239. *α-Methyleneadipic Acid and Some Related Compounds.*

By L. N. Owen and A. G. Peto.

An alleged cyclodehydration reaction, which has been claimed to be applicable to the synthesis of *cyclo*pentane-1 : 3-dicarboxylic acid and *cyclo*pentane-1-acetic-3-carboxylic acid, is erroneous; the products are α-methyleneadipic and α-methylenepimelic acid, respectively. 2-Methylenehexane-1 : 6-diol, obtained by reduction of ethyl α-methyleneadipate, on ozonolysis gives 1 : 7 : 10 : 15-tetraoxa*dispiro*[5 : 2 : 5 : 2]hexadecane (XIII), a simple analogue of a diketose anhydride. Evidence is presented for the allocation of cyclic structures to an anhydro-2 : 4-dinitrophenylhydrazone and a 2 : 4-dinitrophenylosazone derived from 1 : 6-dihydroxyhexan-2-one.

As part of an investigation on hydroxyalkylation reactions, Gault and Daltroff [1, 2] found that base-catalysed interaction of ethyl 2-oxo*cyclo*pentanecarboxylate and formaldehyde gave the 1-hydroxymethyl derivative, which was isolated as its acetate (I). After treatment with concentrated alkali this gave a dicarboxylic acid, $C_7H_{10}O_4$, which was stated to be saturated. It had m. p. 121·5°, gave a diamide, m. p. 224°, and on this evidence was identified as *cis-cyclo*pentane-1 : 3-dicarboxylic acid (III) (which has m. p. 121°; amide, m. p. *ca.* 228°), though no direct comparison with an authentic sample was made and all attempts to convert it into the well-known anhydride were unsuccessful. The formation of this acid was envisaged as proceeding by normal ring fission of the β-keto-ester (I), with hydrolysis, to give the intermediate hydroxy-dicarboxylic acid (II), which was then supposed to undergo cyclodehydration between the hydroxy-group and the α-methylene group adjacent to the remote carboxyl. In later papers [3, 4] a similar reaction was carried out on the *cyclo*hexane analogue (VI) in the expectation that *cyclo*hexane-1 : 3-dicarboxylic acid would be obtained. The product, however, although a dicarboxylic acid of the correct molecular formula, had m. p. 85°, and was thus neither the *cis*- (m. p. 167°) nor the *trans*-form (m. p. 150°) of the *cyclo*hexane acid. Consequently it was assumed that on

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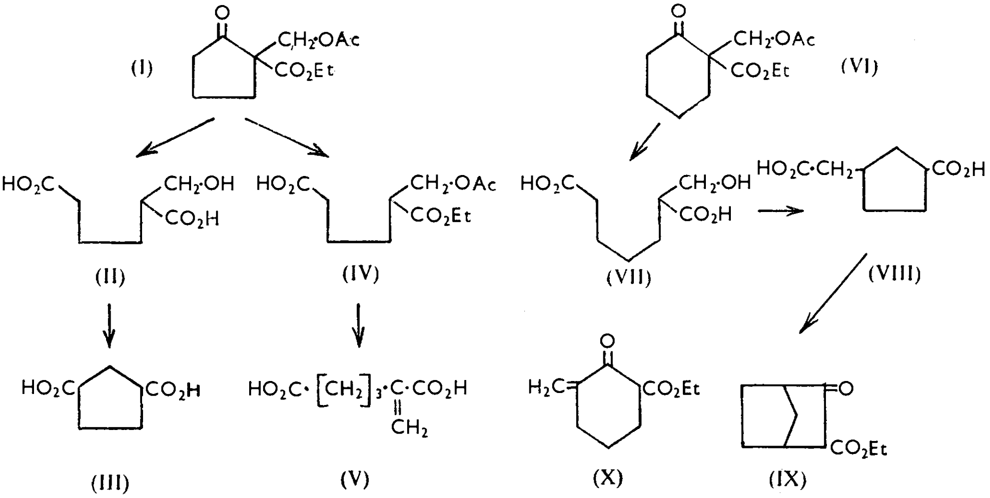
[1] Gault and Daltroff, *Compt. rend.*, 1939, **209**, 997; *Chimie et Industrie*, 1941, 45 bis, **122.**

[2] Daltroff, *Ann. Chim.* (*France*), 1940, **14**, 207.

[3] Gault and Hiong, *Compt. rend.*, 1941, **213**, 353.

