Experimental Section[15]

Spectral Tests.—Assay of the composition of test reaction mixtures was based on the integration of the methyl signals of the isoxazolium salts *vs.* those of the isoxazole at 10–20 cps higher field. Wherever possible integration data for other strong signals was checked against these results. Tests of the preparation of the isoxazolium salts in nitromethane (spectral quality) were conducted with approximately 0.5 *M* concentrations of each reactant, as were hydrolysis tests. With **10**, **11**, and **12** the hydrolysis results were also checked with 0.25 *M* solutions of the isoxazolium salt in nitromethane about 1.1 *M* in water.

N-Benzyl-3,5-dimethylisoxazolium Perchlorate (9).—After 10 months the benzyl alcohol spectral test reaction mixture (45% complete by nmr assay) gave 29% of **9** as a gummy solid on dilution with acetone and ether. The pure salt, mp 120–122°, was obtained after several precipitations. The nmr spectrum consisted of signals at τ 7.43 (s, 3.1), 7.30 (s, 3.0), 4.28 (s, 1.9), 3.15 (s, 1.0), and 2.61 (s, 5.0). The ultraviolet spectrum showed absorption at $\lambda_{max}^{H_2O}$ 232 mμ (ϵ 9200) and showed no significant change after 3 days.

Anal. Calcd for $C_{12}H_{14}ClNO_5$: C, 50.09; H, 4.91; Cl, 12.31; N, 4.87; O, 27.81. Found: C, 50.23; H, 4.98; Cl, 12.34; N, 5.02; O, 27.74.

N-*t*-Butyl-3,5-dimethylisoxazolium Perchlorate (10).—The standard procedure for the preparation of the isoxazolium salts is to add the alcohol (10% excess) and then 70% perchloric acid (10% excess) to the isoxazole slowly with stirring at 0°. On a 50-mmol scale, *t*-butyl alcohol gave 60% of **10** after 2 days upon dilution with acetone followed by a large volume of ether. One precipitation from acetone with ether provided 57% of the pure compound, mp 118–120° dec. The nmr spectrum consisted of signals at τ 8.17 (s, 9.2), 7.38 (broad, 2.9), 7.22 (s, 2.9), and 3.26 (broad, 1.0). The ultraviolet spectrum had an absorption at $\lambda_{max}^{H_2O}$ 231 mμ (ϵ 9100) and showed no change within 1 hr.

Anal. Calcd for $C_9H_{16}ClNO_5$: C, 42.61; H, 6.36; Cl, 13.98; N, 5.52; O, 31.54. Found: C, 42.55; H, 6.28; Cl, 13.88; N, 5.50; O, 31.44.

N-α-Methylbenzyl-3,5-dimethylisoxazolium Perchlorate (11).—The standard procedure with α-methylbenzyl alcohol resulted in a cloudy mixture which partially solidified when stirred overnight. Dilution with acetone and ether the following day gave an 86% yield of **11**. One precipitation provided 82% of the pure compound, mp 83.5–84.5°. The nmr spectrum consists of signals at τ 7.95 (d, J = 7 Hz, 3.1), 7.36 (s, 5.9); 3.90 (m, J = 7 Hz, 0.9), 3.18 (s, 0.9), and 2.68 (s, 5.1).

Anal. Calcd for $C_{13}H_{16}ClNO_5$: C, 51.75; H, 5.35; Cl, 11.75; N, 4.64; O, 26.51. Found: C, 51.76; H, 5.27; Cl, 11.61; N, 4.66; O, 26.72.

N-α,α-Dimethylbenzyl-3,5-dimethylisoxazolium Perchlorate (12).—With α,α-dimethylbenzyl alcohol the standard procedure gave a cloudy mixture which solidified when stirred. After 2 days addition of 1:1 acetone–nitromethane rapidly followed by ether gave 54% of **12**. One precipitation provided 49% of the pure compound, mp 82–83°. The major nmr signals attributable to **12** in a freshly prepared solution were τ 7.93 (s, 3), 7.85 (s, 6), 7.25 (s, 3), 3.16 (s, 1), and 2.56 (s, 5). The abnormally high-field (τ 7.93) methyl singlet is assigned to the 3 substituent, shielded by the benzene ring of the quaternizing group.

