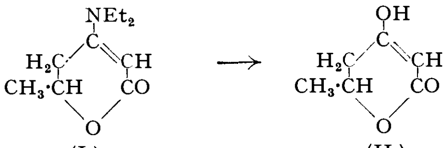
303. *Studies on Compounds Related to Auxin-a and Auxin-b. Part I. (Unsaturated Lactones. Part III.)*

By E. R. H. Jones and M. C. Whiting.

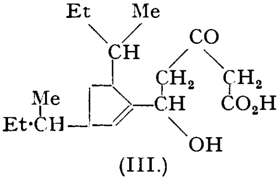
Acidic hydrolysis of some of the β-substituted αβ-ethylenic lactones (*e.g.*, I) described in the preceding paper, under carefully chosen conditions, leads to tetronic acids and hydroxydihydro-2-pyrones (*e.g.*, II). The light-absorption properties of these compounds are discussed and, because of its structural relationship to auxin-b (III), some of the reactions of (II) have been studied.

Moureu and Lazennac (*Compt. rend.*, 1906, **143**, 596; *Bull. Soc. chim.*, 1906, **35**, 1190) found that the adducts obtained from phenylpropiolic ester and various amines were converted on acidic hydrolysis, even under very mild conditions, into benzoylacetic ester. Similar treatment of the β-substituted αβ-ethylenic-γ- and δ-lactones (*e.g.*, I), convenient preparations of which are described in the succeeding paper, should lead to tetronic acids and 4-hydroxy-5 : 6-dihydro-2-pyrones (*cyclo*homotetronic acids) (*e.g.*, II), respectively. The former are comparatively inaccessible and no general method for the synthesis of the latter, which are related to auxin-b (III) as formulated by Kögl and his collaborators (*Z. physiol. Chem.*, 1934, **225**, 215), has yet been described. The possibility of effecting such conversions has therefore been examined.

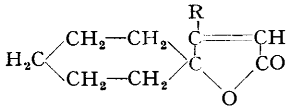
When the lactone (IV; R = NEt_2) was treated with alcoholic oxalic acid, according to the procedure of Moureu and Lazennac (*loc. cit.*), or with cold dilute sulphuric acid, no reaction took place. (Reasons for this resistance to hydrolytic fission have been suggested in the preceding paper.) To effect hydrolysis it was found necessary to heat the lactone with an excess of concentrated hydrochloric acid at 100°, whereupon the *tetronic acid* (IV; R = OH), m. p. 198°, was obtained in 90% yield. Its structure was confirmed by its methylation with methyl iodide and sodium hydroxide to (IV; R = OMe) (cf. succeeding paper). Similar treatment of (V; $R_1 = R_2 =$ Me, R = $[CH_2]_5{>}N$) gave the known γγ-dimethyltetronic acid in 80% yield. In the case of the lactone (V; R_1 = H; R_2 = Pr, R = NEt_2), derived from a secondary acetylenic carbinol, it was found necessary to minimise the further hydrolysis of the primary product by employing only the calculated quantity of acid, isolating the product before the reaction was complete, and rehydrolysing the unchanged amino-lactone, in order to obtain a satisfactory yield (60%) of *hex-1-ene-2 : 3-diol-1-carboxylic acid 1→3-lactone* (*γ-propyltetronic acid*) (V; R_1 = H; R_2 = Pr; R = OH), m. p. 82°. The methoxy-lactones (IV; R = OMe; and V; $R_1 = R_2$ = Me; R = OMe) also underwent hydrolysis to the corresponding tetronic acids on drastic treatment with hydrochloric acid, but the yields were unsatisfactory. Only incomplete hydrolysis to the tetronic acid was observed when (IV; R = OMe) was heated with sodium hydroxide solution. Some of the tetronic acid was obtained from the *trans*-hydroxy-acid, $[CH_2]_5{>}C(OH){\cdot}C(OPh){:}CH{\cdot}CO_2H$, on hydrolysis with hydrochloric acid.



