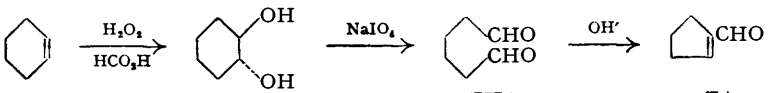
718. *Studies on Compounds Related to Auxin-a and Auxin-b. Part III. The Preparation and Properties of the* cyclo*Pentenyl Analogue of Auxin-b Lactone.*

By J. B. Brown, H. B. Henbest, and E. R. H. Jones.

A convenient method of preparing *cyclo*pent-1-enealdehyde has been devised, which has led to the synthesis of the *cyclo*pentenyl analogue of auxin-b lactone. The properties and reactions of this lactone are compared with those described for auxin-b (Kögl, Haagen-Smit, and Erxleben, *Z. physiol. Chem.*, 1934, **225**, 215). Opening of the ring of the lactone to the corresponding acid (analogous to auxin-b itself) has proved to be impossible, and attempts to prepare this acid by other routes invariably resulted in the production of the lactone. The great stability of this analogue in the lactone form is in contrast to the reported existence of auxin-b only as an open-chain acid.

In order to prepare the unsubstituted *cyclo*pentenyl analogue of auxin-b by the method described in the preceding paper and to examine its properties in detail, it was necessary to have available a substantial quantity of *cyclo*pent-1-enealdehyde (I). This aldehyde has been obtained as a by-product from several reactions (cf. Baeyer and von Liebig, *Ber.*, 1898, **31**, 2106; Willstätter and Sonnenfeld, *Ber.*, 1914, **47**, 2814; Reid and Freer, *J. Amer. Chem. Soc.*, 1926, **48**, 1403; Paquot, *Bull. Soc. chim.*, 1941, **8**, 695; Farmer and Sundralingam, *J.*, 1942, 121).. The only methods which appeared to be adaptable to the preparation of the aldehyde on a reasonable scale were those of Urion (*Ann. Chim.*, 1934, **1**, 5) and Wohl and Schweitzer (*Ber.*, 1906, **39**, 895). The former, involving a pyrolytic dehydration of divinyl glycol over alumina at 300°, gave in our hands low and variable yields of non-homogeneous aldehyde. Wohl and Schweitzer obtained



(II.) (III.) (I.)

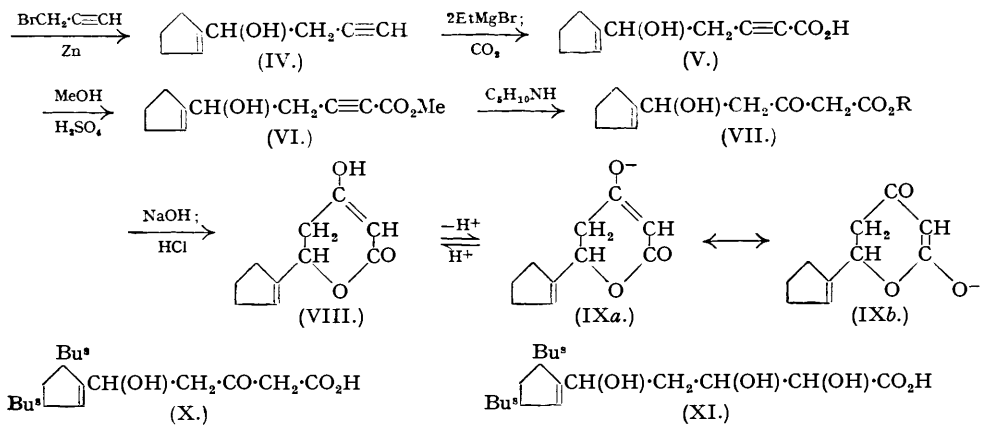
this *cyclo*pentenealdehyde by heating adipaldehyde (III) with water in a sealed tube at 110° (yield, 60%), (III) being obtained (*via* its acetal) from a Kolbe electrolysis of γγ-diethoxybutyric acid. Adipaldehyde is more readily obtained by ozonolysis of *cyclo*hexene, but although this method has been considerably improved (Menzies and Robinson, *J.*, 1924, 2166; Fischer and Löwenberg, *Ber.*, 1933, **66**, 666; Henne and Perilstein, *J. Amer. Chem. Soc.*, 1943, **65**, 2183), a more convenient route proceeds *via* the readily available *trans-cyclo*hexane-1 : 2-diol (II), which can be converted into the dialdehyde with lead tetra-acetate or periodic acid. The diol (II) was prepared (in 400-g. quantities) in over 80% yield from *cyclo*hexene and performic acid, the intermediate monoformyl derivative being hydrolysed to the diol by passage of steam through the solution. This preparation of the diol was found to be more convenient, as well as giving better yields, than the method recently described (*Org. Synth.*, 1948, **28**, 35), in which hydrolysis of the monoformyl derivative is effected with alkali, and the diol is isolated by ethyl acetate extraction and subsequent vacuum-distillation.

Oxidative fission of the diol (II) was effected in aqueous solution with sodium metaperiodate, and the cyclisation of the dialdehyde was investigated to discover a more convenient method than that of Wohl and Schweitzer. Tests showed that the cyclisation was effected by dilute alkali, and this method was then applied to the aqueous solution of adipaldehyde obtained directly from the periodate oxidation. As soon as the oxidation reaction had finished (as observed by the solution temperature beginning to fall), sufficient alkali was added to make the solution 0·5N. (as potassium hydroxide). Ether was then added to remove the product from the alkaline phase as soon as it was formed. Homogeneous *cyclo*pentenealdehyde was obtained consistently in yields of 55—60% (based on glycol) by this method, 50-g. quantities of aldehyde being conveniently prepared in the course of a day.