Anal. Calcd for $C_{14}H_{18}ClNO_5$: C, 53.25; H, 5.75; Cl, 11.23; N, 4.44; O, 25.34. Found: C, 53.45; H, 5.73; Cl, 11.10; N, 4.53; O, 25.54.

N-Benzhydryl-3,5-dimethylisoxazolium Perchlorate (13).—The standard procedure with enough nitromethane to bring the benzhydrol into solution gave a mixture which partially solidified on standing overnight, and dilution with nitromethane and ether gave 70% of **13**. Precipitation gave 63% of the pure compound, mp 160° dec.

Anal. Calcd for $C_{18}H_{18}ClNO_5$: C, 59.42; H, 4.99; Cl, 9.75; N, 3.85; O, 21.99. Found: C, 59.17; H, 5.22; Cl, 9.76; N, 3.93; O, 21.72.

Registry No.—**9**, 16404-24-3; **10**, 16315-65-4; **11**, 16315-66-5; **12**, 16315-67-6; **13**, 16315-68-7.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this research.

(15) Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra (Varian A-60 spectrometer) of **9–12** were recorded in deuteriochloroform solution; chemical shifts are reported in τ values relative to tetramethylsilane as an internal standard (τ 10.00 ppm). Analyses were performed by Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck Institut, Mülheim (Ruhr), West Germany.

Synthesis of Certain Naturally Occurring 2-Pyrones *via* 3,5-Diketo Acids[1]

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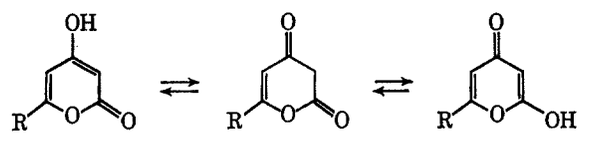
Two naturally occurring 4-methoxy-2-pyrones, 4-methoxyparacotoin and yangonin, were prepared by a three-step procedure involving carboxylation of disodio β-diketones, cyclization of the resulting diketo acids to 4-hydroxy-2-pyrones through the use of acetic anhydride, and O-methylation of the 4-hydroxy-2-pyrones at the 4 position. A partial synthesis of the hydroxypyrone, hispidin, was achieved. The synthesis of anibine was unsuccessful.

A number of 4-hydroxy-2-pyrones[2] and their methyl ethers have been isolated from natural sources.[3] Early interest in these compounds arose from their medicinal properties. In 1953, Birch and Donovan suggested that the 4-hydroxy-2-pyrones are biosynthesized by condensation of two acetate units with appropriate carboxylic acids to give diketo acids which subsequently lactonize.[4] Current interest has stemmed from the



(1) This work was supported by the National Institutes of Health, U. S. Public Health Service (Research Grant GM-12848).

(2) 4-Hydroxy-2-pyrones are in equilibrium with the tautomeric 2-hydroxy-4-pyrones and dihydropyran-2,4-diones. Spectroscopic evidence indicates that the 4-hydroxy-2-pyrone tautomer usually predominates; see F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., London, 1963, Chapter 4.