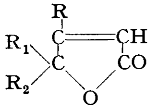
(I.) (II.)



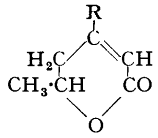
(III.)



(IV.)



(V.)



(VI.)

The hydrolysis of (VI; R = NEt_2) was examined in the hope of finding a general method applicable to the synthesis of 4-hydroxy-5 : 6-dihydro-2-pyrones, which are analogues of the hypothetical lactone of auxin-b, as formulated by Kögl. It is reasonable to expect that such lactones should be convertible into δ-hydroxy-β-keto-acids analogous to auxin-b (III) itself.

Hydrolysis of the amino-lactone with concentrated hydrochloric acid at 100° gave only steam-volatile ketonic material and carbon dioxide. With 2N-hydrochloric acid [in which

(VI; R = NEt_2) is readily soluble] at 20°, an appreciable quantity of syrupy acidic material was obtained, from which a solid, m. p. 118°, could be separated. This exhibited the chemical properties expected of the desired 2-pyrone derivative (II), but the yield was only 5%. Attempts were made to improve the procedure by using continuous extraction to isolate the very water-soluble product, sulphuric or phosphoric acid then being employed. Apparently the product was sensitive to prolonged heating in ethereal solution in the presence of traces of mineral acids, since acidic syrups were obtained which, although giving strong ferric chloride colorations, failed to yield any crystalline material. Similar results followed attempts to use acetic or chloroacetic acid to effect hydrolysis, and the action of a methanolic solution of oxalic acid dihydrate, though giving diethylamine hydrogen oxalate, m. p. 209° (decomp.), in 75% yield, did not afford any of the product, m. p. 118°. It is assumed that in all these cases the 2-pyrone derivative was formed but underwent further reactions with the solvent, or self-condensation. Attention was then directed to the hydrolysis of the corresponding methoxy-lactone (VI; R = OMe). It was found that treatment of a solution in dry ether with carefully controlled quantities of concentrated hydrochloric acid gave a 75% yield of 4-*hydroxy*-6-*methyl*-5 : 6-*dihydro*-2-*pyrone* (II), m. p. 123°, not significantly depressed on admixture with the somewhat impure material, m. p. 118°, mentioned above. The light-absorption properties of the two products were identical.

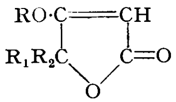
The general chemical properties and the light absorption (see below) of this substance were in agreement with the suggested structure, but with 2 : 4-dinitrophenylhydrazine, in contrast to the tetronic acids, it formed a derivative very readily. This derivative evolved carbon dioxide on recrystallisation from glacial acetic acid, giving the 2 : 4-dinitrophenylhydrazone of ethylideneacetone. This fact, and especially observations on analogous substances (Henbest and Jones, forthcoming publication), suggested that the compound, m. p. 123°, might possibly be crotonylacetic acid (VII). Although stable at 100°, it did in fact decarboxylate on heating to 200° or on acidic hydrolysis, giving ethylideneacetone, isolated as its 2 : 4-dinitrophenylhydrazone.

$CH_3{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$
(VII.)

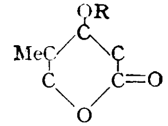
In view of this possibility it was considered desirable to seek further evidence in support of the structure. Treatment of the compound, m. p. 123°, with diazomethane failed to yield a satisfactory product and methylation with methyl iodide and silver oxide gave, not the expected *O*-methyl ether (VI; R = OMe) (described in the succeeding paper) but a substance, m. p. 148—149°, which in view of its chemical and physical properties must be regarded as 4-*hydroxy*-3 : 6-*dimethyl*-5 : 6-*dihydro*-2-*pyrone*, *C*-methylation having taken place. Having failed to obtain confirmation of the proposed structure in this way, it seemed best to synthesise crotonylacetic acid for comparison with the material already obtained. When β-methoxysorbic acid (for preparation, see succeeding paper) was submitted to the hydrochloric acid–ether hydrolysis procedure, *crotonylacetic acid* (VII), m. p. 68—72° (decomp.), was readily obtained in 80% yield. This compound was obviously quite different from that, m. p. 123°, described above, and its chemical properties were more akin to those of typical β-keto-acids; for instance, it was decarboxylated very readily, and on treatment with 2 : 4-dinitrophenylhydrazine hydrochloride solution yielded the derivative of ethylideneacetone directly. In view of this evidence and the entirely different light-absorption properties (see below) of the two compounds in question, eliminating the possibility of *cis–trans*-isomerism, the formulation (VI; R = OH) for the compound, m. p. 123°, must be regarded as established. Further confirmation is provided by the properties described below and by other synthetic work on analogous substances (Henbest and Jones, forthcoming publication).

