

7-Methyl[1]benzopyrano[4,3-d][1]benzoxacino[4,3-b]pyridine-6,16-dione

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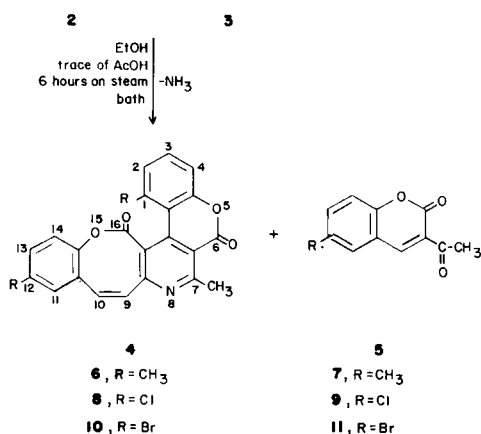
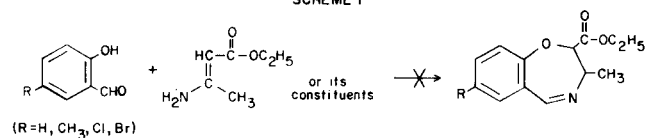
Received April 13, 1980

When equimolar quantities of salicylaldehyde **2** and ethyl 3-amino-2-butenate **3** or its constituents (ethyl 3-oxobutanoate and ammonia) were refluxed on a steam-bath for 6 hours with a trace of acetic acid, two products, a pentacyclic pyridine dilactone **4** and 3-acetyl coumarin **5**, resulted in 15% and 45% yields, respectively. The structure of **4** was elucidated as 7-methyl[1]benzopyrano[4,3-d][1]benzoxacino[4,3-b]pyridine-6,16-dione on the basis of its spectral data. The mechanism of its formation has been discussed. The reaction has been extended to three more substituted salicylaldehydes.

J. Heterocyclic Chem., **17**, 1737 (1980).

In one of our unsuccessful attempts to develop a novel route for the synthesis of 1,4-benzoxazepines **1** (Scheme 1) we investigated the reaction of salicylaldehyde **2** with ethyl 3-amino-2-butenate **3**. Compound **3** was chosen because

SCHEME 1



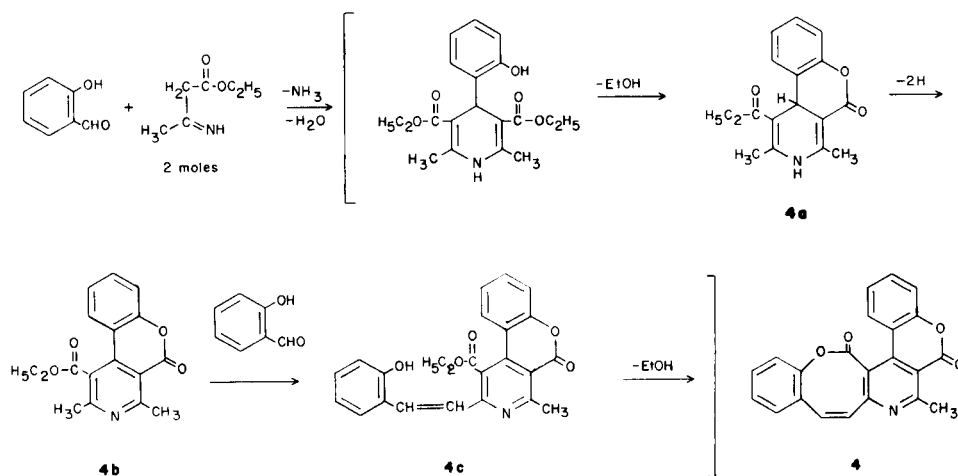
of its multiple functional nature in possessing amino, methyl and carboxy groups. It has also been used as a source of the N-C-C moiety during the construction of 5- and 6-membered aza-heterocycles as in the Nenitzescu reaction (1,2) and in the Hantzsch (3) dihydropyridine synthesis. The possibility also existed that **3** could merely function as a potential source of ethyl 3-oxobutanoate. When **3** was treated with salicylaldehyde in ethanol with a trace of acetic acid on a steam-bath for 6 hours, the elimination of ammonia was observed and two products resulted, a nitrogen containing a nitrogen-free product. The crystalline, pale yellow, highly-insoluble nitrogen containing compound **4**, m.p. 298°, separated out first in 15% yield. After **4** and excess of ethanol were removed, the sticky reddish residue was triturated with petroleum-ether (40-60) to give a nitrogen-free product **5**, m.p. 124°, in 45% yield. Compound **5** was identified as 3-acetyl coumarin by comparison with an authentic sample of 3-acetyl coumarin. The reported method (4,5) for the synthesis of 3-acetyl coumarin is by heating equimolar quantities of salicylaldehyde and ethyl 3-oxobutanoate in ethanol with a trace of pyridine or piperidine.