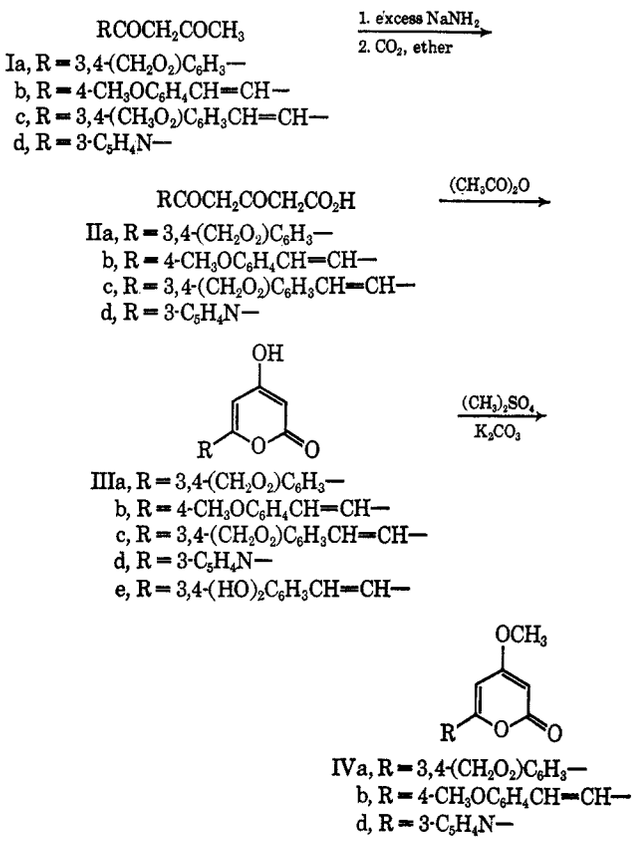
(3) For leading references, see (a) W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **79**, 4507 (1957); (b) O. R. Gottlieb and W. B. Mors, *J. Org. Chem.*, **24**, 17 (1959); (c) R. L. Edwards, D. G. Lewis, and D. V. Wilson, *J. Chem. Soc.*, 4995 (1961); (d) A. Penttila and J. Sundman, *Acta Chem. Scand.*, **15**, 839 (1961); (e) P. E. Brenneisen, T. E. Acker, and S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **86**, 1264 (1964); (f) A. K. Ganguly, T. R. Govindachari, and P. A. Mohamed, *Tetrahedron*, **21**, 93 (1965); (g) T. M. Harris, C. M. Harris, and R. J. Light, *Biochim. Biophys. Acta*, **121**, 420 (1966); (h) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, **89**, 676 (1967).

(4) A. J. Birch and F. W. Donovan, *Aust. J. Chem.*, **6**, 360 (1953).

possible relationship of the pyrones to the biosynthesis of fatty acids, phenols, and tropolones.[5]

A convenient method was described recently for the preparation of 4-hydroxy-2-pyrones.[6] β-Diketones were converted into dianions by reaction with 2 equiv of sodium amide in liquid ammonia. Treatment with carbon dioxide gave carboxylation at the γ position. The 3,5-diketo acids were converted into 4-hydroxy-2-pyrones by treatment with anhydrous, liquid hydrogen fluoride. The cyclizations can also be effected by polyphosphoric acid.[7] The application of this method to the synthesis of certain naturally occurring 2-pyrones has now been investigated (see Scheme I). The compounds chosen for study were 4-methoxyparacotoin (IVa), yangonin (IVb), anibine (IVd), and hispidin (IIIe).

SCHEME I



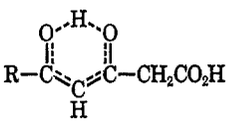
β-Diketones Ia–d were synthesized by conventional methods. The unsaturated diketones Ib and Ic were prepared by acylation of acetone with the phenyl esters of the appropriate cinnamic acids. The procedure has previously been demonstrated to be an excellent method for the preparation of similar unsaturated diketones; the use of phenyl esters minimizes β attack on cinnamate.[8]

The condensation of acetone with phenyl 3-piperonylacrylate afforded diketone Ic having a substantially lower melting point than material reported previously by Lampe and coworkers, which was prepared by acylation of ethyl acetoacetate with 3-piperonylacrylyl chloride followed by hydrolysis and decarboxylation.[9] The material obtained in the present reaction had a sharp melting point and gave satisfactory elemental analyses. The infrared spectrum was consistent with the proposed structure; intense absorption at 1610 cm^{-1} resulted from the enolized β-diketone. The nmr spectrum showed a large coupling constant (J = 16 cps) for the ethylenic hydrogens indicating that the *trans* isomer had been prepared.

The diketones were added to excess sodium amide in liquid ammonia to form the disodio salts. The ammonia was replaced with ether and the resulting suspension was treated with Dry Ice. By this procedure diketo acids IIa–c were isolated in yields of 30–61%. The method was not suitable for the preparation of pyridyl acid IId. Mors and coworkers have reported that alkaline hydrolysis of anibine (IVd) gave the salt of diketo acid IId but that spontaneous decarboxylation occurred on neutralization.[3a] Amine catalysis of the decarboxylation of another diketo acid has been observed,[10] and it seems probable that self-catalysis of decarboxylation occurred during the attempted isolation of diketo acid IId.

