with 5 ml. of $12N$ hydrochloric acid and 35 ml. of ether to give 0.84 g. (94%) of I, m.p. 64–65°, reported m.p. 66°.[2]

B. According to Equation 2. Phenylacetic anhydride, m.p. 71.5–72° (reported m.p. 72.5°[13]) was prepared from phenylacetyl chloride and anhydrous sodium phenylacetate in dry benzene as described previously.[14]

A mixture of 101.5 g. (0.4 mole) of this anhydride, 32 g. (0.2 mole) of diethyl malonate, 0.2 g. of magnesium oxide, and 0.1 g. of copper acetate was combined in a flask fitted with an air condenser and a gas inlet tube reaching to the center of the flask. Oxygen-free nitrogen was passed through the reaction flask for 0.5 hr., then the flask was heated at 190° for 2.5 hr. After cooling, the mixture was shaken with 400 ml. of ether, then washed with 5% sodium hydroxide solution to remove phenylacetic acid (β-diketone I was found not to be appreciably soluble in 5% alkali). The ether was removed, and the residue was treated with saturated copper acetate solution. The resulting precipitate was collected and washed with water, followed by petroleum ether (b.p. 30–60°) until the washes were essentially colorless. There was obtained 35.7 g. (63%) of the gray-blue chelate of I, m.p. 219.0–219.5° dec., which was not depressed on admixture with a sample of the chelate of I prepared by method A.

This chelate was decomposed with $12N$ hydrochloric acid (see above) to give 28.4 g. (90%) of 1,5-diphenyl-2,4-pentanedione (I), m.p. 65.2–66.5° after several recrystallizations from methanol.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.40. Found: C, 80.96; H, 6.22.

This product gave a red enol test with alcoholic ferric chloride.

Synthesis of 1,1,5,5-tetraphenyl-2,4-pentanedione. Diphenylacetic anhydride, m.p. 96.2–97° (reported m.p. 98°[15]) was prepared from diphenylacetic acid and acetic anhydride as described previously.[15]

A mixture of 81.2 g. (0.2 mole) of this anhydride, 16 g. (0.1 mole) of diethyl malonate, 0.2 g. of magnesium oxide, and 0.1 g. of copper acetate was heated at 230° for 2.5 hr., and the reaction mixture worked up essentially as described above for I (under *B*) to give 15.3 g. (35%) of the copper chelate of III, m.p. 230.7–233.5° dec.

Decomposition of 14.7 g. of this chelate with $12N$ hydrochloric acid and ether gave 10.9 g. (80%) of 1,1,5,5-tetraphenyl-2,4-pentanedione (III), m.p. 135–136.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{29}H_{24}O_2$: C, 86.11; H, 5.98. Found: C, 86.02; H, 6.03.

This β-diketone gave a red enol color with ethanolic ferric chloride solution.

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The Reactions of Pyrones with Carboxylic Acids, Esters, and Chloromethyl Ether

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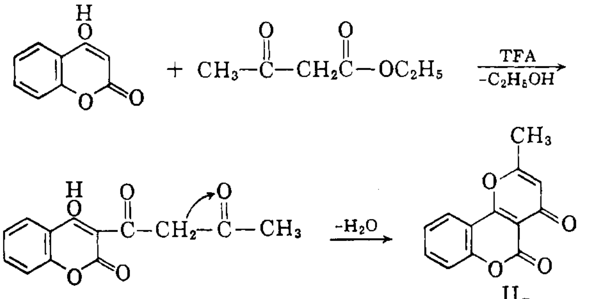
In the recent months investigations of the reaction of 4-pyrones with acyl halides, anhydrides,[1,2] and lactones[3] have been shown to take place in the presence of trifluoroacetic acid to form ketones. Therefore, experiments were designed to ascertain if acids could be used as acylating agents of the several pyrones by using trifluoroacetic acid as a catalyst. When the reaction was tried under the conditions described for the preparation of the compounds of the Ia–f series, good results were obtained.