The formation of **4** (Scheme 2) can be rationalised by in-

Table I

Compound No.	R	M.p. °C	Yield %	Recrystallization Solvent	Molecular Formula	Analysis %			
						Calcd.	Found	N	
4	H	298	15	Methanol	C ₂₂ H ₁₃ NO ₄	Calcd.	74.36	3.66	3.99
						Found	74.32	3.65	3.98
6	CH ₃	284	12	Methanol	C ₂₄ H ₁₇ NO ₄	Calcd.	75.19	4.44	3.66
						Found	75.18	4.42	3.65
8	Cl	300	12	Methanol	C ₂₂ H ₁₁ Cl ₂ NO ₄	Calcd.	62.28	2.59	3.30
						Found	62.30	2.58	3.30
10	Br	>300	15	Methanol	C ₂₂ H ₁₁ Br ₂ NO ₄	Calcd.	51.48	2.14	2.73
						Found	51.42	2.13	2.72
7	CH ₃	121	45	Benzene	C ₁₂ H ₁₀ O ₃	Calcd.	71.28	4.95	—
						Found	71.24	4.92	—

SCHEME 2

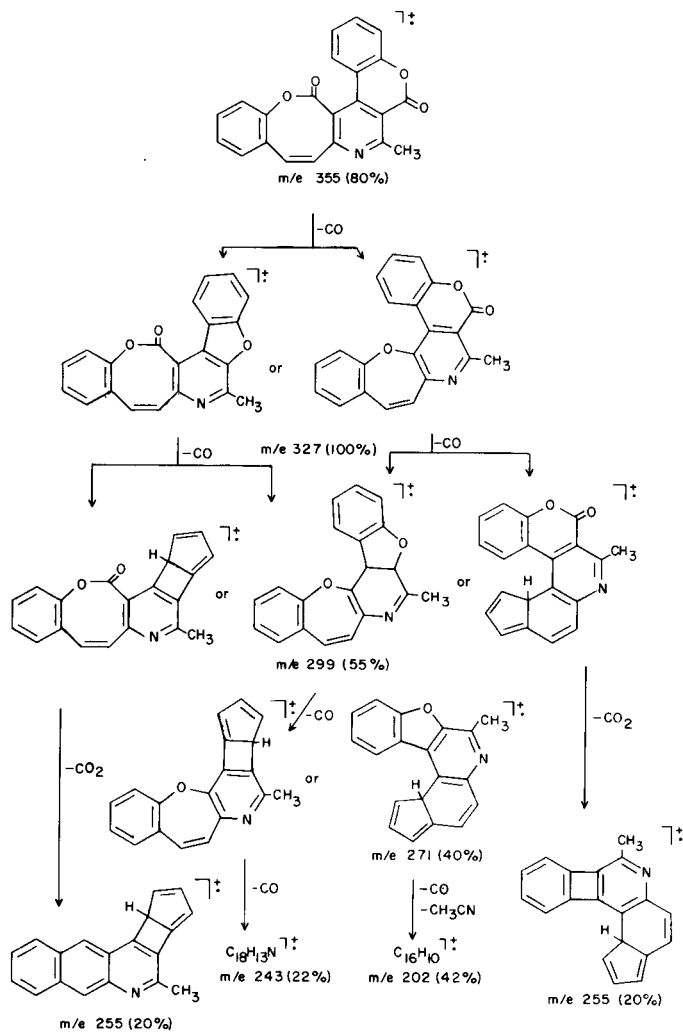


voking its similarity to reactions involving aldehyde with **3**, such as the well-known Hantzsch dihydropyridine synthesis (3). The absence of phenolic-OH and ester carbonyl in the ir spectrum of the final product suggested the formation of a δ -lactone through interaction of phenolic-OH and the ester groups with elimination of ethanol to give **4a** followed by aromatisation to **4b**. One of the α -methyl groups in **4b** then condenses with salicylaldehyde to give a styryl derivative, **4c** which is the precursor of **4**. Attempts at isolation of the postulated or other intermediates were of no avail. Thus, **4** arising by the reaction of two moles of ethyl 3-amino-2-butenoate with two moles of salicylaldehyde with elimination of a mole of ammonia, hydrogen and two moles of ethanol is 7-methyl[1]benzopyrano[4,3-*d*][1]benzoxacino[4,3-*b*]pyridine-6,16-dione. Such a reaction did not proceed with *o*-hydroxyacetophenones or benzophenones. The reaction has been extended to three more substituted salicylaldehydes to give the corresponding pentacyclic pyridine dilactones **6**, **8** and **10**, and substituted 3-acetyl coumarins **7**, **9** and **11**. Excepting 6-methyl-3-acetyl coumarin **7**, the other 3-acetyl coumarins **5**, **9** and **11** obtained during this reaction have already been reported (4,5). Hence, only the pentacyclic pyridine dilactones **6**, **8**, **10** and the unreported 3-acetyl coumarin **7** are given in Table 1.