Diketo acid IIc has not been reported previously. The material gave a satisfactory elemental analysis. The infrared spectrum showed the presence of a carboxylic acid (1730 cm^{-1}) and an enolized β-diketone (1570 cm^{-1}). The nmr spectrum indicated that the *trans* olefinic structure ($J_{CH=CH}$ = 16 cps) had been retained. Diketo acids IIa–b had been prepared previously by alkaline hydrolysis of the corresponding 4-hydroxy-2-pyrones.[3a,11]

The 3,5-diketo acids II existed mainly as monoenols V in potassium bromide pellets and in solution. This assignment is made on the basis of the infrared spectra (KBr) that indicated the presence of unconjugated carboxyl and enolized β-dicarbonyl groups. The nmr spectra showed that the principal tautomer present in solution contained one methylene group between electronegative groups and one vinyl hydrogen of an enolized diketone.



V

The use of hydrogen fluoride for cyclization of diketo acid IIa was unsatisfactory; none of the desired pyrone was obtained and at least two other products were formed but these were not identified. It seems likely that the methylenedioxy group is attacked under the strongly acidic conditions. Borsche and Bodenstein reported that treatment of diketo acid IIb with refluxing acetic anhydride afforded the corresponding 2-acetoxy-4-pyrone, which can be hydrolyzed to give 4-hydroxy-2-pyrone IIIb.[11] In the present study the

(5) (a) G. Ehrensvard, *Exp. Cell Res., Suppl.*, **3**, 102 (1955); (b) R. Bressler and S. J. Wakil, *J. Biol. Chem.*, **237**, 1441 (1962); (c) J. D. Brodie, G. Wasson, and J. W. Porter, *ibid.*, **239**, 1346 (1964); (d) T. E. Acker, P. E. Brenneisen, and S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **88**, 834 (1966); (e) R. J. Light, T. M. Harris, and C. M. Harris, *Biochemistry*, **5**, 4037 (1966); (f) D. J. H. Brock and K. Bloch, *Biochem. Biophys. Res. Comm.*, **23**, 775 (1966); (g) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, **89**, 681 (1967).

(6) T. M. Harris and C. M. Harris, *J. Org. Chem.*, **31**, 1032 (1966).

(7) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

(8) C. R. Hauser, R. S. Yost, and B. I. Ringler, *J. Org. Chem.*, **14**, 261 (1949).

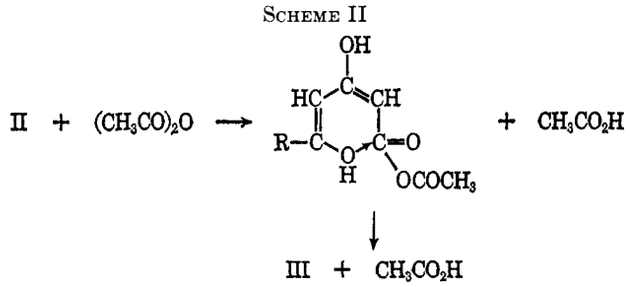
(9) W. Lampe, Z. Buczkowska, J. Frenkl, E. Gliksman-Korngold, M. Tokarska-Kozlowska, R. Nelken, and C. Sieradzka, *Rocz. Chem.*, **9**, 444 (1929); *Chem. Abstr.*, **23**, 4210 (1929).

(10) R. F. Witter and E. Stotz, *J. Biol. Chem.*, **176**, 485 (1948).

(11) W. Borsche and C. K. Bodenstein, *Ber.*, **62**, 2515 (1929).

use of acetic anhydride with IIa at ambient temperature was found to give cyclization directly to IIIa without appreciable O-acetylation and without attack on the methylenedioxy group. The method was employed similarly with IIb and IIc. Pyrones IIIa–c were obtained in yields of 63–79%. The piperonyl pyrones IIIa and IIIc are new compounds. The mechanism of these cyclizations probably involves the initial formation of a mixed carboxylic anhydride between the diketo acid and acetic acid. Cyclization occurs by acylation of the enol (or keto) group at the 5 position (see Scheme II).[12]