Since this work was completed, English and Barber (*J. Amer. Chem. Soc.*, 1949, **71**, 3310) have described the preparation of *cyclo*pentenealdehyde by a similar, but somewhat less convenient route, adipaldehyde being obtained from the diol (II) by lead tetra-acetate oxidation, and the cyclisation being effected by Wohl and Schweitzer's method (overall yield from diol, 52%).

The next stages in the synthesis proceeded smoothly. A modified Reformatsky reaction with propargyl bromide (Henbest, Jones, and Walls, *J.*, 1949, 2696) gave a 75% yield of the

carbinol (IV) which on carboxylation gave the acid (V), converted in turn into its methyl ester (VI) [50% yield from (IV)]. Hydration of this acetylenic ester (VI) to form the keto-ester (VII) was carried out *via* a piperidine adduct as described in the preceding paper, the adduct in this case being extracted and then partially hydrolysed with 0·25N-hydrochloric acid. The keto-ester so obtained could not be purified by distillation owing to dehydration [$-CH(OH)\cdot CH_2\cdot CO- \longrightarrow -CH{=}CH\cdot CO-$], but it could be crystallised at low temperatures. The total crude ester was, however, suitable for hydrolysis; this was carried out with dilute alkali rather than dilute acid



(cf. preceding paper). Acidification then yielded the crystalline 5 : 6-dihydro-4-hydroxy-6-*cyclo*pent-1′-enyl-2-pyrone (VIII). Attempts were made to prepare the acid (VII; R = H), which possesses the same side-chain structure as that suggested for auxin-b (X), but these were unsuccessful (see below).

That the *cyclo*pentenyl lactone exists in solution largely in the enolic form, as in formula (VIII), is indicated by the following observations. The compound dissolves in sodium hydrogen carbonate solution with effervescence, being reprecipitated unchanged on acidification with mineral acid. Potentiometric titration of the lactone with dilute sodium hydroxide solution gave a curve which showed that one equivalent of alkali was being *immediately* neutralised. From this titration, the pK of the enol was found to be 5·15, *i.e.*, it is not as acidic as a saturated carboxylic acid (acetic acid has pK = 4·73; Auerbach and Smolczyk, *Z. physikal. Chem.*, 1924, **110**, 106), but it is appreciably stronger than the related 6-membered ring β-diketone, 5 : 6-dihydro-5 : 5-dimethylresorcinol (pK = 5·25; Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1147). It gives an immediate violet colour with neutral ferric chloride in aqueous methanol. Auxin-b, rather surprisingly for a β-keto-acid, is reported not to give a ferric chloride colour except after irradiation with ultra-violet light in a quartz vessel, although absorption spectroscopic data on auxin-b solutions indicate the presence of an appreciable amount of the enolic form (Kögl, Koningsberger, and Erxleben, *Z. physiol. Chem.*, 1936, **244**, 266). The absorption spectrum of the lactone in water (see figure) or ethanol further confirmed the enolic structure, the enols of β-keto-acids or -esters exhibiting high intensity absorption in the 2500-A. region (cf. Grossman, *Z. physikal. Chem.*, 1924, **109**, 305). Moreover, as with other enols of this type, Beer's law was not obeyed when the concentration of the solution was varied. These results are shown in the figure (curves III and IV), where it can be seen that on dilution of the solution the position of maximum absorption moves towards longer wave-lengths, a result compatible with the production of an increasing proportion of the ionised form (IX) of the enol. Similar shifts of the absorption maxima on dilution of the solution have been observed with ethyl acetoacetate (Morton and Rosney, *J.*, 1926, 706), and the β-diketone, 5 : 6-dihydro-5 : 5-dimethylresorcinol (Blout, Eager, and Silverman, *J. Amer. Chem. Soc.*, 1946, **68**, 566), as well as with auxin-b itself (Kögl, Koningsberger, and Erxleben, *loc. cit.*). The spectrum of the essentially non-ionised enol (VIII) was obtained by measurement in 0·01N-hydrochloric acid (curve I), and the spectrum of the fully-ionised enol (IX) was determined after the addition of one equivalent of sodium hydrogen carbonate to the lactone solution (curve II). The fully-ionised enol exhibited an exceptionally well-defined absorption maximum at 2695 A. ($\varepsilon_{max.}$ = 19,300), which may be compared with the absorption of the enolate ion of ethyl acetoacetate ($\lambda_{max.}$ 2730 A.; $\varepsilon_{max.}$ =

13,900), and the enolate ion of 5 : 6-dihydro-5 : 5-dimethylresorcinol ($\lambda_{max.}$ 2820 A.; $\varepsilon_{max.}$ = 26,300) (Blout *et al., loc. cit.*).

In order to ascertain under what conditions the lactone ring might be opened with alkali to give a salt of the corresponding open-chain acid (VII; R = H), aqueous solutions of the lactone in the presence of one and two molecular proportions of sodium hydroxide were examined spectroscopically. It was found that the absorption spectra of these solutions were identical ($\lambda_{max.}$ 2695 A.; $\varepsilon_{max.}$ = 19,300) with one another and with that obtained in the presence of one equivalent of sodium hydrogen carbonate, and further that this absorption did not change when the solution was kept. These results indicated that the lactone under various degrees of alkalinity gave only the enolate ion (IX), which was unaffected (*i.e.*, the ring was not opened) by further addition of alkali.

FIG. 1.

