

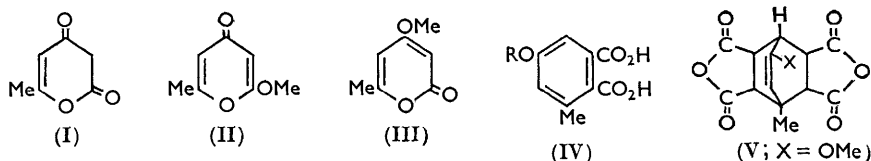
### 103. Pyrones. Part I. Methyl Ethers of Tautomeric Hydroxy-pyrones and the Structure of Yangonin.

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The formation of isomeric monomethyl ethers (II) and (III) in the methylation of the lactone (I) by diazomethane has been confirmed, and the structures have been established by chemical means; the  $\alpha$ -pyrone (III) reacts readily with dienophiles, and the  $\gamma$ -pyrone (II) shows basic properties. The formulation of the natural product yangonin as an  $\alpha$ -pyrone is established by its direct synthesis from the ether (III).

THE 4-hydroxy-2-pyrones, being tautomeric, can give rise to two series of ethers, with  $\alpha$ - and  $\gamma$ -pyrone structures severally. In connection with work on some natural products it became necessary to clarify the distinction between such pairs of compounds; the present account is concerned with the methyl ethers of the keto-lactone (I) and with certain related natural products.

Early workers described an ether, m. p. 81—82°, obtained from the lactone (I) by the action of diazomethane<sup>1</sup> or of methyl iodide on the silver salt.<sup>2</sup> More recently, Arndt and Avan<sup>3</sup> treated the lactone with diazomethane and by repeated recrystallisation raised the m. p. of the product to 86—87°. To this material they assigned the  $\gamma$ -pyrone structure (II) since when hydrogen chloride was passed into an ether solution of the compound an insoluble hydrochloride was formed; other  $\gamma$ -pyrones are known to form such derivatives, but the known  $\alpha$ -pyrones do not.



Janiszewska-Drabarek later found<sup>4</sup> that after methylation with diazomethane the crude product was a mixture of the two ethers (II) and (III), which could be separated by precipitation of the former product (II) as hydrochloride. Wiley and Jarboe,<sup>5</sup> however, were unable to confirm this and concluded that only one ether, of m. p. 89°, is formed. This did not form a hydrochloride and was assigned the  $\alpha$ -pyrone structure (III), since its infrared spectrum showed bands at 1720 and 1250  $\text{cm}^{-1}$ , believed to be characteristic of  $\alpha$ -pyrones. Notwithstanding these statements, Janiszewska-Drabarek's observations were confirmed and extended by Chmielewska *et al.*<sup>6</sup> Structure (II) was assigned to a methyl ether of m. p. 91—92°, forming a hydrochloride and having infrared absorption bands at 1672 and 1248  $\text{cm}^{-1}$  and an ultraviolet absorption maximum at 240  $\text{m}\mu$ . Structure (III) was assigned to the non-basic isomer, m. p. 89—90°, having infrared absorption bands at 1718, 1658, and 1230  $\text{cm}^{-1}$  and an ultraviolet absorption maximum at 280  $\text{m}\mu$ . Our own results with known  $\alpha$ - and  $\gamma$ -pyrones seemed to accord with these conclusions, but in view of the earlier statements it seemed desirable to have some chemical proof of the constitution of these products, if indeed more than one could be obtained.\*

\* Since this work was completed there has appeared an account by Djerassi and co-workers<sup>7</sup> of their own independent confirmation of the results of Janiszewska-Drabarek and Chmielewska, together with an extension of the spectroscopic observations.

<sup>1</sup> Tamburello, *Chem. Zentr.*, 1905, I, 348.

<sup>2</sup> Sproxton, *J.*, 1906, **89**, 1189.

<sup>3</sup> Arndt and Avan, *Chem. Ber.*, 1951, **84**, 344.

<sup>4</sup> Janiszewska-Drabarek, *Roczniki Chem.*, 1953, **27**, 456 (*Chem. Abs.*, 1955, **49**, 3176).