[4] Hiong, *Ann. Chim.* (*France*), 1942, **17**, 269.

this occasion the elimination of water from an intermediate (VII) had involved a methylene group β to the remote carboxyl, to give *cyclo*pentane-1-acetic-3-carboxylic acid (VIII); the discrepancy in melting point from that (137°) recorded by Hintikka and Komppa [5] for this compound was ascribed to stereoisomerism. Hiong's attempt to convert it by cyclisation into norcamphor was unsuccessful, though it underwent the Dieckmann reaction to give a product formulated as the norcamphorcarboxylic ester (IX), from which a corresponding hydroxy-ester and hydroxy-acid were prepared.

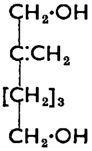


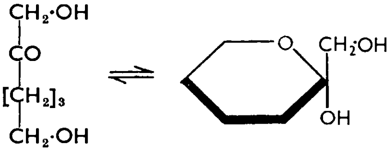
The simplicity of Daltroff's synthesis of *cyclo*pentane-1 : 3-dicarboxylic acid, if genuine, renders it very attractive, and we therefore repeated the preparation as described by her.[2] Recrystallisation of the acid obtained, however, raised the melting point to 128°; furthermore, it was unsaturated, absorbed one mol. of hydrogen over a palladium catalyst, and gave formaldehyde on ozonolysis. The product is therefore not the *cyclo*pentane acid, but α-methyleneadipic acid (V), which has recently been synthesised from acetylenic intermediates by Jones, Whitham, and Whiting.[6] This structure had been rejected by Daltroff [2] on the grounds that addition of bromine water to an *alcoholic* solution of the acid resulted in no decolorisation; we have confirmed this misleading observation, but in *aqueous* solution decolorisation is instantaneous. Daltroff's [2] suggested route for a synthesis of camphoric acid, based on a modification of the supposed cyclodehydration reaction, is of course invalidated. The formation of α-methyleneadipic acid from the acetoxymethyl compound (I) provides a new example of the conversion [7] of a β-acyloxy-ester, by base-catalysed elimination, into an αβ-unsaturated acid, and probably proceeds through the intermediate (IV).

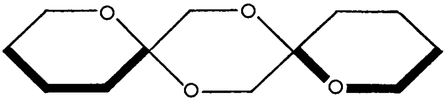
The above observations rendered it highly probable that Hiong's conclusions,[4] based on an even more unlikely mode of dehydration, were also erroneous, and the alkaline fission of the keto-ester (VI) was therefore investigated. The product was again an *unsaturated* acid, identical with the α-methylenepimelic acid synthesised by Jones *et al.*[6] Hiong's failure to convert it into norcamphor is thus understandable and his product of Dieckmann cyclisation must be reformulated as (X) (or the isomer with an endocyclic double bond) with corresponding modifications to the structures of the compounds derived from this. It is worth emphasising that the French workers were led into a sequence of errors entirely as a result of an unreliable method for the detection of unsaturation by a bromine–water test.

[5] Hintikka and Komppa, *Ann. Acad. Sci. Fennicae*, 1918, **10**, *A*, 1.
[6] Jones, Whitham, and Whiting, *J.*, 1954, 1865.
[7] Linstead, Owen, and Webb, *J.*, 1953, 1211.

The ready availability of α-methyleneadipic acid by Daltroff's procedure led us to attempt the preparation of the corresponding glycol. Reduction of either the methyl or the ethyl ester of the acid with lithium aluminium hydride gave a product which although mainly 2-methylenehexane-1 : 6-diol (XI) was shown by quantitative hydrogenation to contain some saturated impurity. Ethylenic linkages are normally unaffected by lithium aluminium hydride, but a few instances of reduction have been reported [8] when the double bond is αβ to an alcohol or keto-function, and the contaminant was thus probably 2-methylhexane-1 : 6-diol. An authentic specimen of the latter was synthesised by hydrogenation of ethyl α-methyleneadipate, followed by reduction of the resulting ethyl α-methyladipate with lithium aluminium hydride, but attempts to prove its presence in the crude unsaturated diol were inconclusive.


