1,3-Dipolar Character of Six-membered Aromatic Rings. Part VIII.[1] [2]Benzopyrano[4,3-b]pyridin-6-ones

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3-Hydroxypyridine (1b), its 6-methyl analogue (1a), and 3-hydroxyquinoline (14) each react with the benzyne precursor phenylium-2-carboxylate (16) to give the [2]benzopyrano[4,3-b]pyridin-6-ones (6b), (6a), and (15).

COUMARINS [2] and isocoumarins [3] occur widely in plants, moulds, bacteria, and lichens; naturally occurring aza-analogues include the alkaloids gentianine (3,4-di-hydro-5-vinylpyrano[3,4-c]pyridin-1-one) [4] and homolycorine.[5] Investigations of the 1,3-dipolar reactivity of six-membered aromatic ring betaines [6] and bases with benzyne,[7] disclosed a new one-step route to the novel isocoumarin-based ring system (6). The nearest known analogues are pyrano[3,2-f]quinolin-3-one (7) [8] and the related bicyclic compounds (8) [9] and (9).[10]

3-Hydroxy-6-methylpyridine (1a) with anthranilic

acid and n-pentyl nitrite gave the benzopyranopyridin-one (6a),† m.p. 138—139°, which readily formed a hydrochloride. The i.r. spectrum showed $\nu_{C=O}$ at 1725 cm^{-1}, consistent with an $\alpha\beta$-unsaturated δ-lactone and the u.v. spectrum corresponded to a system with considerable conjugation. Structure (6a) is supported by the low-resolution mass spectrum (Scheme 2). The base peak at m/e 211 is the molecular ion (10a) and prominent fragments correspond to successive loss of carbon monoxide (m/e 183; 56·0%) (11a) and a hydrogen atom

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† Although (6) is the only product isolated under the conditions specified, t.l.c. shows the presence of a cycloadduct. Modification of the reaction conditions can cause the cycloadduct to become the major product.

[1] Part VII, N. Dennis, A. R. Katritzky, T. Matsuo, S. K. Parton, and Y. Takeuchi, preceding paper.
[2] (a) S. M. Sethna and N. M. Shah, *Chem. Rev.*, 1945, **36**, 1; (b) S. Wawzonek in ' Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York, vol. 2, 1951, p. 173.
[3] R. D. Barry, *Chem. Rev.*, 1964, **64**, 229; ref. 2b, p. 217.
[4] T. R. Govindachari, K. Nagarajan, and S. Rajappa, *Chem. and Ind.*, 1956, 1017.
[5] T. Kitagawa, W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 1955, 1066.
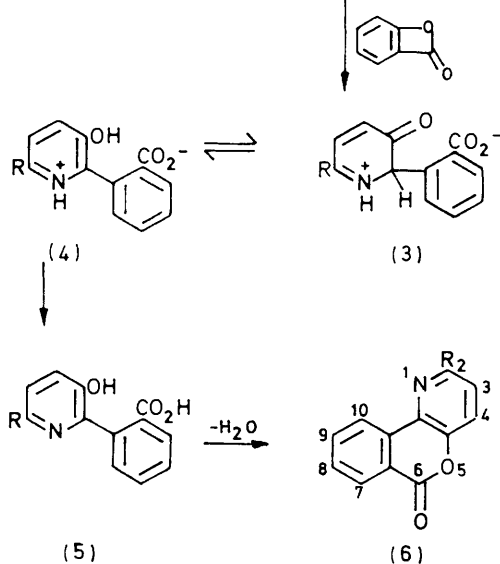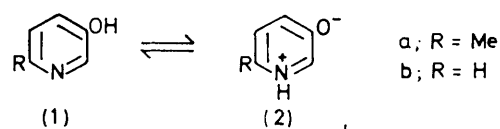[6] N. Dennis, A. R. Katritzky, and Y. Takeuchi, *J.C.S. Perkin I*, 1972, 2054.
[7] N. Dennis, A. R. Katritzky, and S. K. Parton, *J.C.S. Chem. Comm.*, 1972, 1237; N. Dennis, A. R. Katritzky, S. K. Parton, and Y. Takeuchi, *ibid.*, p. 707.
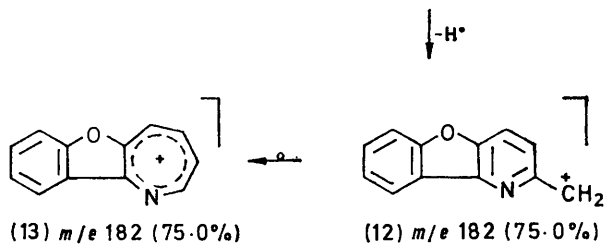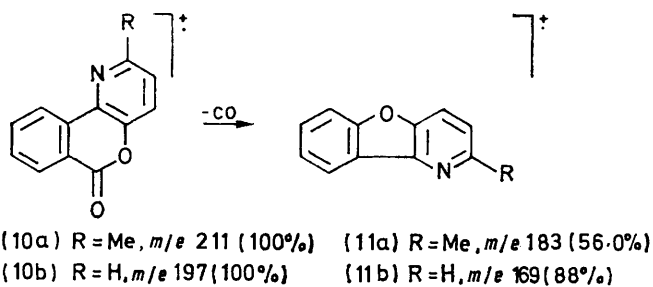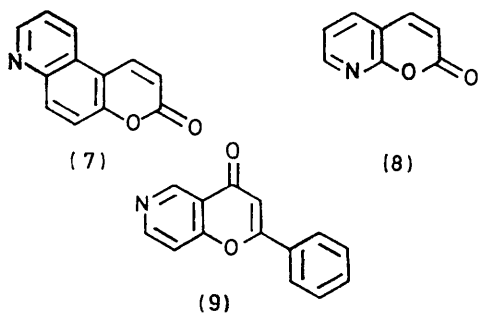[8] K. J. Liska, A. F. Fentiman, jun., and R. L. Foltz, *Tetrahedron Letters*, 1970, 4657.
[9] D. Bonnetaud, G. Queguiner, and P. Pastour, *J. Heterocyclic Chem.*, 1972, **9**, 165.
[10] G. Lhommet, H. Sliwa, and P. Maitte, *Bull. Soc. chim. France*, 1972, 1435.