In view of its relationship to the proposed structure for auxin-b (III) (Kögl *et al.*, *loc. cit.*) the properties of the 2-pyrone derivative were examined in some detail. This dissolves with effervescence in sodium hydrogen carbonate solution and gives an immediate deep crimson colour with ferric chloride solution. Tetronic acids on treatment with sodium nitrite and then hydrochloric acid give a violet colour fading after about one minute; (VI; R = OH) gave a similar but even more transient colour. The 2 : 4-dinitrophenylhydrazone has already been mentioned and the *semicarbazone*, m. p. 200°, was obtained very readily in excellent yield. A p-*phenylphenacyl ester*, m. p. 174—174·5°, was obtained only in poor yield; it gave analyses corresponding to $C_{20}H_{18}O_4$ and presumably has the structure (VI; R = $O{\cdot}CH_2{\cdot}CO{\cdot}C_6H_4{\cdot}C_6H_5$). Treatment with formaldehyde and a trace of piperidine gave the 3 : 3′-*methylenebis*-(4-*hydroxy*-6-*methyl*-5 : 6-*dihydro*-α-*pyrone*), m. p. 172° (decomp.) (cf. Anschütz and Quitmann, *Annalen*, 1928, **462**, 97).

Light-absorption data for the compounds described in this paper, together with data for analogous substances, are presented in the accompanying table. It will be seen that the correspondence between the maxima and intensities for these hydroxy-compounds and the related *O*-methyl derivatives described in the succeeding paper is very close, indicating that in alcoholic solutions the enolic form predominates in both cases. This supports Kummler's view (*J. Amer. Chem. Soc.*, 1938, **60**, 859; 1940, **62**, 3292) that tetronic acids exist in solution largely in the enolic form. The wave-length differences, already commented on (succeeding paper), between the 5- and 6-membered ring lactones, are again conspicuous. The data for crotonylacetic acid indicate that this substance also exists in alcoholic solution to a large extent as the enol; the $\lambda_{max.}$ difference (150 A.) between this substance and its *O*-methyl derivative is rather larger than those observed (*ca.* 20 and 60 A.) between the corresponding cyclic compounds, but the conjugation in the acyclic compounds is more extensive and hydrogen bonding is probably involved.



Type A (5-membered ring).



Type B (6-membered ring).

Type.			$\lambda_{max.}$, A.	$\varepsilon_{max.}$
A	R = H	R_1R_2 = $[CH_2]_5>$	2240	13,000
A	R = H	R_1 = R_2 = Me	2230	13,500
A	R = H	R_1 = Pr, R_2 = H	2230	13,500
Cf. [1] A	R = Me	R_1R_2 = $[CH_2]_5>$	2210	15,500
B	R = H		{2390 2420	12,000 12,000
Cf. [1] B	R = Me		2340	17,000
		$CH_3·CH:CH·C(OH):CH·CO_2H$	2800	6,500
		Cf.[1] $CH_3·CH:CH·C(OMe):CH·CO_2H$	2650	15,500

[1] Succeeding paper.

Work is being continued along the lines indicated in this paper and in other directions with the object of synthesising compounds with structures more closely related to those which have been given to auxins-a and -b.

EXPERIMENTAL.