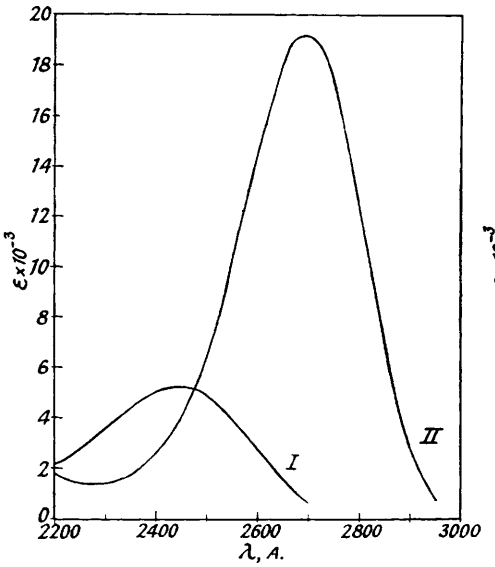
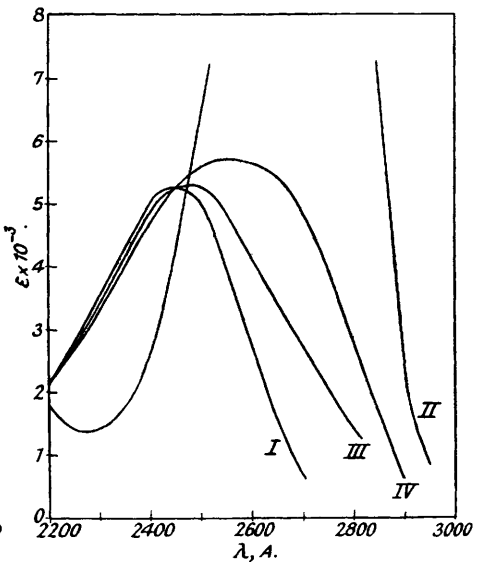


FIG. 2.

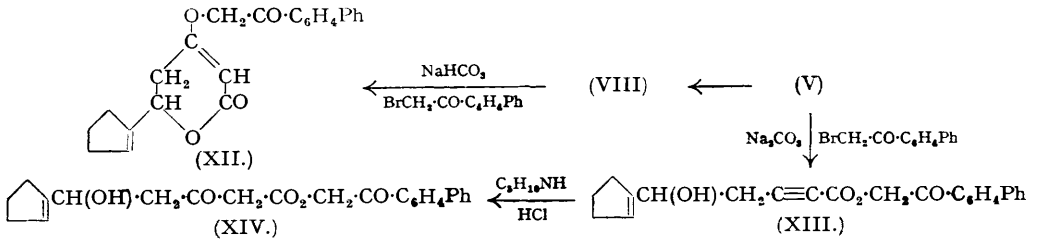


Curve I. cyclo*Pentenyl lactone* (VIII) *in aqueous* 0·01N-*hydrochloric acid.*
Curve II. ,, ,, *in aqueous alkaline solution.*
Curve III. ,, ,, (0·0198%) *in water.*
Curve IV. ,, ,, (0·0062%) *in water.*

This conclusion was subsequently verified by chemical experiments (see below). Before this was done the possibility that the high-intensity absorption at 2695 A. is due to a (resonating) anion of the corresponding open-chain acid (VII; R = H) was also considered—that is to say, the possibility that in alkaline solution (even sodium hydrogen carbonate solution) the lactone ring very quickly opens to give the open-chain acid (VII; R = H) as its anion. δ-Lactones are known to undergo ring fission in alkaline solution with considerable ease (Charlton, Haworth, and Peat, *J.*, 1926, 89). The dilute-alkaline hydrolysis of ethyl acetoacetate was therefore studied spectroscopically in order to observe, when hydrolysis was complete, the absorption of an authentic β-keto-acid anion, *i.e.*, the acetoacetate anion. A parallel study was made of the alkaline hydrolysis of the keto-ester (VII; R = Me). The two experiments gave strikingly different results. As the hydrolysis of the acetoacetic ester proceeded, the initial high-intensity absorption at 2730 A. ($\varepsilon_{max.}$ = 13,900), characteristic of the enolate ion [$CH_3 \cdot C(O^-)=CH \cdot CO_2Et$], diminished steadily, falling to the value of ε = 2100 after four hours (hydrolysis virtually complete; cf. Grossman, *loc. cit.*). Hydrolysis of the keto-ester (VII; R = Me) proceeded very rapidly to give a solution with maximal absorption at 2695 A. ($\varepsilon_{max.}$ = 17,600), which remained constant at this value, and which is identical (allowing for the difficulty of obtaining the initial keto-ester in a pure condition) with that shown by the lactone (VIII) in alkaline solution (see above). The considerable difference in absorption spectrum between the products of the hydrolysis of the two esters can only be explained with reference to the presence of the δ-hydroxyl group in the keto-ester (VII; R = Me), which enables lactonisation to take place. It is therefore suggested that alkaline hydrolysis of the keto-ester (VII; R = Me) takes

place with lactonisation to give the enolate ion (IX) of the lactone. One further difference was observed between these hydrolysis experiments. The solution obtained by acidifying the ethyl acetoacetate hydrolysate (*i.e.*, a solution of acetoacetic acid) exhibited only very low intensity absorption, whereas acidification of the other hydrolysate (from VII; R = Me) gave a solution with light absorption identical with that observed for the lactone (VIII) in dilute acid solution (Figure, curve I). Moreover, the lactone could readily be isolated from this solution by ether extraction, either immediately or after the lapse of some time.