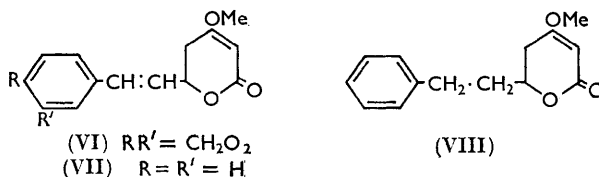
<sup>5</sup> Wiley and Jarboe, *J. Amer. Chem. Soc.*, 1956, **78**, 624.

<sup>6</sup> Chmielewska, Cieslak, and Kraczkiewicz, *Roczniki Chem.*, 1956, **30**, 1009 (*Chem. Abs.*, 1957, **51**, 8733).

<sup>7</sup> Herbst, Mors, Gottlieb, and Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 2427.

Methylation of the lactone (I) with diazomethane and treatment of the product with dry hydrogen chloride in ether gave, without any especial difficulty, both the products described by the Polish workers, though with dimethyl sulphate only the lower-melting non-basic isomer (III) was formed. The two compounds gave a mutual depression of m. p. and were distinct in fusion analysis; only the basic isomer (II) formed a picrate, of m. p. 124.5—126°.

It is known that  $\alpha$ -pyrones generally behave as dienes in the Diels–Alder reaction, frequently with ready elimination of the lactone group as carbon dioxide. Thus, since it can react in the  $\alpha$ -pyrone form, the lactone (I) behaves in this way, and gives the phthalic acid derivative (IV; R = H) when heated with diethyl acetylenedicarboxylate.<sup>8</sup> When the basic methyl ether, presumably (II), was treated similarly, little or no carbon dioxide was evolved and the starting material was recovered, but the non-basic isomer (III) readily evolved the theoretical amount of carbon dioxide under these conditions and the phthalic acid derivative (IV; R = Me) was formed. The reaction proceeds fairly cleanly and we cannot explain the failure of Wiley and Jarboe<sup>5</sup> to obtain this product. Similarly, when the ether (III) was heated with maleic anhydride, carbon dioxide was again evolved; in this case the diadduct (V) was obtained. These diene reactions, and the structure of the acid (IV; R = Me), establish beyond doubt the structure of the non-basic ether, m. p. 87.5—88.5°, as the  $\alpha$ -pyrone (III) and provide a firmer basis for comparisons using spectroscopic data.



It seems likely that in the work of Arndt and Avan, a mixture of ethers (II) and (III) was in fact obtained, from which only the former was isolated by recrystallisation. Conversely, in the experiments of Wiley and Jarboe, it is possible that the  $\gamma$ -pyrone (II) was decomposed because of the presence of water during the attempted preparation of the hydrochloride, since this isomer is relatively easily hydrolysed by acid.<sup>6</sup>

In an attempt to explain the formation of both products in the reaction of the lactone (I) with diazomethane, contrasting with the exclusive formation of the ether (III) by methylation with dimethyl sulphate and alkali, we studied the ultraviolet absorption spectrum of the lactone under various conditions in the hope of detecting its tautomeric equilibria. In a range of solvents with varying dielectric constant (water–ethanol–dioxan–hexane mixtures) and in aqueous solutions of pH 1–4, the lactone (I) shows an absorption spectrum closely similar to that of the  $\alpha$ -pyrone (III), with no sign of the presence of the tautomeric 2-hydroxy-4-pyrone. Above pH 6, when it can exist only as a single species (the derived anion), absorption maxima at 276 and 233 m $\mu$  were observed, suggesting that, in the anion, both the electronic transitions observed individually in  $\alpha$ - and  $\gamma$ -pyrones are simultaneously possible.