In order to evaluate the procedure 6-benzoylkojic acid was used as the model compound, as it had been prepared previously and its properties determined.[4] Compound Ic, produced by the action of benzoic acid on kojic acid in the presence of trifluoroacetic acid, gives a melting point within experimental error of that recorded for 6-benzoylkojic acid and it gives the proper carbonyl absorption at 1718 cm.$^{-1}$ The other members of the Ia–f series also give the expected carbonyl absorption frequencies[5] when chelation and other displacement factors are considered.

As carboxylic acids were found to react with pyrones under the conditions related above, esters were tried to determine if they, too, could be induced to react under similar conditions. In this instance, also, 6-benzoylkojic acid was used as the model compound to evaluate the acylation of pyrones by esters. Not only were the expected results realized but a novel condensation was uncovered. The compounds formed by this method are given as the IIa–e series in Table II. The structure for 2-hydroxymethyl-6-(2′-hydroxymethyl-5′-hydroxy-4′-pyrone-6′-pyranyl[3,2-*b*]pyran-4,8-dione is given as is the equation for the preparation of 8-methylbenzopyranyl[3,2-c]pyran-2,10-dione (IId). Compound IIe is formed similarly by the same novel



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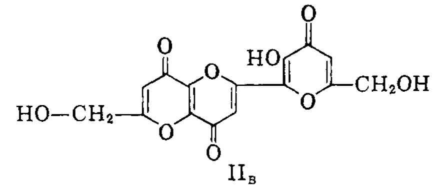

IIE

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TABLE I

KETONES FROM THE REACTION OF 4-PYRONES WITH CARBOXYLIC ACIDS

Compound No.	Pyrone Used	Acid Used	Yield, %	M.P.	Empirical Formula	Calculated (Found) Carbon	Hydrogen	Chlorine
Ia[a]	Kojic acid	Chloroacetic	33	143	$C_8H_7ClO_5$	43.95 44.28	3.22 3.27	16.21 16.44
Ib	Kojic acid	Salicylic	65	212	$C_{13}H_{10}O_6$	59.54 59.85	3.84 3.96	
Ic	Kojic acid	Benzoic	100	188[a]	$C_{13}H_{10}O_5$	63.41 63.02	4.09 3.72	
Id	2-Methyl-4-pyrone	Benzoic	68	135.5	$C_{13}H_{10}O_3$	72.88 72.59	4.70 4.89	
Ie	2-Methyl-4-pyrone	Salicylic	59	160	$C_{13}H_{10}O_4$	67.82 67.49	4.37 4.52	
If	2-Methyl-4-pyrone	*m*-Nitrobenzoic (2 moles)	80	109	$C_{20}H_{12}N_2O_8$ Nitrogen, calcd.—6.86; Found—7.15	58.82 58.47	2.96 3.40	

[a] Ia = 2-Hydroxymethyl-5-hydroxy-6-chloroacetyl-4-pyrone: 3179, 1748, 1647, 1613, 1176 (principal absorption bands, infrared region, cm.$^{-1}$); Ib = 2-hydroxymethyl-5-hydroxy-6-salicyl-4-pyrone: 3236, 1678, 1639, 1610, 1205; Ic = 2-hydroxymethyl-5-hydroxy-6-benzoyl-4-pyrone: 3236, 1715, 1645, 1608, 1585, 1253; Id = 2-methyl-6-benzoyl-4-pyrone: 1695, 1429, 1330, 1294; Ie = 2-methyl-6-salicyl-4-pyrone: 1667, 1613, 1445, 1366, 1250; If = 2-methyl-3,6-di(*m*-nitrobenzoyl)-4-pyrone: 1667, 1645, 1558, 1531, 1220. [b] Melting point is in agreement with 188° published previously.[4]