That the substance responsible for the 2695 A. absorption band is the enolate ion (IX) receives further confirmation in the following way. A sodium hydrogen carbonate solution of the lactone (VIII), on treatment with *p*-phenylphenacyl bromide, gave a crystalline derivative, m. p. 184—188°, formulated as (XII).



If sodium hydrogen carbonate had opened the lactone ring, the resultant derivative would then be represented by (XIV). However, this latter derivative has been prepared by an unambiguous route, and is different in melting point (110—111°), solubility, and stability from (XII). The route employed involved the preparation of the *p*-phenylphenacyl ester (XIII) of the acetylenic acid, and hydration of this derivative by the piperidine method.

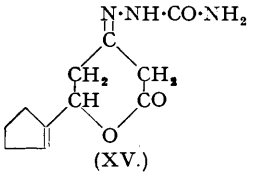
The above results show that the open-chain acid (VII; R = H), which possesses the same side-chain structure as auxin-b, does not exist in the free state but only in the form of the corresponding lactone, even in alkaline solution. The work of Kögl, Haagen-Smit, and Erxleben (*loc. cit.*), on the other hand, indicates that auxin-b (and its derivatives, with one possible exception, see below) shows no tendency to lactonise. It might be argued that the two *sec.*-butyl groups attached to the *cyclo*pentene nucleus in auxin-b prevent or hinder lactonisation. However, such an explanation is rendered much less likely by Kögl, Haagen-Smit, and Erxleben's observations (*ibid.*, 1933, **216**, 31) on the closely related auxin-a (XI), which is stereochemically identical with auxin-b in the di-*sec.*-butyl*cyclo*pentene part of the molecule (Kögl *et al.*, *loc. cit.*). With auxin-a, ready interconversion of lactone and open-chain forms was observed, either form being obtained merely by appropriate seeding of a supersaturated aqueous solution. Furthermore, examination of molecular models of auxins-a and -b indicates that the two *sec.*-butyl groups can readily assume positions that do not interfere with lactone formation.

Having the *cyclo*pentenyl analogue of auxin-b lactone available, it was of considerable interest to perform on it those experiments carried out by Kögl, Haagen-Smit, and Erxleben (*loc. cit.*) on auxin-b, which led to the elucidation of the structure of the side chain. These reactions were: (*a*) preparation of a *p*-phenylphenacyl ester, (*b*) formation of a semicarbazone, (*c*) reaction with methanolic hydrogen chloride, and (*d*) hydrogenation; they will be discussed in that order. The difference in behaviour with ferric chloride between the synthetic lactone and auxin-b has already been commented upon.

The reaction between the lactone (VIII) and *p*-phenylphenacyl bromide, leading to the formation of the enol-lactone derivative (XII), has already been described, the yield being of the order of 20%. *p*-Phenylphenacyl derivatives were obtained in similar yields from the methyl lactone (Jones and Whiting, *J.*, 1949, 1419), and the phenyl lactone (Henbest and Jones, preceding paper). Auxin-b was reported to form a *p*-phenylphenacyl derivative in 70% yield, which was taken as additional evidence for the presence of a carboxylic acid group in the molecule, the derivative being presumed to possess a structure analogous to that of the ester (XIII).

Auxin-b was reported to form a semicarbazone in 45% yield, which was believed to possess the normal structure of a semicarbazone of a β-keto-acid [*i.e.*, containing the grouping, ·C(:N·NH·CO·NH₂)·CH₂·CO₂H]. The *cyclo*pentenyl lactone reacted rapidly with semicarbazide acetate in methanol solution at room temperature to yield a crystalline, rather insoluble semicarbazone in nearly quantitative yield (similar derivatives were obtained in excellent yields in

the methyl and phenyl series). This semicarbazone gave the correct analytical data for a compound with the " normal " semicarbazone structure (XV), but this formulation was ruled out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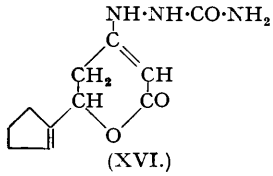
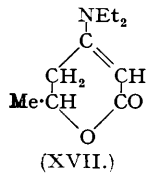

(XVI.)

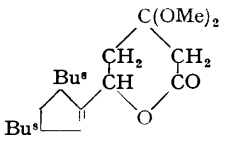

(XVII.)

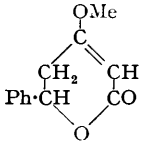
because its absorption spectrum ($\lambda_{max.}$ 2670 A.) was markedly different from that of ethyl acetoacetate semicarbazone ($\lambda_{max.}$ 2270 A.), the absorption of the latter being similar to those of saturated ketone semicarbazones. Evidence in favour of the alternative semicarbazide structure (XVI) was obtained by comparing the light absorption of the lactone-semicarbazone and the diethylamino-lactone (XVII) (Jones and Whiting, *loc. cit.*) with those of analogous

	$\lambda_{max.}$	$\varepsilon_{max.}$		$\lambda_{max.}$	$\varepsilon_{max.}$
(XVI)	2670 A.	17,900	(XVII) ...	2910 A.	28,000
$PhNH{\cdot}NH{\cdot}CO{\cdot}NH_2$	2335	11,000	$Ph{\cdot}NEt_2$...	2600	15,000

phenyl compounds, 4-phenylsemicarbazide and diethylaniline. The data in the above Table show that if the lactone-semicarbazone is represented by (XVI), its light absorption properties fall very well into line with those of the other three compounds of known structure.

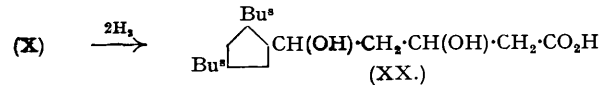
(XVIII.)