(m/e 182; 75·0%) (12) or (13) (cf. ref. 11). The fission (10a) ⟶ (11a) was confirmed by the metastable

(1)   (2)   a; R = Me
              b; R = H

(4)   (3)

(5)   (6)

SCHEME 1

(7)   (8)

(9)

(10a) R = Me, m/e 211 (100%)   (11a) R = Me, m/e 183 (56·0%)
(10b) R = H, m/e 197 (100%)   (11b) R = H, m/e 169 (88%)

(13) m/e 182 (75·0%)   (12) m/e 182 (75·0%)

SCHEME 2

peak (m/e 158·7) due to the transition $211^+ \longrightarrow 183^+ + 28$. Smaller fragment ions occurred at m/e 155 (15·9%) and 127 (16·9%), which correspond to the loss of hydrogen cyanide[12] and carbon monoxide, respectively. The most abundant ion (m/e 118) in the mass spectrum of coumarin[13] corresponds to the loss of carbon monoxide.

The n.m.r. assignments (Table) for the product (6a) are supported by double-irradiation experiments. Irradiation at the frequency corresponding to H-7 caused

Proton n.m.r. spectra of benzopyranopyridinones [a]

	Compound		
δ	(6a) [b]	(6b) [b]	(15) *
2		8·64 [c]	
3	7·30 [d]	7·46 [c]	
4	7·58 [d]	7·70 [c]	8·02 [d]
7	8·76 [e]	8·72 [e]	8·94 [e]
8	7·70 [f]	7·74 [f]	7·74 [f]
9	7·86 [f]	7·95 [f]	7·96 [f]
10	8·41 [e]	8·42 [e]	8·43 [e]
11			8·22 [g]
2-Me	2·71		
J	(6a) [b]	(6b) [b]	(15) *
2,3		4·50	
2,4		1·50	
3,4	8·50	8·50	
7,8	8·00	8·00	8·00
7,9	1·50	1·50	1·50
7,10	1·00	1·00	1·00
8,9	7·50	7·50	7·50
8,10	1·50	1·50	1·50
9,10	7·75	7·75	7·75

* Numbered to correspond with (6a and b); see illustrated formula.