SCHEME II



4-Hydroxy-2-pyrones IIIa and IIIb were converted into 4-methoxyparacotoin (IVa) and yangonin (IVb), respectively, in yields of 69 and 89% by treatment with methyl sulfate and potassium carbonate. The product melting points were identical with ones of natural materials. This procedure for methylation of 4-hydroxy-2-pyrones III has been reported to form selectively the 4-methoxy derivatives.[13] Treatment of hydroxypyrones III with diazomethane has given mixtures of 4-methoxy-2-pyrones IV and the isomeric 2-methoxy-4-pyrones.[13a,14]

Previous syntheses of 4-methoxyparacotoin include (a) the condensation of diethyl phenylmercaptomalonate with 3,4-methylenedioxyacetophenone to give a pyrone from which thiophenol was cleaved with Raney nickel and (b) cyclization of 1-aryl-5,5-dichloropent-4-en-1-yn-3-one by means of hydrochloric acid.[15] Yangonin has been synthesized by two routes. One involves a condensation between *p*-methoxycinnamoyl chloride and diethyl 3-oxoglutarate[11] and the other a condensation of *p*-methoxybenzaldehyde with 4-methoxy-6-methyl-2-pyrone.[13a]

The conversion of IIIc into hispidin (IIIe) requires removal of the methylene bridge of the piperonyl system. In our hands a satisfactory procedure could not be found. The dioxole ring must be opened without disturbing the pyrone and the released formaldehyde must not recondense with the product. It is concluded that a more labile blocking group should be employed and preferably one that does not liberate formaldehyde. Edwards and Wilson have reported the successful use of methoxymethyl groups in a synthesis of hispidin.[16]

In summary, although the described method for synthesis of 4-hydroxy- and 4-methoxy-2-pyrones is not completely general, it nevertheless provides a direct method for the preparation of many of these compounds.

Experimental Section[17]

β-Diketones I. 1-(3,4-Methylenedioxyphenyl)-1,3-butanedione (Ia).—A mixture of 9.0 g (0.05 mol) of methyl piperonylate, 3.2 g (0.055 mol) of acetone, and 3.0 g (0.125 mol) of sodium hydride in 100 ml of tetrahydrofuran was refluxed for 2.5 hr. The solvent was removed under reduced pressure and the residue was dissolved in ether and water. The aqueous layer was separated, acidified, and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, dried, and evaporated to afford 3.7 g (36% yield) of diketone Ia, mp 89.5–91° (lit.[3a] mp 91–92°).

6-(*p*-Methoxyphenyl)-5-hexene-2,4-dione (Ib).—A mixture of 2.54 g (0.010 mol) of phenyl *p*-methoxycinnamate,[18] 0.70 g (0.012 mol) of acetone, and 0.026 mol of sodium amide (prepared from 0.60 g of sodium in liquid ammonia) was refluxed in ether for 3 hr. The mixture was extracted with water and the aqueous solution was treated with carbon dioxide to precipitate the diketone. Recrystallization from methanol–water gave 0.44 g (20% yield) of diketone Ib, mp 88–89° (lit.[19] mp 93°).

6-(3,4-Methylenedioxyphenyl)-5-hexene-2,4-dione (Ic).—Condensation of phenyl 3,4-methylenedioxycinnamate[20] and acetone effected by sodium amide gave after recrystallization from methanol 24% of diketone Ic: mp 95.5–96.2° (lit.[9] mp 123–125°); ν_{max} 1640, 1610, 1450, and 1260 cm^{-1}; δ_{CDCl_3} 2.15 (CH_3), 5.62 (4-CH), 6.00 ($-OCH_2O-$), 6.15 and 6.41 (2-CH), and 7.40 and 7.67 ppm (1-CH).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.34; H, 5.40.