(XI)


(XII) (XIIa)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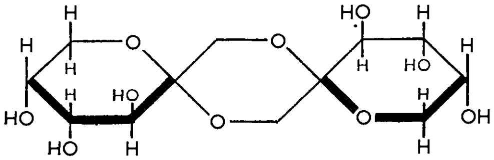
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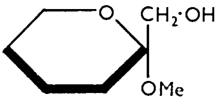
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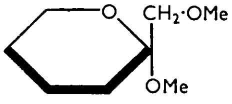
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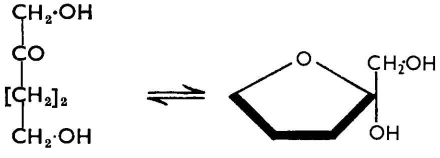
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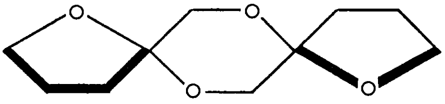
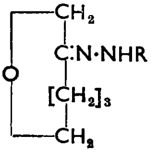

(XVIII)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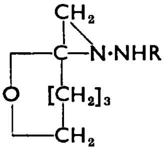
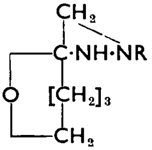
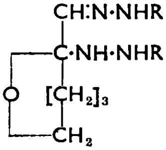

(XX)


(XXI)


(XXII)

(R = 2 : 4-dinitrophenyl)

Ozonolysis of the unsaturated diol would be expected to give 1 : 6-dihydroxyhexan-2-one (XII), a compound of interest as a simple analogue of the ketohexoses, particularly as it should exist in the pyranose form (XII*a*). When the ozonolysis was carried out, formaldehyde was produced, and after decomposition of the ozonide with zinc and acetic acid a crystalline solid $C_{12}H_{20}O_4$ (analysis and molecular weight) was obtained; this formula corresponds to two mols. of the expected ketol (XII) less two mols. of water. It was neutral, slowly reduced boiling Fehling's solution, and gave no reaction with 2 : 4-dinitrophenylhydrazine in cold aqueous sulphuric acid, though when heated with the latter reagent it gave a 2 : 4-dinitrophenylosazone. The substance is therefore 1 : 7 : 10 : 15-tetraoxa*dispiro*[5 : 2 : 5 : 2]hexadecane (XIII), derived by intermolecular dehydration from

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[8] Brown, *Organic Reactions*, 1951, **6**, 481; Jenny and Grob, *Helv. Chim. Acta*, 1953, **36**, 1936.

the pyranose form (XII*a*) of the ketol. Because of the presence of the two *spiro*-systems it can exist in a racemic and in a *meso*-form, but on the present evidence an allocation of configuration is not possible (the structure shown is the *meso*-form). The compound is thus the simplest analogue of diheterolevulosan-I (XIV), one of the products obtained [9] by dehydration of fructose; the corresponding bimolecular dianhydride of sorbose has recently been prepared.[10] The furanose analogue of (XIII), 1 : 6 : 9 : 13-tetraoxa*dispiro*[4 : 2 : 4 : 2]-tetradecane (XVIII), which has been obtained [11] from tetrahydro-2 : 3-dihydroxypyran, and also [12] as a by-product from the hydrogenation of furfuryl alcohol, is reported to be readily hydrolysed by dilute aqueous acid to give 1 : 5-dihydroxypentan-2-one (XVII), but, in contrast, fission of (XIII) with dilute acid does not occur readily, and the relative stabilities of the two compounds thus parallel those of the furanosides and pyranosides of the common sugars.

Reaction of the *dispiro*-compound (XIII) with boiling methanolic hydrogen chloride was expected to give the " methyl glycoside " (XV), but the product gave analyses for $C_8H_{16}O_3$ and must therefore be tetrahydro-2-methoxy-2-methoxymethylpyran (XVI); possibly the primary hydroxy-group in a product (XV) may be sufficiently reactive to undergo etherification during the prolonged period necessary to bring all the starting material into reaction. Hydrolysis of the dimethoxy-compound with aqueous acid gave a non-homogeneous product (probably because of some accompanying elimination) which gave a yellow 2 : 4-dinitrophenylhydrazone, $C_{12}H_{14}O_5N_4$. This formula contains one mol. of water less than that of a 2 : 4-dinitrophenylhydrazone of the ketol (XII); furthermore, the infrared spectrum indicated the absence of a hydroxyl group. Possible formulæ for the anhydro-compound are (XIX), (XX), and (XXI). The ultraviolet light absorption, though similar to that of a simple 2 : 4-dinitrophenylhydrazone, does not necessarily favour (XIX), as the other two structures represent unknown systems. The derivative, with excess of the reagent, gave the normal 2 : 4-dinitrophenylosazone, described above. This, also, showed no infrared absorption corresponding to the presence of a hydroxyl group, which suggests that it exists as the cyclic structure (XXII). There has been controversy over the structures of the sugar osazones,[13] and it is still uncertain whether the sugar chain is in the cyclic or acyclic form. Simple compounds of the type (XII), which are free from the complications brought about by the presence of the larger number of hydroxyl groups in true sugars, offer obvious possibilities for the study of the osazone problem, and it is intended to continue this aspect of the work.