[a] In p.p.m. relative to internal Me$_4$Si; coupling constants in Hz. [b] In CCl$_4$. [c] Quartet. [d] Doublet. [e] Doublet of quartets. [f] Triplet of doublets. [g] Complex.

the sextets due to H-8 and H-9 to collapse to quartets. Similarly, irradiation at the frequency of H-10 again changed the sextets of H-9 and H-8 to quartets. Irradiation at the frequency of H-8 caused the eight peaks due to H-7 to collapse to a quartet, and irradiation at the frequency of H-9 similarly changed the H-10 signal. Signals for H-8 and H-9 are too close together for mutual decoupling to be observed, as was the case with the signals for the pyridine ring protons.

3-Hydroxypyridine (1b) similarly gave the benzopyranopyridinone (6b),† with similar i.r. and u.v. spectral features. The low-resolution mass spectrum (Scheme 2) of compound (6b) shows the molecular ion as the base peak at m/e 197. The major ion at m/e 169 (87·5%) (11b) corresponds to loss of carbon monoxide. A smaller fragment (m/e 140; 25%) corresponds to further loss of an HCO radical.

The n.m.r. assignments for (6b) (Table) are supported by decoupling experiments. For the pyridine ring, irradiation in turn at the frequencies of H-2,

† Footnote as on page 750.

[11] W. G. Cole, D. H. Williams, and A. N. H. Yeo, J. Chem. Soc. (B), 1968, 1284.
[12] R. E. Deck and S. S. Chang, Chem. and Ind., 1965, 1343.
[13] C. S. Barnes and J. L. Occolowitz, Austral. J. Chem., 1964, 17, 975.

H-3, and H-4 caused the quartets due to the other two protons in this group to collapse to doublets. In the case of the benzene ring protons, irradiation in turn at the frequencies of H-10 and H-7 in each case caused the sextets due to H-9 and H-8 to collapse to quartets. The H-9 and H-8 signals were too close to each other for direct decoupling.

Further support for the n.m.r. assignments for (6b) was obtained by the use of the lanthanide shift reagent, tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium(III) [Eu(fod)₃],[14,15] which changed the n.m.r. spectrum to a first-order system. Signals for five of the protons were resolved into quartets, and those for the other two were resolved into sextets. The graph
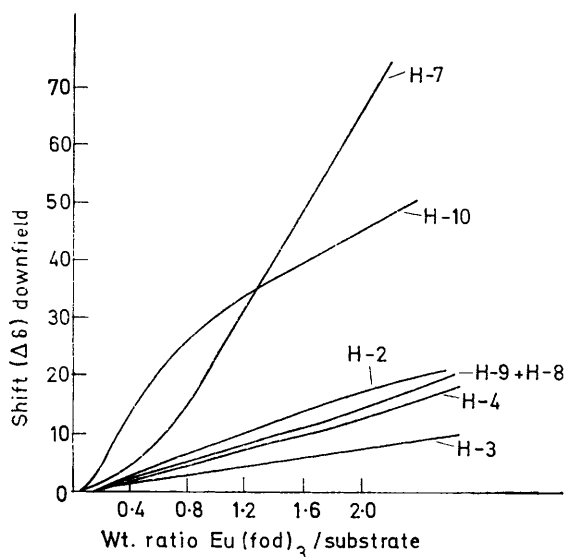

FIGURE 1   Graph of $\Delta\delta$ vs. wt. ratio of Eu(fod)₃ to substrate for the benzopyranopyridine (6b)

of downfield shift vs. weight ratio of Eu(fod)₃ to substrate (Figure 1) indicates that the shift reagent initially forms a pseudocomplex preferentially with the nitrogen atom rather than with the carbonyl system: H-10 is influenced to the greatest extent, H-7 somewhat less, and H-2, H-9, H-8, H-4, and H-3 successively less. However, with increasing concentration of Eu(fod)₃, the sites on the nitrogen atom became increasingly saturated and the curve for H-10 begins to level off. Proton 7 then becomes increasingly sensitive, implying a significant complexation of the carbonyl site. Liska, Fentiman, and Foltz [8] found that pyrano[3,2-f]quinolin-3-one formed a pseudo-complex with tris(dipivaloylmethanato)europium(III) [Eu(dpm)₃] to a greater extent at the nitrogen atom than at the coumarin carbonyl system.

Chemical proof for structure (6b) was obtained by reductive decarboxylation with zinc and soda-lime to give 2-phenylpyridine.