Two questions arose in this connection. Could the same product be obtained by the use of the constituents of ethyl 3-amino-2-butenoate (ammonia and ethyl-3-oxobutanoate) and could the yield of the dilactone be increased by increasing the stoichiometric proportions? We found that the same compound was obtained by refluxing equimolar proportions of ethyl 3-oxobutanoate, ammonia and salicylaldehyde together in ethanol with a trace of acetic acid for 6 hours in about the same yield. However, an increase in time or temperature or an increase in any one of the reactants was of little avail in increasing the yields.

An interesting feature about the formation of the dilactone **4** is that in spite of the many references concerning

SCHEME 3



the use of ethyl 3-oxobutanoate and salicylaldehyde and ammonia in the synthesis of 3-acetyl coumarin or substituted dihydropyridines of the Hantzsch type, this is the first instance of the formation of an oxacine ring under these conditions.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The uv spectra were obtained on a Beckmann DB spectrophotometer. The ir spectra were recorded on a Perkin-Elmer Model 337 instrument. The nmr spectra were attempted on a Varian T-60 spectrometer. Mass spectra were run on a Perkin-Elmer Hitachi instrument at 70 eV.

Reaction of Salicylaldehyde with Ethyl 3-Amino-2-butenate.

To 2.4 g. (0.02 mole) of salicylaldehyde **2** in 25 ml. of ethanol was added 2.6 g. (0.02 mole) of ethyl 3-amino-2-butenate **3**. The reaction mixture was refluxed for 6 hours on a steam-bath with a trace of acetic acid. A pale yellow crystalline solid (0.53 g., 15%) **4** separated out and was filtered and washed with ethanol and recrystallised with difficulty from a large excess of methanol, m.p. 298°; uv (methanol): δ max nm (log ϵ) 244 (3.47), 278 (3.43) and 317 (3.21); ir (nujol): ν max cm^{-1} 1710, 1700 (split carbonyl), 1600, 1580, 1140, 1120, 1050, 955 (*trans*-olefinic hydrogens), 750, 670 and 610; nmr could not be recorded on account of its poor solubility even in DMSO- d_6 or TFA; ms: m/e 355 (M^+ , 80%), 327 (100), 299 (55), 271 (40), 255 (20), 243 (22), 241 (20), 229 (20), 202 (42), 189 (50), 149 (6.5), 89 (11.2), 88 (6) and 28 (100).

The mass spectrum of **4** (Scheme 3) showed the consecutive loss of two 28 units as CO, indicating the presence of four oxygen atoms or a dilactone system; ms: m/e 355 (M^+) 327 (M^+ - CO), 299 (M^+ - 2 CO).

After separating **4**, the excess of ethanol was removed under reduced

pressure, leaving behind a sticky red residue which after trituration with petroleum-ether (40-60) gave 2 g. (45%) of a pale yellow compound **5**, recrystallised from benzene, m.p. 124°; ir (chloroform) showed the absence of phenolic OH but the presence of a dicarbonyl group. Elemental analysis indicated the absence of nitrogen. Mixture m.p. and the superimposable ir spectrum with an authentic sample of 3-acetyl coumarin (**4**) confirmed the structure of **5** as 3-acetyl coumarin.

In a similar manner, other substituted salicylaldehydes afforded the corresponding pyridine dilactones **6**, **8**, **10** and 3 acetyl coumarins **7**, **9** and **11**. Data regarding the pentacyclic pyridine dilactones and the unreported 6-methyl-3-acetyl coumarin **7** are given in Table 1.

Reaction of Salicylaldehyde with Ethyl 3-Oxobutanoate and Ammonia.

To 2.4 g. (0.02 mole) of salicylaldehyde **2** in ethanol was added 2.6 g. (0.02 mole) of ethyl 3-oxobutanoate and 2.0 ml. of ammonia (d_4^{20} 0.91, 24%) and the reaction mixture was refluxed for 6 hours on a steam-bath with a trace of acetic acid. At the end of this period a pale yellow crystalline solid (0.5 g.), which had separated was filtered, washed with ethanol and recrystallised with difficulty from a large excess of methanol. Mixture m.p. with **4** was undepressed. After separating **4**, the excess of ethanol was removed under reduced pressure leaving behind a sticky residue which was trituated with petroleum ether (40-60) to give **5**.

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