1-(3-Pyridyl)-1,3-butanedione (Id) was prepared by the method of Kuick and Adkins.[21]

3,5-Diketo Acids II.[6] 5-(3,4-Methylenedioxyphenyl)-3,5-dioxopentanoic Acid (IIa).—To a stirred suspension of 0.035 mol of sodium amide (prepared from 0.81 g of sodium) in 200 ml of liquid ammonia was added 2.06 g (0.010 mol) of diketone Ia. After 30 min, the ammonia was evaporated on the steam bath as an equal volume of ether was added. The ether was refluxed for several minutes to ensure complete removal of ammonia. Dry Ice was added to the suspension. The reaction mixture was poured into a mixture of ice and 30 ml of 12 *N* hydrochloric acid. The resulting ethereal solution was extracted with cold, 5% sodium bicarbonate solution. The aqueous extract was immediately acidified and extracted with ether. The ethereal solution was dried and evaporated under reduced pressure to give 0.75 g (30% yield) of diketo acid IIa, mp 128–129°. Recrystallization from chloroform gave mp 134–135° dec (lit.[3a] mp 125–130°); ν_{max} 1720, 1635, 1610, 1270, 1035, and 910 cm^{-1}; $\delta_{acetone\text{-}d_6}$ 3.52 (2-CH_2), 6.2 ($-OCH_2O-$), and 6.53 ppm (4-CH).

7-(*p*-Methoxyphenyl)-3,5-dioxo-6-heptenoic Acid (IIb).—The dianion of 0.436 g (0.0020 mol) of diketone Ib was carboxylated to give 0.321 g (61% yield) of diketo acid IIb, mp 125–126°. Recrystallization from chloroform–hexane gave mp 132–133° dec (lit.[11] mp 126–127°); ν_{max} 1710, 1640, 1575–1610, 1270, 1180, and 980 cm^{-1}; $\delta_{acetone}$ 3.50 (2-CH_2), 3.88 (*p*-CH_3O), 5.95 (4-CH), 6.50 and 6.77 (6-CH), and 7.52 and 7.78 ppm (7-CH).

(12) The use of this method for the selective lactonization of 3,5,7-triketo acids will be described in a subsequent paper. Under suitable conditions triketo acids can also be cyclized to form γ-pyrones, β-resorcylic acids, and acylphloroglucinols; see K. G. Hampton, T. M. Harris, C. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 4263 (1965), and T. M. Harris and R. L. Carney, *J. Amer. Chem. Soc.*, **89**, 6734 (1967).

(13) (a) J. D. Bu'Lock and H. G. Smith, *J. Chem. Soc.*, 502 (1960); (b) H. Nakata, *Bull. Chem. Soc. Jap.*, **33**, 1693 (1960).

(14) D. Herbst, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959); H. Nakata, *Bull. Chem. Soc. Jap.*, **33**, 1688 (1960); I. Chmielewska, J. Cieslak, K. Gorczynska, B. Kontnik, and K. Pitakowska, *Tetrahedron*, **4**, 36 (1958).

(15) A. Lefeuvre and C. Mentzer, *Bull. Soc. Chim. Fr.*, 623 (1964); M. Julia and C. Binet du Jassonneix, *Compt. Rend.*, **253**, 872 (1961).

(16) R. L. Edwards and D. V. Wilson, *J. Chem. Soc.*, 5003 (1961).

(17) Melting points below 200° were determined in open capillaries using a silicone oil bath. Higher melting points were determined with a Kofler hot stage. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined by the potassium bromide pellet method using a Beckman IR-10 spectrometer. Nmr spectra were determined with a Varian A-60 spectrometer. Tetramethylsilane was employed as an internal standard.

(18) P. A. Foote, *J. Amer. Pharm. Soc.*, **17**, 958 (1928).

(19) W. Borsche and C. Walter, *Ber.*, **60**, 2112 (1927).

(20) D. H. R. Barton and D. W. Jones, *J. Chem. Soc.*, 3563 (1965). The nmr spectrum indicated that the ester had *trans* configuration: δ_{CDCl_3} 6.02 ($-OCH_2O-$), 6.32 and 6.58 (2-CH), and 7.67 and 7.93 ppm (3-CH, $J_{CH=CH}$ = 16 cps).

(21) L. F. Kuick and H. Adkins, *J. Amer. Chem. Soc.*, **57**, 143 (1935).