[14] R. von Ammon and R. D. Fischer, Angew. Chem. Internat. Edn., 1972, 11, 675.
[15] R. E. Rondeau and R. E. Sievers, J. Amer. Chem. Soc., 1971, 93, 1522.

3-Hydroxyquinoline (14) reacted to give the benzopyranoquinolinone (15) in low yield. The low-resolution mass spectrum of compound (15) shows the molecular ion as the base peak at m/e 247. The major

(14)   (15)
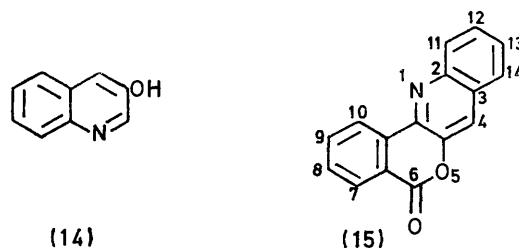
ion at m/e 219 (98%) corresponds to the loss of carbon monoxide and the prominent fragment at m/e 190 (90%) to further loss of an HCO radical. The transition $247^+ \longrightarrow {}^+219^+ + 28$ was confirmed by a metastable peak (m/e 194·17). The n.m.r. assignments for (15) (Table) are supported by decoupling experiments. For the benzene ring protons, irradiation in turn at the frequencies of H-10 and H-7 in each case caused the sextets due to H-9 and H-8 to collapse to quartets. Again the H-9 and H-8 signals were too close for direct decoupling. The assignments were further confirmed by the use of Eu(fod)₃, which changed the n.m.r. spectrum to a first-order system. Signals for three of the protons were resolved into quartets and those for two others into sextets. Again the graph of downfield shift vs. weight ratio of Eu(fod)₃ to substrate (Figure 2) indicates that the shift reagent forms a pseudo-complex preferentially with the nitrogen atom.
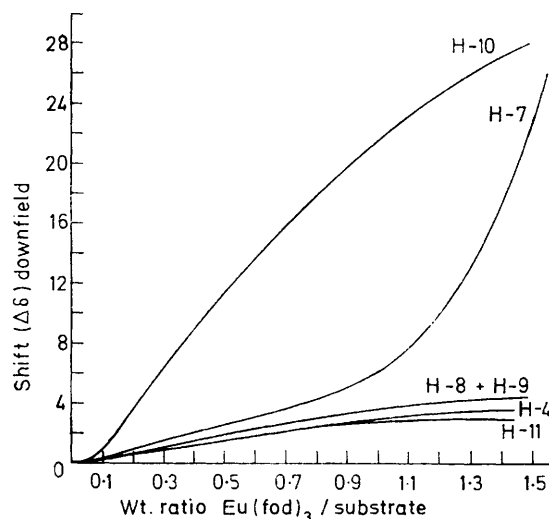

FIGURE 2   Graph of $\Delta\delta$ vs. wt. ratio of Eu(fod)₃ to substrate for the benzopyranoquinoline (15)

The generation of benzyne by diazotisation of anthranilic acid with an alkyl nitrite in an aprotic solvent has been described by Freidman and Logullo.[16] The benzyne

[16] L. Friedman and F. M. Logullo, J. Amer. Chem. Soc., 1963, 85, 1549.

precursor [17] (16) has been postulated [18] as an intermediate in the aqueous decomposition of diazotised anthranilic [^{18}O]acid. The intermediate (16) is in equilibrium with the β-lactone (17), and (16) has also been trapped with various reagents including cyclohexyl isocyanide,[19] nickel tetracarbonyl,[20] dimethylformamide,[21] and recently acetone [22] and thiobenzophenone.[23] Dibenzopyranone, a hypothetical product of addition of benzyne to the benzyne precursor (16), has not been observed [24] although in one case, a 30% yield of xanthone was reported.[25] This was attributed to the reaction of benzyne with the keten (18) in equilibrium with the benzyne precursor (16) and with the β-lactone (17). In this present work, we have successfully trapped the benzyne precursor (16) with 3-hydroxy-6-methylpyridine, 3-hydroxypyridine, and 3-hydroxy-quinoline to yield benzopyranopyridinones in preparatively useful yields.