(Except where specially referred to, the starting materials employed in the experiments below are described in the succeeding paper.)

*Lactone of β-Hydroxy-β-(1-hydroxy*cyclo*hexyl)acrylic Acid* (IV; R = OH).—(*a*) The lactone (IV; R = NEt_2) (4·6 g.) was heated on the steam-bath with concentrated hydrochloric acid (15 c.c.) for 45 minutes. The product (3·2 g.) obtained on cooling and diluting with water had m. p. 196—197°; after crystallisation from ethyl acetate the *lactone* formed prisms, m. p. 198° (2·8 g.) (Found: C, 63·95; H, 7·1. $C_9H_{12}O_3$ requires C, 64·25; H, 7·2%). Methylation: the lactone (0·5 g.), methyl iodide (2 g.), and 4N-sodium hydroxide solution (0·7 c.c.) were added to methanol (3 c.c.); after 5 days the neutral fraction was isolated with ether in the usual way; it solidified and was extracted with hot light petroleum (b. p. 40—60°); the solution on cooling yielded a solid, m. p. 90—98°, which after crystallisation from aqueous methanol had m. p. 104°, undepressed on admixture with an authentic specimen of (IV; R = OMe); the petrol-insoluble solid was crystallised from acetone–light petroleum, giving a small quantity of material, m. p. 210—215°, which was not investigated further.

(*b*) The lactone (IV; R = OMe) (1 g.) was heated under reflux with concentrated hydrochloric acid (5 c.c.) and methanol (2 c.c.) for 2½ hours. On cooling and dilution, a precipitate separated; crystallisation from ethyl acetate gave the tetronic acid (0·4 g.), m. p. 195—197°, undepressed on admixture with a specimen prepared by method (*a*).

(*c*) The lactone (IV; R = OMe) (2 g.) was heated under reflux with a solution of potassium hydroxide (1 g.) in water (10 c.c.) and methanol (4 c.c.) for 5 hours. A small amount of starting material was recovered on cooling and dilution. A solid separated from the filtrate on acidification, and after crystallisation from aqueous methanol, then ethyl acetate, the tetronic acid (*ca.* 200 mg.) was obtained as prisms, m. p. 196°, undepressed on admixture with an authentic specimen.

(*d*) *trans*-β-Phenoxy-β-(1-hydroxy*cyclo*hexyl)acrylic acid (100 mg.) was heated under reflux with concentrated hydrochloric acid (1 c.c.) and methanol (1 c.c.) for 2 hours. The mixture was cooled, diluted, and extracted with ether. The extract was washed thoroughly with sodium hydrogen carbonate solution and these washings gave on acidification a precipitate of the tetronic acid (*ca.* 15 mg.) which after crystallisation from ethyl acetate–light petroleum had m. p. 195—197°, undepressed on admixture with an authentic specimen.

γ-Lactone of 3-*Methylbut*-1-*ene*-2 : 3-*diol*-1-*carboxylic Acid* (*γγ-Dimethyltetronic Acid*) (V; R_1 = R_2 = Me, R = OH).—(*a*) The lactone (V; R_1 = R_2 = Me, R = $N<[CH_2]_5$) (1·9 g.) was heated on the steam-bath with concentrated hydrochloric acid (2 c.c.) for 45 minutes. The tetronic acid (1·0 g.),

m. p. 139—140°, separated on cooling and seeding. After crystallisation from ethyl acetate-benzene, it formed plates, m. p. 142° (Benary, *Ber.*, 1907, **40**, 1082, gives m. p. 142—143°).

(*b*) The lactone (V; $R_1 = R_2 =$ Me, R = OMe) (300 mg.) was heated under reflux with concentrated hydrochloric acid (2 c.c.) for 2 hours. After cooling and addition of water (5 c.c.), the solution was extracted with ether, the extract was washed with sodium hydrogen carbonate solution, the washings were acidified, and the tetronic acid (*ca.* 50 mg.) was isolated with ether. After crystallisation from ethyl acetate–light petroleum, it had m. p. 142°, undepressed on admixture with a specimen prepared by route (*a*).