The unambiguous characterisation of the ethers (II) and (III) makes it possible to clear up some uncertainties regarding certain related natural products. Thus from kava resin (from *Piper methysticum*), Borsche and others<sup>9</sup> isolated a series of 6-styryl derivatives of methoxypyrones. Three of these, *viz.*, methysticin (VI), kawain (VII), and marindinin<sup>10</sup> (VIII), are 5,6-dihydropyrones, and on treatment with alkali the ring is opened without effect on the methoxyl groups; the products are  $\alpha\beta$ -unsaturated  $\beta$ -methoxy-acids, and so

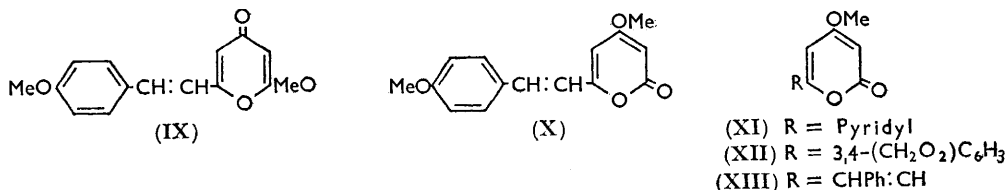
<sup>8</sup> Alder and Rickert, *Ber.*, 1937, **70**, 1363.

<sup>9</sup> Borsche and Gerhardt, *Ber.*, 1914, **47**, 2902; Borsche and Roth, *Ber.*, 1921, **54**, 2229; Borsche and Peitzsch, *Ber.*, 1930, **63**, 2414; Borsche and Bodenstein, *Ber.*, 1929, **62**, 2515.

<sup>10</sup> Van Veen, *Rec. Trav. chim.*, 1939, **58**, 521.

the compounds (VI)—(VIII) have always been formulated as hydrogenated  $\alpha$ -pyrones. Moreover, kawain has been synthesised by unambiguous routes.<sup>11</sup> However, the major constituent of kava resin, yangonin, is a true pyrone, and since on alkaline hydrolysis the methoxyl group is removed simultaneously with the ring-opening, Borsche *et al.* formulated it as a 2-methoxy-4-pyrone (IX).

The published syntheses of yangonin involve methylation as a final step and hence are not unambiguous. Thus, by treatment of the corresponding 4-hydroxy-compound (yangonolactone) with diazomethane, Chmielewska *et al.* obtained two substances, only one of which was identical with natural yangonin. This showed a peak in the infrared spectrum at  $1724\text{ cm.}^{-1}$  and was formulated as the  $\alpha$ -pyrone (X), Borsche's structure (IX) being assigned to the isomeric second product ( $\text{C}=\text{O}$  peak at  $1667\text{ cm.}^{-1}$ ). We were able to



confirm directly these spectroscopical deductions by an unambiguous synthesis of yangonin, by the reaction of the  $\alpha$ -pyrone (III) with *p*-methoxybenzaldehyde in presence of magnesium methoxide.

In the case of certain constituents of the rosewoods (*Aniba* species),<sup>12,13</sup> the situation is somewhat similar, since the three compounds (XI)—(XIII) all resemble yangonin, in

#### Ultraviolet absorption spectra of the lactone (I).

Buffer solution <sup>a</sup>	NaOAc-HCl				KH <sub>2</sub> PO <sub>4</sub> -NaOH		Na <sub>2</sub> B <sub>4</sub> O <sub>7</sub> -NaOH-KCl		
pH .....	1.1	3.3	4.2	5.2	6.1	7.4	8.0	9.0	10.0
$\lambda_{\text{max.}}$ (m $\mu$ ) .....	284	283	282	277, 230	276, 233	276, 233	276, 233	276, 233	276, 233
$\lambda_{\text{min.}}$ (m $\mu$ ) .....	240	240	245	249	249	250	249	249	250

<sup>a</sup> Vogel, "Textbook of Quantitative Inorganic Analysis," Longmans, Green and Co., London, 2nd edn., 1952, p. 868.

#### Infrared absorption spectra (carbonyl and enol-ether bands, in $\text{cm.}^{-1}$ ).

$\alpha$ -Pyrone	C=O	C-O	$\gamma$ -Pyrone	C=O	C-O
5-Aroyl- <sup>5</sup> .....	1740	1245, 1264	2,6-Dimethyl- .....	1672	Absent
6-Alkyl-4-methyl- <sup>a</sup> .....	1736	1227	6-Methyl-2-styryl- .....	1665	"
			3-Hydroxy-2-methyl- (maltol) .....	1656	"
4-Methoxy-6-methyl- (III) .....	1722, 1736	1250, 1265	2-Methoxy-6-methyl- (II) .....	1677, 1692	1260
Yangonin (X) <sup>b</sup> .....	1720	1250	Pseudoyangonin <sup>b</sup> (IX)...	1667	1258
" .....	1724	1258			
Compound (XI) <sup>12</sup> .....	1732				
Compound (XII) <sup>12</sup> .....	1738				
Compound (XIII) <sup>13</sup> .....	1724				