(16)   (17)

(18)   (19)   (20)
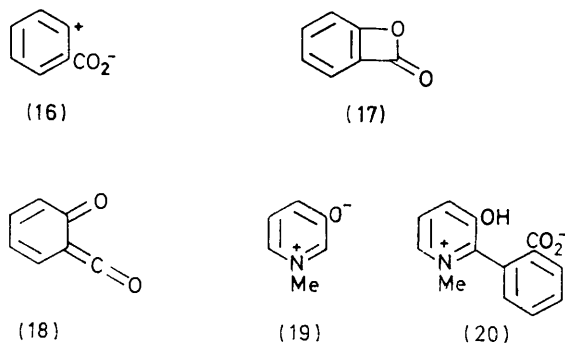
3-Hydroxypyridine is in equilibrium with the betaine (2b),[26] which is attacked by the benzyne precursor (16) at C-2, leading via the betaines (3b) and (4b) to the phenolic carboxylic acid (5b). Dehydration, under the reaction conditions, leads to the product (6b) (Scheme 1). Support for the intermediacy of a species of the type (4b) is provided by the reaction of 1-methyl-3-oxidopyridinium (19) [27] with the established [28] benzyne precursor 1-(2-carboxyphenyl)-3,3-dimethyltriazene to produce the betaine (20), which was isolated and characterised.[29] Similarly the reaction of the methyl betaine (19) with benzenediazonium-2-carboxylate [30] also gave the carboxylic betaine (20), in good yield. The N-methylbetaine (20) cannot undergo ring closure by dehydration.

The scope of this investigation is being extended to include amino- and thio-derivatives of pyridine and quinoline.

[17] R. Gompper, G. Seybold, and B. Schmolke, Angew. Chem. Internat. Edn., 1968, 7, 389.
[18] M. Stiles and H. Huisman, personal communication in R. W. Hoffmann, ' Dehydrobenzene and Cycloalkynes,' in the series ' Organic Chemistry,' ed. A. T. Blomquist, Academic Press, New York, 1967, vol. 11, p. 76.
[19] R. Knorr, Chem. Ber., 1965, 98, 4038.
[20] S. Yaroslavsky, Chem. and Ind., 1965, 765.
[21] S. Yaroslavsky, Tetrahedron Letters, 1965, 1503.
[22] G. P. Chiusoli and C. Venturello, Chem. Comm., 1969, 771.
[23] D. C. Dittmer and E. S. Whitman, J. Org. Chem., 1969, 34, 2004.
[24] M. Stiles and L. Friedman, personal communications in ref. 18, p. 238.

M.p.s were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer 257 grating spectrophotometer, a Unicam SP 800A spectrophotometer, a Hitachi–Perkin-Elmer RMU-6E mass spectrometer, and a Varian HA-100 MHz n.m.r. spectrometer. Compounds were purified until they were observed as single spots on t.l.c. [Kieselgel PF254; benzene–ethanol (80 : 20)]. G.l.c. was performed on a Perkin-Elmer F11 gas chromatograph with a flame-ionisation detector, using stainless steel columns [2 m × ⅛ in; 15% Carbowax (80—100 mesh; Chromosorb W support) or 15% Apiezon L (80—100 mesh; Chromosorb P support) packing at 220° oven temperature].

2-Methyl [2]benzopyrano[4,3-b]pyridin-6-one (6a).— 3-Hydroxy-6-methylpyridine (9·0 g, 0·081 mol), n-pentyl nitrite (8 ml + 3 × 10 ml) and 1,2-dichloroethane (100 ml) were heated to reflux (76°) with stirring. Anthranilic acid (14 g, 0·102 mol) in bis-(2-methoxyethyl) ether (20 ml) was added dropwise during 1 h. After a further 3 h under reflux, the cooled mixture was extracted with chloroform (3 × 60 ml) and the organic layer was washed with water (3 × 15 ml), dried (Na$_2$SO$_4$), and evaporated at 0·5 mmHg. The brown residue, on preparative thick-layer chromatography (Kieselgel PF254) with benzene-ethanol (80 : 20), gave the benzopyranopyridine (6a), which crystallised from light petroleum (b.p. 60—80°) as prisms (2·8 g, 29%), m.p. 138—139° (Found: C, 73·7; H, 4·4; N, 6·5. C$_{13}$H$_9$NO$_2$ requires C, 73·9; H, 4·3; N, 6·6%); ν_{max} (Nujol) 3106 (CH), 1725 (six-membered lactone C=O), 1600 (C=C), 1240 (C–O–C), and 890—690 cm^{-1}; λ_{max} (EtOH) 318·5 (ε 6800), 301·0 (6300), 248·0 (5000), and 225·0 (18,300) nm; m/e 211.