7-(3,4-Methylenedioxyphenyl)-3,5-dioxo-6-heptenoic Acid (IIc).—The dianion of 0.348 g (0.0015 mol) of diketone Ic was carboxylated to give 0.208 g (50% yield) of diketo acid IIc, mp 118–120°. Recrystallization from chloroform gave mp 122–123° dec; ν_{max} 1730, 1630, 1610, 1540–1580, and 1130 cm^{-1}; $\delta_{acetone\text{-}d_6}$ 3.48 (2-CH_2), 5.93 (4-CH), 6.10 (-OCH_2O-), 6.48 and 6.75 (6-CH), and 7.45 and 7.72 ppm (7-CH).

Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 60.63; H, 4.19.

5-(3-Pyridyl)-3,5-dioxopentanoic Acid (IId).—Treatment of the disodium salt of diketone Id with Dry Ice gave an ether-insoluble, tan salt. Acidification afforded only unaltered diketone. Moreover, addition of the salt directly to anhydrous, liquid hydrogen fluoride gave no apparent formation of pyrone.

6-Substituted 4-Hydroxy-2-pyrones III. 4-Hydroxy-6-(3,4-methylenedioxyphenyl)-2-pyrone (IIIa).—Treatment of diketo acid IIa with anhydrous, liquid hydrogen fluoride apparently affected adversely the piperonyl ring system. As an alternative, the diketo acid (0.100 g, 0.00040 mol) was added to 10 ml of acetic anhydride. Initially the mixture was homogeneous; however, after 1 hr white crystals began to appear. After 16 hr the mixture was cooled and the crystals were separated by filtration, washed with water, and dried. Recrystallization from 95% ethanol gave 0.068 g (73% yield) of pyrone IIIa, mp 257–258° (lit.[22] mp 255–257°).

4-Hydroxy-6-(*p*-methoxystyryl)-2-pyrone (IIIb).—Treatment of 0.262 g (0.0010 mol) of diketo acid IIb with acetic anhydride afforded after recrystallization from methanol 0.155 g (63% yield) of pyrone IIIb, mp 235–237° (lit.[11] mp 238°).

4-Hydroxy-6-(3,4-methylenedioxystyryl)-2-pyrone (IIIc).—Diketo acid IIc (0.097 g, 0.00035 mol) and acetic anhydride gave 0.077 g (79% yield) of the monohydrate of pyrone IIIc: mp 230–234°, mp 233–236° after recrystallization from ethanol; ν_{max} 1620–1670 and 3300–3500 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}O_6 \cdot H_2O$: C, 60.87; H, 4.38. Found: C, 60.68; H, 4.50.

6-Substituted 4-Methoxy-2-pyrones IV. 4-Methoxyparacotoin (IVa).—A mixture of 0.0348 g (0.00015 mol) of pyrone IIIa, 2 g of potassium carbonate, and 1 ml of methyl sulfate in acetone was refluxed for 1.5 hr and allowed to stand at ambient temperature for 18 hr. Salts were removed by filtration and the solution was concentrated to give a partially crystalline mixture. The crystals were washed with ether, with 5% sodium hydroxide solution, and with water to give 0.0255 g (69% yield) of pyrone IVa, mp 221–222°. Recrystallization from methanol gave mp 223–224° (lit.[30] mp 222–224°).

Yangonin (IVb).—Methylation of 0.122 g (0.00050 mol) of pyrone IIIb afforded 0.115 g (89% yield) of yangonin, mp 152.5–154°. Recrystallization from methanol gave mp 154–155° (lit.[11] mp 153–154°).

Registry No.—Ic, 16526-73-1; IIc, 16526-74-2; IIIc, 16526-75-3; IVa, 6969-80-8; IVb, 500-62-9.

(22) A. Resplandy, *Bull. Soc. Chim. Fr.*, 1332 (1962).

The Reaction of Some Keto Acids with Anthranilic Acid Anthranilamides, Orthanilamides, and Salicylamide[1]

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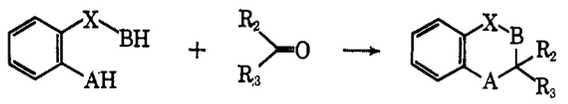
Received November 20, 1967

The reaction of 2-acyl- and 2-aroylbenzoic acids and 3- and 4-oxoalkanoic acids with anthranilic acid, anthranilamides, salicylamide, and orthanilamides has been demonstrated to be a useful technique for preparing heterocyclic systems containing nitrogen, oxygen, and sulfur heteroatoms.

