro-4-methyl-1-oxophthalazine.*—The dibromide (1·5 g.) was dissolved, with stirring, in hot glacial acetic acid (25 c.c.), and bromine (0·75 g.) added dropwise. After a short time decolorisation occurred and hydrogen bromide was evolved. After all the bromine had been added, the solution was allowed to cool for about 30 min. and the precipitated solid was collected. Recrystallized from alcohol–water this formed colourless prisms (0·45 g., 30%) of 6 : 7-*dibromo*-1 : 2 : 5 : 6 : 7 : 8-*hexahydro-4-methyl-1-oxophthalazine*, m. p. 204° (Found: C, 34·0; H, 3·1; N, 8·9. $C_9H_{10}ON_2Br_2$ requires C, 33·5; H, 3·1; N, 8·7%).

Action of Alcoholic Potassium Hydroxide on 6 : 7-*Dibromo*-1 : 2 : 5 : 6 : 7 : 8-*hexahydro-4-methyl-1-oxophthalazine.*—The dibromo-compound (0·35 g.) was heated with potassium hydroxide (0·132 g.) in methyl alcohol (12·5 c.c.) under reflux for 30 min., then allowed to cool, and water (10 c.c.) was added. 1 : 2-Dihydro-4-methyl-1-oxophthalazine which separated was collected, washed with a little water, and crystallized from alcohol–water; it formed colourless needles (0·14 g., 80·5%), m. p. 222° alone or in admixture with an authentic specimen prepared by condensing acetophenone-*o*-carboxylic acid with hydrazine (Found: C, 67·7; H, 5·0; N, 17·7. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·0; N, 17·5%).

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THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

THE DEPARTMENT OF SUGAR CHEMISTRY AND TECHNOLOGY,
IMPERIAL COLLEGE OF TROPICAL AGRICULTURE,
TRINIDAD, BRITISH WEST INDIES.

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