(XIX).

Auxin-b, when heated under reflux in methanol solution containing hydrogen chloride (1·5%) gives in 70% yield a crystalline dimethoxy-lactone, formulated as (XVIII). The lactone (VIII), on similar treatment, rapidly gave a black intractable tar from which no pure compound could be isolated. The same reaction performed with the phenyl lactone did not lead to appreciable charring, but the only product isolated (in low yield) was the crystalline monomethoxy-lactone (XIX) (cf. preceding paper).

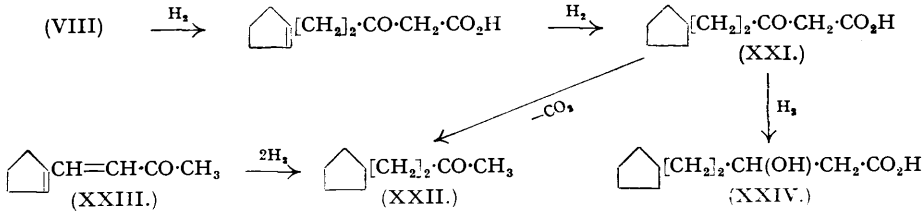
Hydrogenation of the lactone (VIII) was next investigated. Auxin-b was reported to take up two molecules of hydrogen to give a crystalline tetrahydro-compound, the analysis of which agreed with the βδ-dihydroxy-acid (XX). This dihydroxy-acid formed a mono-3 : 5-dinitro-


(XX.)

benzoate, a surprising result in view of the fact that auxin-a (the closely related αβδ-trihydroxy-acid) formed a tris-3 : 5-dinitrobenzoate. The lactone (VIII), when hydrogenated in acetic acid solution in the presence of Adams's catalyst (the same conditions as used for auxin-b), took up two molecules of hydrogen quickly, and a third molecule more slowly. The uptake of a third molecule of hydrogen can be readily explained if the first hydrogen molecule effects hydrogenolysis of the hydroxyl group on the carbon atom adjacent to the double bond (cf. hydrogenolysis of simpler unsaturated lactones in this series; Dr. J. English, private communication). That the hydrogenation did in fact proceed by this course (depicted in the scheme below) was shown by interrupting the hydrogenation after the uptake of two molecules. The saturated keto-acid (XXI) so obtained was thermally decarboxylated to give the ketone (XXII), isolated in 40% yield as its 2 : 4-dinitrophenylhydrazone. This derivative was identical with a sample prepared from the ketone obtained by hydrogenation of 4-*cyclo*pent-1′-enylbut-3-en-2-one (XXIII), the latter ketone being prepared in turn from *cyclo*pent-1-enealdehyde and acetone by Heilbron, Jones, Toogood, and Weedon's method (*J.*, 1949, 1827). Uptake of the third molecule of hydrogen by the lactone gave the β-hydroxy-acid (XXIV).

The analogues of auxin-b lactone so far prepared, containing methyl, propenyl,

*spirocyclo*hexyl, phenyl, *p*-chlorophenyl (this paper; Experimental), styryl and *cyclo*pentenyl groups in place of the di-*sec.*-butyl*cyclo*pentenyl group, have been tested for growth-promoting activity by Bentley's " straight-growth method " (*J. Exp. Bot.*, 1950, **1**, 201), in which the elongation of coleoptile sections, when placed in an aqueous solution of the substance under test, is measured. All the above substances were inactive at concentrations from 10^{-4} to 10^{-8}. They were also inactive in Moewus's cress-root test (*Biol. Z.*, 1949, **68**, 118), at concentrations from 10^{-8} to 10^{-11}.



Since this work was completed, Kögl and de Bruin (*Rec. Trav. chim.*, 1950, **69**, 729) have described the preparation of the *cyclo*pentenyl lactone (VIII) by another route. The light-absorption properties of the lactone, ethyl acetoacetate, and auxin-b were compared in ethanol solution, but no other comparisons with auxin-b were described.

It is now clear from English and Barber's studies (*loc. cit.*) on the preparation of substituted *cyclo*pentenealdehydes and from the work described in this paper that the synthesis of a lactone with a *structure* identical with that of the hypothetical lactone of auxin-b should not be too difficult a task. However, much effort would certainly be required to surmount the considerable stereochemical obstacles involved in a total synthesis. In view of the doubts that the above results cast upon the structure proposed for auxin-b, further work on its isolation and properties is clearly desirable.

Experimental.

(All m. p.s were taken on a Köfler block and are corrected. Light-absorption data were determined in ethanol solution with a Beckman spectrophotometer unless stated otherwise.)

trans-cyclo*Hexane*-1 : 2-*diol* (II).—*cyclo*Hexene (375 g.), purified by shaking it with saturated sodium bisulphite solution, drying it (Na_2SO_4) and distilling it, was added to formic acid (1500 g.; *d* 1·20) in a 3-l. three-necked flask equipped with a stirrer, thermometer, reflux condenser, and dropping funnel. The temperature of the mixture was raised to 45° by passing steam into a water-bath surrounding the flask. Hydrogen peroxide (585 g.; 100 vol.) was added during 1·5 hours with stirring (at the interface between the 2 phases) and cooling, the internal temperature being maintained at 55—60°; the mixture finally becoming homogeneous. Most of the formic acid was removed *in vacuo* (water pump), and the residual crude monoformyl ester was hydrolysed by steam-distillation until 750 c.c. of aqueous formic acid distillate had been collected. The remainder of the solvents were evaporated *in vacuo* to give a pale-yellow syrup which readily solidified. One recrystallisation from acetone gave colourless diol (426 g.; 82%), m. p. 96—97° (pure diol has m. p. 103·5—104°), sufficiently pure for the periodate oxidation.