The reaction of an aldehyde or ketone (**2**) with an anthranilic acid (**1a**), anthranilamide (**1b**), salicylamide (**1c**), or orthanilamide (**1d**) has found general synthetic application in the synthesis of a variety of 1,2-dihydro-4H-3,1-benzoxazin-4-ones[2] (**3a**), 1,2,3,4-tetrahydroquinazolin-4-ones[3] (**3b**), 2,3-dihydro-4H-1,3-benzoxazin-4-ones[2,4] (**3c**), and 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides[5] (**3d**).



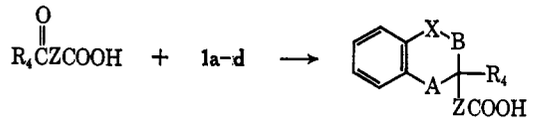
1a, X = CO; A = NH; B = O
b, X = CO; A = NR; B = NR_1
c, X = CO; A = O; B = NH
d, X = SO_2; A = NH; B = NR_1

R, R_1 = H, alkyl, etc.

2, R_2, R_3 = H, alkyl, etc.

3a, X = CO; A = NH; B = O
b, X = CO; A = NR; B = NR_1
c, X = CO; A = O; B = NH
d, X = SO_2; A = NH; B = NR_1

Extension of the carbonyl component (**2**) of this reaction to include ω-acylcarboxylic acids (**4a**) and *o*-acylbenzoic acids (**4b**) suggests that intermediates such as **5** could be formed. Further cyclization of the free carboxy group in **5** with an available nitrogen atom (A or B) could then lead to a variety of tricyclic or tetracyclic systems.



4a, Z = $(CH_2)_{2,3}$
b, Z = *o*-C_6H_4

5

R_4 = alkyl, aryl

Selleri and Caldini[6] and more recently Kratzl and Weinstock[7a] have reported that the reaction of phthaldehydic acids (**6**) with 2-aminobenzenesulfonamides (**7**) gave 6,6a-dihydro-11H-isoindolo[1,2-*c*][1,2,4]benzo-

(1) Portions of this paper were presented at the American Chemical Society Metropolitan Regional Meeting, Stevens Institute of Technology, Hoboken, N. J., Feb 1965.

(2) R. L. McKee in "The Chemistry of Heterocyclic Compounds, Five- and Six-Membered Compounds with Nitrogen and Oxygen," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1962, Chapter XIV, pp 341–375.

(3) F. Russo and M. Ghelardoni, *Ann. Chim.* (Rome), **56**, 839 (1966); K. H. Hauptmann, *Arzneim.-Forsch.*, **15**, 610 (1965); C. H. Boehringer Sohn, Netherlands Patent Appl. 302,479 (Oct 25, 1966) [*Chem. Abstr.*, **64**, 9743 (1966)]; J. W. Bolger, U. S. Patent 3,257,397 (June 21, 1966) [*Chem. Abstr.*, **65**, 8933 (1966)]; E. S. Schipper, U. S. Patent 3,265,697 (Aug 9, 1966) [*Chem. Abstr.*, **65**, 15399 (1966)].

(4) J. Maillard, M. Vincent, P. Delaunay, V.-V. Tri, and R. Jolly, *Bull. Soc. Chim. Fr.*, 2525 (1966); U. M. Teotino, L. P. Friz, A. Gandini, and D. Della Bella, *J. Med. Chem.*, **6**, 248 (1966).

(5) Numerous examples of this system are reported in "Diuretics," G. De-Stevens, Academic Press Inc., New York, N. Y., 1963.

(6) R. Selleri and O. Caldini, *Boll. Chim. Farm.*, **100**, 323 (1961).

(7) (a) K. Kratzl, R. Weinstock, and H. Ruis, *Oesterr. Chem.-Ztg.* **66**, 315 (1965); (b) R. Weinstock and K. Kratzl, *Monatsh. Chem.*, **96**, 1586 (1965); K. Kratzl, R. Weinstock, and H. Ruis, *ibid.*, **96**, 1592 (1965); (c) K. Kratzl and H. Ruis, *ibid.*, **96**, 1596, 1603 (1965).