TABLE II

KETONES AND CHROMONES BY THE REACTION OF PYRONES AND ESTERS

Compound No.	Pyrone or Phenol Used	Ester Used	Yield, %	M.P.	Empirical Formula	Calculated (Found) Carbon	Hydrogen	Chlorine
IIa[a]	Kojic acid	Ethyl chloroacetate	59	143.5[b]	$C_8H_7ClO_5$	43.95 44.31	3.22 3.24	16.22 16.01
IIb	Kojic acid	Diethyl malonate	61	145	$C_{15}H_{10}O_9$	53.90 54.29	3.01 2.49	
IIc	Kojic acid	Ethyl benzoate	62	186–187[c]	$C_{13}H_{10}O_5$	63.41 63.28	4.09 4.17	
IId	4-Hydroxycoumarin	Ethyl acetoacetate	83	252	$C_{13}H_8O_4$	68.42 68.64	3.53 3.71	
IIe	Phloroglucinol	Bromo-di-ethylmalonate	44	Above 330	$C_{15}H_9BrO_7$	47.26 47.41	2.38 2.59	

[a] IIa = 2-hydroxymethyl-5-hydroxy-6-chloroacetyl-4-pyrone: 3175, 1748, 1653, 1613, 1155 (significant infrared absorption frequencies in cm.$^{-1}$, KBr pellet); IIb = 2-hydroxymethyl-6-(2′-hydroxymethyl-5′-hydroxy-4′-pyrone-6′)pyranyl[3,2-*b*]-pyran-4,8-dione: 3175, 1656, 1626, 1608, 1224; IIc = 2-hydroxymethyl-5-hydroxy-6-benzoyl-4-pyrone: 3236, 1712, 1642, 1610, 1585, 1255; IId = 8-methylbenzopyranyl[3,2-c]pyran-2,10-dione: 3344, 1727, 1631, 1613; IIe = 3-bromo-5,7,2′,4′,6′-pentahydroxyflavone: 3333, 1600, 1590. [b] In good agreement with results in Chart I in which the compound was prepared using a different method. [c] In good agreement with results in Chart I and in fair agreement with previous results mentioned at end of Chart I. A mixture melting point with I_C was not depressed.

TABLE III

METHOXY METHYLATION OF PYRONES

No.	Pyrone Used	Moles of Chloromethyl Ether Used	Yield	M.P.	Empirical Formula	Calculated (Found) Carbon	Hydrogen	Chlorine
IIIa	Kojic acid	1	57	205	$C_8H_{10}O_5$	51.61 51.50	5.41 5.20	
IIIb	α-Chloro-α-deoxy kojic acid	1	68	165	$C_8H_9ClO_4$	46.95 46.68	4.43 4.29	17.32 17.18
IIIc	Coumarin	1	57	70	$C_{11}H_{10}O_3$	69.46 69.28	5.29 5.04	
IIId	Kojic acid	2	45	211	$C_{10}H_{14}O_6$	52.17 52.41	6.12 6.04	

[a] IIIa = 2-hydroxymethyl-5-hydroxy-6-methoxymethyl-4-pyrone: 222 and 267 (absorption maxima range, 200–350 mμ); IIIb-2-chloromethyl-5-hydroxy-6-methoxymethyl-4-pyrone: 220 and 273.5; IIIc = 3-methoxymethyl coumarin: 213.5, 273 and 310; IIId = 2-hydroxymethyl-3-methoxymethyl-5-hydroxy-6-methoxymethyl-4-pyrone: 217 and 270.

condensation and its pentacetylated malononitrile derivative is given as compound IV. These two compounds serve as confirmatory proof of the course of the reaction.

Methoxymethylation of pyrones by chloromethyl ether in the presence of trifluoroacetic acid is described and the compounds produced are given in chart III as members of the IIIa–d series.

The results given show that mono- or di-methoxymethylation may take place depending upon the mole ratios of the reactants. The probable structures of the compounds produced are reflected in the names assigned to the members of the series

EXPERIMENTAL[6]

Preparation of compounds of Ia–f *series.* A mixture consisting of 0.1 mole of the pyrone, 0.1 mole of the acid, and 20 ml. of trifluoroacetic acid was refluxed for 15 hours. The reaction mixture was then diluted with 60–80 ml. of water and chilled in the freezing compartment of the refrigerator. The precipitate was filtered off and dried in air to give the crude yields listed in Table I. Compound If required 0.2 mole of the organic acid to 0.1 mole of the pyrone and 25 ml. of trifluoroacetic acid was used.