[2]Benzopyrano[4,3-b]pyridin-6-one (6b).—3-Hydroxy-pyridine (9·0 g, 0·094 mol) was treated as above. Water (100 ml) was added to the cooled mixture, and the product was extracted into chloroform (3 × 60 ml). The organic layer was dried (Na$_2$SO$_4$) and evaporated at 0·5 mmHg. The brown residue was purified by preparative thick-layer chromatography (Kieselgel PF254) with benzene-ethanol (80 : 20) to yield the benzopyranopyridine (6b), which crystallised from light petroleum (b.p. 60—80°) as prismatic needles (2·5 g, 23%), m.p. 133—134° (Found: C, 72·8; H, 3·8; N, 7·1. C$_{12}$H$_7$NO$_2$ requires C, 73·0; H, 3·6; N, 7·1%); ν_{max} (Nujol) 3106 (CH), 1725 (six-membered lactone C=O), 1600 (C=C), 1240 (C–O–C), and 890—690 cm^{-1}; λ_{max} (EtOH) 313·0 (ε 9850), 297·5 (9850), and 222·0 (30,200) nm; m/e 197.

Conversion of the Benzopyranopyridine (6b) into 2-Phenyl-pyridine.—An intimate mixture of the benzopyrano-pyridine (30 mg, 1·5 × 10^{-4} mol) and zinc–soda lime (2 g; 1 : 1) (made from freshly activated zinc dust) was heated gently at first and then more strongly in a hard-glass test-tube. The distillate was collected as a pale

[25] F. M. Beringer and S. J. Huang, J. Org. Chem., 1964, 29, 445.
[26] R. Kuhn and G. Wendt, Ber., 1939, 72, 305; D. A. Prins, Rec. Trav. chim., 1957, 76, 58; A. Albert and J. N. Phillips, J. Chem. Soc., 1956, 1294.
[27] A. R. Katritzky and Y. Takeuchi, J. Chem. Soc. (C), 1971, 874.
[28] J. Nakayama, O. Simamura, and M. Yoshida, Chem. Comm., 1970, 1222.
[29] Y. Takeuchi, N. Dennis, A. R. Katritzky, and I. Taulov, 3rd Internat. Congress of Heterocyclic Chemistry, Sendai, Japan, 1971.
[30] M. Stiles and R. G. Miller, J. Amer. Chem. Soc., 1960, 82, 3802.

yellow liquid, b.p. 139° at 12 mmHg (lit.,[31] 146° at 15 mmHg); g.l.c. retention time 27·2 (Apiezon) or 13·65 min Carbowax); m/e 155; picrate, m.p. 174° (lit.,[32] 175—176°).

[2]*Benzopyrano*[4,3-*b*]*quinolin-5-one* (15).—3-Hydroxy-quinoline[33] (6 g, 0·041 mol) was treated as for 3-hydroxy-pyridine. Water (50 ml) was added to the cooled mixture. Extraction with chloroform (3 × 30 ml) and the usual work-up gave a brown residue which was purified by thick-layer chromatography (Kieselgel PF254) with benzene-ethanol (80 : 20) to yield the *product* (15), which crystallised from ethanol as white prismatic needles (2·2 g, 20%),

m.p. 229—231° (Found: C, 77·6; H, 3·8; N, 5·5. $C_{16}H_9NO_2$ requires C, 77·7; H, 3·7; N, 5·7%); $\nu_{max.}$ (CHBr$_3$) 1725 (six-membered lactone C=O), 1605 (C=C), 1595, and 1250 (C-O-C) cm^{-1}; $\lambda_{max.}$ (EtOH) 355·5 (ε 4400), 343·5 (5200), 328 (4700), 265 (15,000), 256 (12,900), 242 (14,100), 225·5 (13,200), and 208 (13,800) nm; m/e 247.

[31] C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, *J. Amer. Chem. Soc.*, 1957, **79**, 6340.

[32] J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 1940, 349.

[33] W. H. Mills and W. H. Watson, *J. Chem. Soc.*, 1910, **97**, 753.