cyclo*Pent*-1-*enealdehyde* (I).—Sodium paraperiodate (250 g.) was suspended in water (3 l.), concentrated nitric acid (58 c.c.) was added, and the mixture was stirred until the solid dissolved. The solution was then adjusted to pH 4 by the addition of sodium hydroxide solution. *trans-cyclo*Hexane-1 : 2-diol (110 g.) was added with stirring to the periodate solution at 19°; the temperature then rose to 33°. The solution was cooled to 25° during 20 minutes; ether (400 c.c.) and potassium hydroxide solution (350 c.c.; 20%) were then added. The mixture was stirred vigorously for 30 minutes, the layers were separated, and the aqueous phase was extracted several times with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Distillation gave *cyclo*pent-1-enealdehyde (51·2 g., 58%), b. p. 52°/20 mm., n_D^{17} 1·4892. Light absorption: Maximum, 2370—2380 A.; $\varepsilon_{max.}$ = 13,500. It has an odour similar to but more pungent than that of benzaldehyde.

This aldehyde could be kept for several months without appreciable deterioration if stored at 0° in nitrogen in the presence of a little quinol.

1-cyclo*Pent*-1′-*enylbut*-3-*yn*-1-*ol* (IV).—The Reformatsky reaction was carried out by the general method described by Henbest, Jones, and Walls (*loc. cit.*). Once the reaction had started, the solution of *cyclo*pent-1-enealdehyde (48 g.) and propargyl bromide (60 g.) in dry ether (100 c.c.)–dry tetrahydrofuran (50 c.c.) was added with vigorous stirring to the zinc wool (39 g.) as fast as possible. External cooling with dry ice in alcohol was employed to control the exothermic reaction, the solution being maintained in a state of gentle ebullition. By performing the reaction as quickly as possible, the yield of carbinol was greatly improved, and much less polymeric material was obtained. Isolation with ether gave the *carbinol* (52 g., 75%), b. p. 53°/0·06 mm., n_D^{15} 1·5020 (Found: C, 78·8; H, 8·8. $C_9H_{12}O$ requires C, 79·35; H, 8·9%). (Low carbon values are often given by βγ-acetylenic carbinols; cf. Henbest, Jones, and Walls, *loc. cit.*)

The 3 : 5-*dinitrobenzoate* was prepared by allowing the carbinol to react with 3 : 5-dinitrobenzoyl chloride in the presence of diethylaniline at 20° overnight. Isolation with ether, and chromatographic

analysis gave a solid product, which on recrystallisation from methanol formed small needles, m. p. 105—105·5° (Found: C, 58·15; H, 4·55. $C_{16}H_{14}O_6N_2$ requires C, 58·2; H, 4·25%).

4-Hydroxy-4-cyclopent-1′-enylbut-1-yne-1-carboxylic Acid (V) *and its Methyl Ester* (VI).—A solution of ethylmagnesium bromide in ether (150 c.c.) was prepared from magnesium (21 g.). A solution of the carbinol (IV) (52 g.) in dry benzene (200 c.c.) was added with stirring to the Grignard solution cooled to −15° during one hour, the resulting clear solution being stirred for a further two hours at −10°. This solution was autoclaved with solid carbon dioxide for 18 hours at room temperature. The product was separated into a neutral and an acid fraction; the latter gave the acid (V) (52 g., 78%) as a pale-brown syrup. Attempted purification of a sample by molecular distillation at 10^{-5} mm. resulted in much decomposition, and the remainder of the acid was converted directly into the methyl ester.

A solution of the acid (47 g.) in methanol (500 c.c.) containing concentrated sulphuric acid (5 c.c.) was kept at 20° for 56 hours. Isolation with ether, followed by distillation from a short-path still gave the *methyl* ester (VI) (25 g., 50%), b. p. 100° (bath temp.)/10^{-4} mm. This material could not be obtained completely pure by fractional distillation; a middle fraction had b. p. 116°/0·1 mm., n_D^{22} 1·5065 (Found: C, 67·25; H, 7·05. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·25%).

5 : 6-*Dihydro-4-hydroxy-6-cyclopent-1′-enyl-2-pyrone* (VIII).—A solution of the methyl ester (VI; 3 g.) in dry ether (15 c.c.) was cooled to 5°. Pure piperidine (2·67 g.; 2 equivs.) was added, and the temperature of the solution then rose to 29°. After being kept at 20° for two hours, and more ether being added, the solution was extracted as quickly as possible with three 50 c.c. portions of 0·25N-hydrochloric acid. Ether (75 c.c.) was added to the combined acid extracts, and the mixture was kept at 20° overnight. The ethereal layer was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated *in vacuo*. The residual keto-ester (VII; R = Me) (2·63 g.) was a pale-yellow oil, to which was added 0·1N-sodium hydroxide solution (250 c.c.), the solution then being kept at 20° for two hours. After being extracted with ether to remove neutral material, the solution was acidified with N-hydrochloric acid, and the liberated lactone extracted several times with ether. Evaporation of the dried (Na_2SO_4) ethereal extracts *in vacuo* gave a solid residue, which was triturated with ether–light petroleum (4 : 1) to yield the pyrone (1·7 g., 60%), m. p. 84—86°. The product was obtained pure by dissolving it in hot (80°) water, filtering it to remove some oily material and cooling it to 0°, these operations being carried out as quickly as possible to minimise losses due to the instability of the pyrone. The pure *pyrone* had m. p. 96—98° (Found: C, 66·3; H, 6·55. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·65%). Light absorption in ethanol (0·0115%): Maximum, 2410 A.; $\varepsilon_{max.}$ = 9700. In 0·01N-hydrochloric acid (aqueous; 0·0219%): Maximum, 2450 A.; $\varepsilon_{max.}$ = 5250. In water (0·0056%) containing one equivalent of sodium hydrogen carbonate: Maximum 2695 A.; $\varepsilon_{max.}$ 19,300.