<sup>a</sup> Wiley and Esterle, *J. Org. Chem.*, 1957, **22**, 1257. <sup>b</sup> Chmielewska, Cieslak, Gorczynska, Kontnik, and Pitakowska, *Tetrahedron*, 1958, **4**, 36.

that ring-opening with alkali also removes the methoxyl group. The possibility that these compounds might be  $\gamma$ -pyrones does not appear to have been considered; \* however, with the structure of yangonin firmly established as (X), comparisons between the published spectroscopic data are adequate to confirm the structures originally

\* Cf. however, footnote (p. 502) and reference 7.

<sup>11</sup> Fowler and Henbest, *J.*, 1950, 3642; Kostermans, *Nature*, 1950, **166**, 788.

<sup>12</sup> Gottlieb and Mors, *J. Amer. Chem. Soc.*, 1958, **80**, 2263; Gottlieb, Mors, and Djerassi, *ibid.*, 1957, **79**, 4507.

<sup>13</sup> Gottlieb and Mors, *J. Org. Chem.*, 1959, **24**, 17.

assigned to these compounds. In general (cf. Tables), it appears that  $\alpha$ -pyrones have carbonyl bands at frequencies significantly higher than those for the corresponding  $\gamma$ -pyrones, though the absolute values are subject to some influence from the other substituents.

#### EXPERIMENTAL

*Methylation of "Triacetic Acid Lactone" with Diazomethane.*<sup>6</sup>—5-Hydroxy-3-oxohex-4-enoic acid lactone ("triacetic acid lactone")<sup>14</sup> (I) (8 g.) was added in portions with shaking to a dry solution of diazomethane (from 25 g. of *N*-nitrosomethylurea) in ether (300 ml.). Nitrogen was evolved and the solution was kept for 24 hr. at room temperature. A small quantity of sediment was filtered off, and dry hydrogen chloride passed through the solution until precipitation was complete (about 25 min.). The hydrochloride of the ether (II) (2.7 g.) was filtered off and washed with ether.

The filtrate on evaporation gave the crude methyl ether (III) (5.27 g.), which was purified by chromatography on alumina (grade "H"), with 1:1 benzene-light petroleum (b. p. 60–80°) followed by benzene as eluants, and finally recrystallised from light petroleum, giving 4-methoxy-6-methyl-2-pyrone (III) as needles, m. p. 87.5–88.5°,  $\lambda_{\text{max}}$ . 280  $\mu$ . ( $\log \epsilon$  3.81) in 95% ethanol (for infrared spectrum, see Table).

The precipitated hydrochloride was suspended in ether (30 ml.) and shaken with a slight excess of triethylamine, and the ether was decanted. Extraction of the precipitate with more ether (2  $\times$  30 ml.) followed by evaporation of the extracts gave the crude methyl ether (II) (2.0 g.) which was purified by recrystallisation from light petroleum, giving 2-methoxy-6-methyl-4-pyrone (II) as needles, m. p. 92.5–94° (Found: C, 59.9; H, 5.6. Calc. for  $\text{C}_7\text{H}_8\text{O}_3$ : C, 60.0; H, 5.8%),  $\lambda_{\text{max}}$ . 240  $\mu$ . ( $\log \epsilon$  4.17) in 95% ethanol (for infrared spectrum, see Table). The compound formed a yellow *picrate*, m. p. 124.5–126° (Found: C, 42.3; H, 3.0.  $\text{C}_{13}\text{H}_{11}\text{O}_{10}\text{N}_3$  requires C, 42.3; H, 3.0%).

A mixture of the ethers (II) and (III) melted gradually between 55° and 83° and the two were distinct on fusion analysis.