EXPERIMENTAL

Ethyl 1-acetoxymethyl-2-oxo*cyclo*pentanecarboxylate, b. p. 122—123°/0·4 mm., n_D^{17} 1·4542, was obtained in an overall yield of 68% from ethyl 2-oxo*cyclo*pentanecarboxylate by the method of Daltroff,[2] who recorded b. p. 160—162·5°/17 mm. and 53% yield.

α-Methyleneadipic Acid.—The acetoxy-ester (117 g.) was cautiously added to sodium hydroxide (90 g.) in 50% aqueous ethanol (900 c.c.). When the exothermic reaction had subsided the solution was boiled under reflux for 2 hr. and then concentrated under reduced pressure to small bulk and acidified by the addition of 17% hydrochloric acid (450 c.c.). The mixture was cooled to 0°, and the precipitated solid was collected, dried in a vacuum, and extracted with ether (Soxhlet). Evaporation of the ethereal extract gave α-methyleneadipic acid (76 g., 88%), m. p. 124°, raised to 128° on recrystallisation from water, undepressed on admixture with an authentic specimen (Found : C, 53·3; H, 6·4%; equiv., 79·8; hydrogenation no., 159. Calc. for $C_7H_{10}O_4$: C, 53·2; H, 6·4%; equiv., 79·1; *M*, 158). Light absorption in EtOH : no max. >2100 Å. Ozonolysis of the acid in acetic acid gave formaldehyde (dimedone derivative, m. p. and mixed m. p. 188°).

Reaction of the acid with boiling methanolic hydrogen chloride gave the methyl ester (96%), b. p. 117°/8 mm., n_D^{21} 1·4469. Daltroff,[2] for " methyl *cyclo*pentane-1 : 3-dicarboxylate," recorded b. p. 126—130°/17 mm.

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[9] Schlubach and Behre, *Annalen*, 1933, **508**, 16.

[10] Wolfrom and Hilton, *J. Amer. Chem. Soc.*, 1952, **74**, 5334.

[11] Hurd and Edwards, *J. Org. Chem.*, 1949, **14**, 680.

[12] Swadesh and Dunlop, *ibid.*, p. 692.

[13] Percival, *Adv. Carbohydrate Chem.*, 1948, **3**, 23; Barry, McCormick, and Mitchell, *J.*, 1955, 222.

The acid (23·7 g.), ethanol (80 c.c.), carbon tetrachloride (250 c.c.), and toluene-*p*-sulphonic acid (1·5 g.), boiled together with azeotropic removal of the water formed, gave the *ethyl ester* (28·1 g.), b. p. 94°/0·2 mm., n_D^{17} 1·4436 (Found : C, 61·8; H, 8·55. $C_{11}H_{18}O_4$ requires C, 61·6; H, 8·5%).

α-Methylenepimelic Acid.—When carried out by Hiong's procedure,[4] reaction of ethyl 1-acetoxymethyl-2-oxo*cyclo*pentanecarboxylate with 40% aqueous sodium hydroxide gave a product which, after recrystallisation from benzene, furnished α-methylenepimelic acid, m. p. and mixed m. p. 87—88°. An aqueous solution instantly decolorised bromine water, but decolorisation was very slow when bromine water was added to an alcoholic solution of the acid.

Ethyl α-Methyladipate.—A solution of ethyl α-methyleneadipate (6·6 g.) in ethanol (90 c.c.) was shaken with 10% palladium–charcoal (1 g.) and hydrogen until no further absorption occurred. Distillation of the product gave ethyl α-methyladipate (6·1 g.), b. p. 128—129°/14 mm., n_D^{19} 1·4270. Dieckmann [14] gives b. p. 127—129°/13 mm.