γ-Lactone of Hex-1-*ene*-2 : 3-*diol*-1-*carboxylic Acid* (*γ-Propyltetronic Acid*) (V; $R_1 =$ H, $R_2 =$ Pr, R = OH).—The lactone (V; $R_1 =$ H, $R_2 =$ Pr, R = NEt_2) (2·2 g.) was heated on the steam-bath with concentrated hydrochloric acid (1·1 c.c.) for 20 minutes. The solution was cooled, diluted with water, and extracted with ether. The ethereal extract was thoroughly washed with saturated sodium hydrogen carbonate solution and evaporated; the residue was heated on the steam-bath with concentrated hydrochloric acid (0·4 c.c.) for 20 minutes, cooled, diluted, and extracted with ether. This extract was well washed with sodium hydrogen carbonate solution; the combined carbonate washings were acidified and extracted with ether. The extract was dried and evaporated, and the residual oil dissolved in benzene; on adding light petroleum and seeding, a solid (1·0 g.), m. p. 80—81°, separated; after recrystallisation from water the *tetronic acid* formed plates, m. p. 83° (Found: C, 59·4; H, 7·1. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%).

4-*Hydroxy*-6-*methyl*-5 : 6-*dihydro*-2-*pyrone* (II).—(*a*) The lactone (VI; R = OMe) (810 mg.) was dissolved in dry ether (20 c.c.), concentrated hydrochloric acid (216 mg.) was added, and the mixture was set aside at 20° for 48 hours, the solid which separated being occasionally powdered by stirring with a glass rod. After cooling to 0° the *pyrone* (550 mg.) was collected; it formed small prisms, m. p. 123—124°, unchanged by recrystallisation from ethyl acetate (Found: C, 56·15; H, 6·25. $C_6H_8O_3$ requires C, 56·25; H, 6·25%). It was readily soluble in water or alcohol, less readily in ethyl acetate, and only sparingly soluble in ether or benzene. It dissolved with effervescence in sodium hydrogen carbonate solution and gave a crimson-purple colour with ferric chloride solution and an extremely transient violet colour on treatment with sodium nitrite, followed by dilute hydrochloric acid. It could be kept for some months without appreciable decomposition.

(*b*) The lactone (VI; R = NEt_2) (3 g.) was dissolved in 2N-hydrochloric acid (10 c.c.). After standing at 20° for 24 hours the solution was saturated with potassium chloride and extracted with ether (7 × 15 c.c.). The syrup obtained on evaporation of the dried extract was dissolved in benzene, and on adding light petroleum the crude hydroxy-2-pyrone (130 mg.) separated as brownish prisms, m. p. 115—116°. After crystallisation from benzene the m. p. was 118°, undepressed on admixture with an authentic specimen prepared according to route (*a*).

The 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way, separated very slowly as a light brownish-yellow powder (60% yield). It decomposed without melting at 210—230°; it was almost completely insoluble in ordinary organic solvents except boiling glacial acetic acid which decomposed it rapidly (in less than 1 minute) to ethylideneacetone 2 : 4-dinitrophenylhydrazone, m. p. 158—159°, which was readily isolated by adding water. It could, however, be crystallised (with slight decomposition) from ethyl acetoacetate pre-heated to 150°; it then formed small dull-yellow laths, decomposing above 220° (Found: C, 46·85; H, 4·25. $C_{12}H_{12}O_6N_4$ requires C, 46·75; H, 3·95%).

The *semicarbazone*, prepared at room temperature in 75% yield, formed prismatic needles, m. p. 200° (decomp.), from water (Found: C, 45·35; H, 6·05. $C_7H_{11}O_3N_3$ requires C, 45·4; H, 6·0%). Light absorption: Maximum, 2650 A., ε = 26,000.

The *p-phenylphenacyl* ester, prepared in methanol in the usual way (10% yield), had m. p. 169—173°. After crystallisation from benzene–light petroleum (b. p. 80—100°) it formed fine needles, m. p. 174—174·5° (Found: C, 74·95; H, 5·4. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·65%).