The intermediate keto-ester could be purified considerably by low-temperature crystallisation from ether–light petroleum (4 : 1), from which it separated as a granular solid, m. p. *ca.* −10°, n_D^{22} 1·5003. Light absorption: Maximum, 2480 A.; $\varepsilon_{max.}$ = 1700 (cf. light absorption of ethyl acetoacetate: Maximum, 2450 A.; $\varepsilon_{max.}$ 1300).

Reactions of 5 : 6-*Dihydro-4-hydroxy-6-cyclopent-1′-enyl-2-pyrone* (VIII).—(a) *With* p-*phenylphenacyl bromide.* The lactone (0·5 g.) and sodium hydrogen carbonate (0·23 g.) were dissolved in ethanol (5 c.c.)–water (5 c.c.). A solution of *p*-phenylphenacyl bromide (0·72 g.; 95% theoretical amount) in ethanol (15 c.c.) was added, and the resultant mixture heated under reflux for 2·5 hours. Cooling the clear solution gave a solid (0·3 g.), m. p. 155—170°, which after being washed with warm ether, followed by two recrystallisations from nitromethane and two recrystallisations from ethanol had m. p. 184—188° (Found: C, 76·95; H, 6·1. $C_{24}H_{22}O_4$ requires C, 77·0; H, 5·9%). Light absorption: Maximum, 2890 A.; $\varepsilon_{max.}$ = 24,100; Minimum, 2540 A.; $\varepsilon_{min.}$ = 9800.

(b) *With semicarbazide.* A solution of semicarbazide acetate in methanol (1 c.c.) [prepared from semicarbazide hydrochloride (0·15 g.) and potassium acetate (0·15 g.)] was added to the lactone (0·3 g.) dissolved in a few drops of methanol. Within a few minutes, a crystalline precipitate appeared, which after 15 minutes was filtered off; the *semicarbazone* (XVI) (0·38 g.) had m. p. 211° (decomp.), unchanged on recrystallisation from ethylene glycol, from which it crystallised as plates (Found: C, 55·2; H, 6·05; N, 17·75. $C_{11}H_{15}O_3N_3$ requires C, 55·7; H, 6·35; N, 17·7%). Light absorption: Maximum, 2670 A.; $\varepsilon_{max.}$ = 17,900.

Ethyl acetoacetate semicarbazone prepared from the ester and semicarbazide acetate at room temperature had m. p. 129° (Satish Chandra, *Quart. J. Ind. Chem. Soc.*, 1926, **3**, 37, gives m. p. 129°). Light absorption: Maximum, 2270 A.; $\varepsilon_{max.}$ = 11,400.

(c) *Hydrogenation.* Platinic oxide (30 mg.) was suspended in glacial acetic acid (10 c.c.) and hydrogen was admitted with shaking. When the catalyst was fully reduced, the lactone (0·25 g.) was added. Hydrogenation was stopped after an uptake of hydrogen of 65·7 c.c. (theory for two moles., 65·5 c.c.). The catalyst was filtered off and the solution refluxed for five minutes in order to decarboxylate β-keto-acids. After cooling and the addition of water, the products were isolated with ether; the ethereal solution after evaporation gave a liquid residue which was treated directly with an excess of methanolic 2 : 4-dinitrophenylhydrazine sulphate. Chromatographic purification and recrystallisation from methanol gave 4-cyclo*pentylbutan-2-one* 2 : 4-*dinitrophenylhydrazone* (0·16 g., 40%) as orange-red needles, m. p. 95·5—96° (Found: C, 56·35; H, 6·35. $C_{15}H_{20}O_4N_4$ requires C, 56·2; H, 6·25%). Light absorption: Maxima, 2290 and 3640 A.; $\varepsilon_{max.}$ = 16,000 and 21,200, respectively; Minimum, 2960 A.; $\varepsilon_{min.}$ = 2100. These absorption data correspond to those of a 2 : 4-dinitrophenylhydrazone of a saturated ketone (Braude and Jones, *J.*, 1945, 498).

The same 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 95·5—96°) was obtained from the hydrogenation product of 4-*cyclo*pent-1′-enylbut-3-en-2-one (Heilbron, Jones, Toogood, and Weedon, *loc. cit.*)—this hydrogenation being carried out in ethanol solution with a palladium-black catalyst.