2-*Methylhexane*-1 : 6-*diol.*—A solution of ethyl α-methyladipate (6·3 g.) in dry ether (23 c.c.) was added to a stirred solution of lithium aluminium hydride (1·9 g.) in dry ether (15 c.c.). The mixture was boiled under reflux for 3 hr., then cooled, cautiously treated with water, and acidified with dilute sulphuric acid. The ethereal layer was removed, and the aqueous portion was continuously extracted with ether for 24 hr. The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give an oil which still contained some unchanged ester (saponification test). It was therefore boiled under reflux with N-sodium hydroxide in 50% ethanol (30 c.c.) for 4 hr. The ethanol was then removed by evaporation, and extraction of the alkaline solution with ether furnished 2-*methylhexane*-1 : 6-*diol* (1·4 g.), b. p. 105—107°/0·1 mm., n_D^{21} 1·4556 (Found : C, 63·8; H, 12·3. $C_7H_{16}O_2$ requires C, 63·6; H, 12·2%).

Treatment of the diol with a slight excess of naphthyl *iso*cyanate for 3 hr. at 100° in a sealed tube gave the *di-α-naphthylurethane*, m. p. 152° (from aqueous ethanol) (Found : C, 74·0; H, 6·5; N, 6·2. $C_{29}H_{30}O_4N_2$ requires C, 74·0; H, 6·4; N, 5·95%).

2-*Methylenehexane*-1 : 6-*diol.*—A solution of methyl α-methyleneadipate (4 g.) in dry ether (50 c.c.) was added during 20 min. to a stirred solution of lithium aluminium hydride (1·2 g.) in dry ether (80 c.c.) at 0°. Stirring was maintained for a further hour, and the product was isolated as described above. Distillation gave (i) 0·8 g., b. p. 60—90°/0·05 mm., n_D^{19} 1·4499—1·4575, containing some unchanged ester, and (ii) 1·2 g., b. p. 90—95°/0·05 mm., n_D^{19} 1·4732—1·4742. Redistillation of (ii) gave 2-*methylenehexane*-1 : 6-*diol*, b. p. 122°/0·4 mm., n_D^{18} 1·4749 (Found: C, 64·4; H, 10·8. $C_7H_{14}O_2$ requires C, 64·6; H, 10·8%). The *di-α-naphthylurethane* had m. p. 115—116° [from light petroleum (b. p. 60—80°)] (Found : C, 74·6; H, 6·3; N, 6·2. $C_{29}H_{28}O_4N_2$ requires C, 74·3; H, 6·0; N, 6·0%).

Higher yields of the diol (50—60%) were obtained by performing the reaction for the same time in boiling ether, but the products were still not homogeneous. Quantitative hydrogenation of a fraction, b. p. 103°/0·3 mm., n_D^{17} 1·4760, in ethanol over a platinum catalyst, resulted in the absorption of only 70% of the theoretical amount of hydrogen.

Ozonolysis of 2-*Methylenehexane*-1 : 6-*diol.*—Ozonised oxygen was passed through a solution of the diol (3·9 g.) in dry ethyl acetate (90 c.c.) at 0°, and the issuing gases were led through a small wash-bottle containing water. When no more ozone was absorbed, the ethyl acetate was removed under reduced pressure, and the oily residue was heated on the steam-bath with water (20 c.c.), acetic acid (80 c.c.), and zinc dust (10 g.) for 30 min. A portion of the filtered solution gave with dimedone a precipitate of the formaldehyde derivative, and a further quantity was isolated by similar treatment of the wash-water from the ozonisation. The yield of the derivative, m. p. and mixed m. p. 187°, corresponded to a yield of 20% of formaldehyde. Another portion of the filtrate, on treatment with aqueous 2 : 4-dinitrophenylhydrazine sulphate, gave formaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 161—162°, in quantity corresponding to a 24% yield. Pure compounds containing the $:CH_2$ group usually give *ca.* 30% under these conditions of ozonolysis.

The residual filtrate was evaporated under reduced pressure to dryness and the residue was extracted with ether (Soxhlet) until the remaining zinc salts gave no ketonic reaction. Evaporation of the extract gave an oil, which was triturated with cold petroleum (b. p. 40—60°) (2 × 15 c.c., and 3 × 10 c.c.); the soluble material (0·3 g.), recovered from the petroleum solution, solidified, and on recrystallisation from methanol gave square plates or cubes of 1 : 7 : 10 : 15-*tetraoxa*dispiro[5 : 2 : 5 : 2]*hexadecane*, m. p. 161° [Found: C, 63·0; H, 8·9%; *M* (Rast),

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[14] Dieckmann, *Annalen*, **1901**, **317**, 69.

237. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%; *M*, 228], only sparingly soluble in water, neutral, and non-reducing to aqueous permanganate. It reduced Fehling's solution on prolonged boiling.

In another experiment, ozonolysis of the diol (8 g.) was followed by decomposition of the ozonide by hydrogenation of the ethyl acetate solution over palladium–charcoal. Evaporation of the filtered solution then gave a semi-solid residue, from which the *dispiro*-compound (1·9 g.) was isolated by trituration with water (4 × 2 c.c.) in the centrifuge, the residual solid then being recrystallised from methanol.

Further small quantities of the solid were obtained by treatment of the oily residues with boiling 2N-hydrochloric acid for 45 min., followed by evaporation, and extraction of the residue with light petroleum as before.

Fission of 1 : 7 : 10 : 15-*Tetraoxa*dispiro[5 : 2 : 5 : 2]*hexadecane*.—(i) The compound (36 mg.) was heated on the steam-bath with alcoholic 2 : 4-dinitrophenylhydrazine sulphate (24 c.c., containing 0·4 g. of base and 4·5 c.c. of sulphuric acid). Precipitation of a solid began after a few minutes, and after 1 hr. it was collected and washed with dilute sulphuric acid (yield, 141 mg., 84%). Recrystallisation from pyridine gave the red 6-*hydroxy*-2-*oxohexanal di*-2 : 4-*dinitrophenylhydrazone*, m. p. 224—226° (Found: C, 44·2; H, 3·8; N, 22·8. $C_{18}H_{18}O_9N_8$ requires C, 44·1; H, 3·7; N, 22·85%). With aqueous sodium hydroxide and ethanol it gave the deep violet colour characteristic[15] of 2 : 4-dinitrophenylosazones. Light absorption max. in $CHCl_3$: *ca.* 3950 and 4380 Å (ε 35,300) (broad bands). Infrared absorption max. in paraffin mull: 3270 and 3160 cm.$^{-1}$ (NH); no indication of OH.

(ii) A solution of the compound (1·5 g.) in 3% methanolic hydrogen chloride (10 c.c.) was boiled under reflux for 17 hr., and then neutralised with silver carbonate. Evaporation of solvent from the filtered solution and distillation of the residue gave *tetrahydro*-2-*methoxy*-2-*methoxymethylpyran* (1·7 g.), b. p. 110°/50 mm., n_D^{20} 1·4382 (Found: C, 60·0; H, 10·1; O, 29·95. $C_8H_{16}O_3$ requires C, 60·0; H, 10·0; O, 30·0%). Treatment of a portion with 2N-hydrochloric acid for 1 hr. on the steam-bath, followed by addition of aqueous 2 : 4-dinitrophenylhydrazine sulphate to the cooled solution, gave a sticky yellow precipitate. This was occasionally triturated during 2 hr., and was then collected, washed, and recrystallised from dioxan to give a yellow *compound*, m. p. 164° [Found: C, 48·8; H, 5·0; N, 19·3%; *M* (Rast), 299. $C_{12}H_{14}O_5N_4$ requires C, 49·0; H, 4·8; N, 19·0%; *M*, 294]. Light absorption max.: in EtOH, 3550 (ε 25,000); in $CHCl_3$, 3600 Å (ε 24,000). Infrared absorption max. in CCl_4: 3197 and 3098 cm.$^{-1}$ (NH); OH bands were absent.

The filtrate from the preparation of the derivative was treated with a further quantity of the reagent and heated on the steam-bath for 2 hr. to give a flocculent precipitate, which on recrystallisation from pyridine furnished the red 2 : 4-dinitrophenylosazone, m. p. 223—225°, identical with that described above. The same osazone was also obtained by heating the yellow derivative, m. p. 164°, with an excess of the reagent.

This work was carried out during the tenure (by A. G. P.) of a University of London Postgraduate Studentship. We are grateful to Professor E. R. H. Jones, F.R.S., for authentic specimens of the unsaturated acids. Microanalyses were by Mr. F. H. Oliver and his staff (Organic Microanalytical Laboratory), and the ultraviolet and infrared absorption spectra were determined by Mrs. A. I. Boston and Mr. R. L. Erskine, B.Sc., A.R.C.S., respectively (Organic Spectrographic Laboratory).

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[15] Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 758.