3 : 3′-*Methylenebis*-(4-*hydroxy*-6-*methyl*-5 : 6-*dihydro*-α-*pyrone*).—The hydroxy-2-pyrone (II) (350 mg.) was dissolved in water (3 c.c.) and treated with 40% formaldehyde solution (0·15 c.c.) and a trace of piperidine. After 30 minutes at 0°, the separated product (110 mg.), m. p. 148—150°, was collected. Crystallisation from aqueous methanol and then benzene–light petroleum (b. p. 60—80°) gave the *methylene* compound of m. p. 170—172° (decomp.; variable) (Found: C, 58·25; H, 5·9. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

Ethylideneacetone.—(*a*) On hydrolysis of the 2-pyrone derivative (II) with hot 2N-sulphuric acid, ethylideneacetone was formed; it was isolated from the steam-distillate as its 2 : 4-dinitrophenylhydrazone, m. p. 158—159° (after crystallisation from ethyl acetate–methanol) undepressed on admixture with an authentic specimen.

(*b*) When heated at atmospheric pressure, (II) (100 mg.) decomposed at about 200°; a small quantity of a colourless liquid distilled, and this on treatment with 2 : 4-dinitrophenylhydrazine reagent gave the derivative of ethylideneacetone, m. p. 158—159° (after crystallisation from ethyl acetate–methanol) undepressed on admixture with an authentic specimen.

4-*Hydroxy*-3 : 6-*dimethyl*-5 : 6-*dihydro*-2-*pyrone.*—4-Hydroxy-6-methyl-5 : 6-dihydro-2-pyrone (200 mg.) was dissolved in methanol (1 c.c.); dry silver oxide (300 mg.; *ca.* 160% of theoretical) and methyl iodide (1 c.c.) were added. After 3 days at 20° the silver iodide was filtered off and the excess of methyl iodide and methanol were removed under reduced pressure, leaving a syrup which on scratching solidified partly. Trituration with benzene gave the 2-*pyrone* (42 mg.; 20%), m. p. 147—148° (slight decomp.). After crystallisation from ethyl acetate it formed plates, m. p. 148—149° (slight decomp.) (Found: C, 58·9; H, 7·35. $C_7H_{10}O_3$ requires C, 59·15; H, 7·1%). It was sparingly soluble in benzene, more readily in ethyl acetate or water. It gave a purple colour with ferric chloride and dissolved with effervescence in sodium hydrogen carbonate solution. Light absorption: Maxima, 2450 and 2490 A.; ε = 13,500.

Crotonylacetic Acid.—β-Methoxysorbic acid (400 mg.) was suspended in dry ether (10 c.c.) and cooled to 0°. Concentrated hydrochloric acid (84 mg.; *i.e.*, 4 drops from a calibrated capilliary pipette) was added and the mixture was shaken occasionally. After 2½ hours at 0° the acid had dissolved completely;

the ether was then decanted from the aqueous layer and evaporated under reduced pressure. During the latter operation the product crystallised; trituration with light petroleum gave a product (280 mg.; 80%), m. p. 61—66° (decomp.). After crystallisation from light petroleum (b. p. 60—80°) containing a little benzene the *keto-acid* was obtained as prismatic needles m. p. 68—72° (decomp.) (Found: C, 56·05; H, 5·95. $C_6H_8O_3$ requires C, 56·25; H, 6·25%). It was readily soluble in the usual organic solvents other than light petroleum, gave a deep red colour with ferric chloride, and dissolved with effervescence in sodium hydrogen carbonate solution. It lost carbon dioxide very readily on heating, but could be kept at room temperature for some weeks without decomposition.

On treatment with 2 : 4-dinitrophenylhydrazine reagent (aqueous) the derivative of ethylideneacetone was obtained, m. p. 158—159° (after crystallisation from ethyl acetate–methanol) undepressed on admixture with an authentic specimen.

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