*Methylation with Dimethyl Sulphate.*—A mixture of the lactone (I) (3 g.), dimethyl sulphate (3 g.), and anhydrous potassium carbonate (10 g.) in pure ethyl methyl ketone (50 ml.) was heated under reflux, with stirring, for 15 hr., then allowed to cool, filtered, and evaporated. The solid residue (3.1 g.) was recrystallised from light petroleum (b. p. 60–80°), to give the ether (III) as pale yellow needles, m. p. 77–87°; further recrystallisation raised the m. p. to 87–88°. The mother-liquors were combined and subjected to chromatography on alumina; no fraction showing the ultraviolet absorption of the isomer (II) was detected.

*Diels-Alder Reactions of the Ether (III).*—(i) *With diethyl acetylenedicarboxylate.* A mixture of the ether (III) (2.0 g.) and diethyl acetylenedicarboxylate (3.3 g.) was heated under nitrogen for 1.5 hr. at 170–180° and a further 2 hr. at 190–200°; carbon dioxide was evolved. After cooling, the product was heated under reflux with excess of 10% sodium hydroxide solution, washed with ether, acidified with dilute hydrochloric acid, and extracted with ether (5  $\times$  40 ml.). Evaporation of the extracts gave a residue which crystallised on trituration with ether (yield 1.54 g.) and recrystallised from acetone-chloroform, giving 5-methoxy-3-methylphthalic acid (IV; R = Me), needles, m. p. 176–181° (lit.,<sup>15</sup> 184°) [Found: equiv., 102. Calc. for  $\text{C}_8\text{H}_8\text{O}(\text{CO}_2\text{H})_2$ : equiv. 105]. The acid was converted into the anhydride, m. p. 140–141° (lit.,<sup>15</sup> 139°) by heating it with acetic anhydride, and by hot dilute hydrochloric acid into 5-methoxy-3-methylbenzoic acid, m. p. and mixed m. p. (with authentic material prepared by Meldrum's method<sup>15</sup>) 132–133°.

(ii) *With maleic anhydride.* Maleic anhydride (0.5 g.) and the ether (III) (0.5 g.) were heated under reflux in toluene (5 ml.) for 10 hr.; after cooling, the adduct (8-methoxy-1-methyl-1,2-ethenocyclohexane-2,3,5,6-dicarboxylic dianhydride) (V) was filtered off (0.1 g.), recrystallised from benzene, and sublimed at 180°/0.05 mm., giving needles, m. p. 333–336° (Found: C, 57.6; H, 4.5.  $\text{C}_{14}\text{H}_{12}\text{O}_7$  requires C, 57.5; H, 4.1%). The infrared spectrum of the adduct (in Nujol mull) showed carbonyl bands at 1860, 1840, and 1790  $\text{cm}^{-1}$ .

When the methyl ether (II) (100 mg.) was heated with diethyl acetylenedicarboxylate (160 mg.), carbon dioxide was evolved only very slowly, even after 2½ hr. at 180°.

*Synthesis of Yangonin (X).*—The methyl ether (III) (500 mg.) was added to magnesium

<sup>14</sup> Collie, *J.*, 1891, **59**, 612.

<sup>15</sup> Meldrum, *J.*, 1911, **99**, 1716.

methoxide in methanol (from 200 mg. of magnesium and 10 ml. of methanol), and *p*-methoxybenzaldehyde (500 mg.) in methanol (12 ml.) was added. After 4 hours' heating under reflux, the solvent was evaporated under reduced pressure, and after acidification of the residue with dilute hydrochloric acid the product was extracted with ethyl acetate ( $3 \times 20$  ml.), washed with water ( $3 \times 15$  ml.), dried ( $\text{MgSO}_4$ ), and evaporated. The residue (850 mg.) was a mixture of a crystalline solid and a yellow oil, the latter being removed by trituration with ether. The crystals (160 mg.), m. p.  $151\text{--}154^\circ$ , had m. p.  $155\text{--}157^\circ$  after recrystallisation from methanol, and were identified as yangonin by comparison of the ultraviolet and infrared spectra with an authentic sample and by mixed m. p. ( $154\text{--}155^\circ$ ).

We are grateful to Dr. B. K. Blount for a sample of natural yangonin.

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