When the hydrogenation of the lactone proceeded to completion under the above conditions, three moles of hydrogen were absorbed, the third at a considerably slower rate than the first two. The product was a viscous acid, essentially 2-hydroxy-4-*cyclo*pentylbutane-1-carboxylic acid. This acid was difficult to purify owing to its instability.

p-*Phenylphenacyl Ester* (XII) *of the Acetylenic Acid, and its Hydration.*—Redistilled methyl ester (VI; 2 g.) in methanol (30 c.c.) was added to a solution of potassium hydroxide (1·2 g.) in water (30 c.c.) The homogeneous solution was kept at room temperature for 48 hours; the acid (1·8 g.) was then isolated with ether. It was suspended in water (5 c.c.) and sodium carbonate was added until no more carbon dioxide was evolved. A few drops of 0·01N-hydrochloric acid were added to bring the pH to between 6 and 7, followed by a warm solution of *p*-phenylphenacyl bromide (2·3 g.; 75% of theoretical amount) in ethanol (40 c.c.), the mixture then being heated under reflux for two hours. The hot solution was decanted from a small amount of oily material and then cooled to 0° whereupon a solid (1·32 g.), m. p. 93—106°, separated. This material was triturated with 20-c.c. and 10-c.c. portions of dry ether to give nearly pure ester (0·99 g.), m. p. 108—110°. Recrystallisation from methanol gave the pure p-*phenylphenacyl* ester, m.p. 111—112° (Found: C, 76·5; H, 6·15. $C_{24}H_{22}O_4$ requires C, 77·0; H, 5·9%). Light absorption: Maximum, 2860 A.; $\varepsilon_{max.}$ = 23,200; Minimum, 2420 A.; $\varepsilon_{min.}$ = 3700.

Hydration of the above *p*-phenylphenacyl ester was accomplished by the addition of piperidine (0·16 c.c., 2 moles) to a solution of the ester (0·24 g.) in dry dioxan (1·6 c.c.) at 15°. The temperature of the solution rose to 20°, and it was then maintained at 35° for one hour. Ether (5 c.c.) was added and the solution was quickly extracted with three 8-c.c. portions of 0·25N-hydrochloric acid. Ether (8 c.c.) was added to the combined acid extract, which was kept at 20° for four hours; the ethereal layer was separated and the aqueous layer extracted several times with ether. The combined ethereal extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was recrystallised from aqueous methanol to give the p-*phenylphenacyl* ester (XIV) (0·09 g.), m. p. 109—111° (Found: C, 74·25; H, 6·6. $C_{24}H_{24}O_5$ requires C, 73·45; H, 6·15%). Light absorption: Maximum, 3000 A.; $\varepsilon_{max.}$ = 15,900. Minimum, 2560 A.; $\varepsilon_{min.}$ = 8400. This compound was unstable in ethanol solution at room temperature, the light absorption properties altering markedly.

1-p-*Chlorophenylbut*-3-*yn*-1-*ol.*—A mixture of *p*-chlorobenzaldehyde (30 g.; m. p. 45°) (*Org. Synth.*, Coll. Vol. II, p. 133) and propargyl bromide (25 g.) in ether (40 c.c.) and benzene (40 c.c.) was added at a moderate rate to activated zinc wool (14 g.). When the reaction was complete, the carbinol was isolated in ether; distillation then gave 1-p-*chlorophenylbut*-3-*yn*-1-*ol* (17·1 g., 50%), b. p. 92—95°/0·07 mm., n_D^{16} 1·5605, m. p. 32° (Found: C, 66·7; H, 5·1. $C_{10}H_9OCl$ requires C, 66·5; H, 5·0%). The non-volatile residue from the above distillation was triturated with benzene to give a solid, which after recrystallisation from benzene, gave 1 : 5-*di*-p-*chlorophenylpent*-2-*yn*-1 : 5-*diol* (1·4 g.), m. p. 138° (Found: C, 63·85; H, 4·2. $C_{17}H_{14}O_2Cl_2$ requires C, 63·55; H, 4·4%).

4-p-*Chlorophenyl*-4-*hydroxybut*-1-*yne*-1-*carboxylic Acid and its Methyl Ester.*—The above carbinol (12 g.) in dry benzene (50 c.c.) was added slowly to a solution of ethylmagnesium bromide in ether (40 c.c.) [prepared from magnesium (3·6 g.)]. Carboxylation was then effected by Haynes and Jones's procedure (*J.*, 1946, 503). Recrystallisation of the crude acetylenic acid from benzene gave 4-p-*chlorophenyl*-4-*hydroxybut*-1-*yne*-1-*carboxylic acid* (8·9 g., 60%) as needles, m. p. 113—115° (Found: C, 58·1; H, 3·9. $C_{11}H_9O_3Cl$ requires C, 58·8; H, 4·05%). Light absorption: Maximum, 2670 A.; $\varepsilon_{max.}$ = 270.

A solution of the acid (5 g.) in methanol (100 c.c.) containing concentrated sulphuric acid (5 c.c.) was kept at room temperature for 24 hours. Isolation with ether gave the *methyl* ester (3·55 g., 70%), b. p. 135° (bath temp.; short path still)/10^{-5} mm., m. p. 35·5° (Found: C, 60·7; H, 4·95. $C_{12}H_{11}O_2Cl$ requires C, 60·4; H, 4·65%).

6-p-*Chlorophenyl*-5 : 6-*dihydro*-4-*hydroxy*-2-*pyrone.*—Pure piperidine (0·25 c.c.) was added to a solution of the above methyl ester (0·52 g.) in dry ether (1·5 c.c.). After one hour at room temperature, more ether was added and the solution was extracted with N-hydrochloric acid (30 c.c.). After a further three hours at room temperature an oil (keto-ester) had separated from the acid extract. 5N-Hydrochloric acid (30 c.c.) was then added and the mixture was kept at room temperature overnight (16 hours). The solid was washed with a little ether to give crude pyrone (0·12 g.), m. p. 120—125°. Rapid recrystallisation from hot (80°) water gave the pure *pyrone*, m. p. 127—131° (Found: C, 58·7; H, 4·0. $C_{11}H_9O_3Cl$ requires C, 58·8; H, 4·05%). Light absorption: Maximum, 2420 A.; $\varepsilon_{max.}$ = 10,000.

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