The analytical samples were obtained in the following manner: Ia and Ib, recrystallized twice from ethanol; Ic, recrystallized three times from ethanol; Id and Ie, recrystallized twice from heptane; If recrystallized once from ethanol and once from heptane.

Preparation of compounds of IIa–d *series.* One tenth mole of the pyrone was mixed with 0.1 mole of the ester and 20 ml. of trifluoroacetic acid and the mixture refluxed for 15 hours. At the termination of the reaction period 40 ml. of absolute ethanol was added and the mixture was allowed to stand in the freezer for at least 12 hours. The precipitates were dried in air.

The analytical samples of the several compounds were obtained in the following manner: IIa, recrystallized twice from ethanol then twice from heptane; IIb, extracted with heptane then recrystallized from ethyl acetate; IIc, recrystallized 3 times from ethanol; IId, recrystallized once from ethanol.

Preparation of compounds of the IIIa–d *series.* Fifteen milliliters of chilled trifluoroacetic acid was mixed with 0.1 mole of the pyrone and 0.1 mole of cold chloromethyl ether. The mixture was gently heated, in an efficient all glass reflux assembly in a glass heating mantle. The heating was continued until hydrogen chloride vapors were no longer evolved (usually complete in about an hour). The reaction mixture was diluted, in each case, with 40 ml. of absolute ethanol and chilled. The precipitated compound was filtered off and dried in air.

Analytical samples were obtained by recrystallizing the compounds twice from ethanol.

The synthesis of compound IV. A 3-g. sample of IIE was refluxed for 90 minutes with 25 ml. of acetic anhydride and 4 g. of malononitrile. The mixture was then diluted with water, chilled, and filtered. The compound was dried in air to give a brown material of the pentaacetylmalononitrile derivative, yield 60%. The compound was recrystallized once from heptane, m.p. dec. above 195°.

Anal. Calcd. for $C_{26}H_{19}BrN_2O_{11}$: C, 50.74; H 3.11; N, 4.55. Found: C, 50.52; H, 3.02; N, 4.38.

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Microbiological Transformations. VIII. The Oxidation of Androstenedione at C-16

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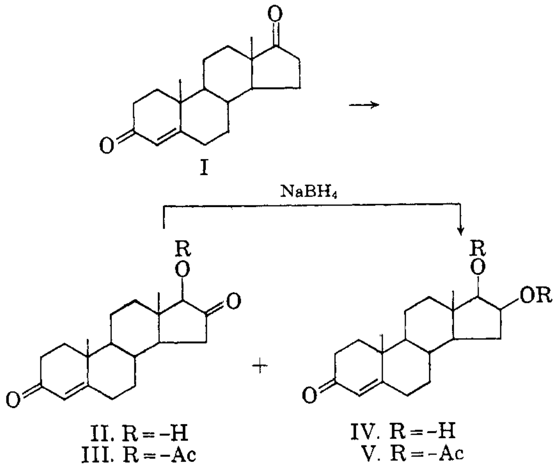
The recently reported microbiological hydroxylation of 17α,21-dihydroxy-4-pregnene-3,20-dione (Reichstein's compound S) at C-19 using *Corticium sasakii*[2] prompted us to investigate the oxidation of 4-androstene-3,17-dione (I) with this same genus. A simple preparation of 19-hydroxyandrostenedione would be most useful to the commercial production of the biologically active norsteroids,[3] 17α-ethyl-19-nortestosterone and 17α-ethynyl-17β-hydroxy-19-nor-5(10)-androsten-3-one.



Incubation of 4-androstene-3,17-dione (I) with *Corticium centrifugum*, A.T.C.C. 11908, produced 16-ketotestosterone (II) and 16β-hydroxytestosterone (IV). The position of oxidation in II was readily determined by the fact that the compound gave a positive blue-tetrazolium test,[4] but showed no appreciable change in its ultraviolet spectrum over a 24-hour period when allowed to stand in 0.1*N* methanolic potassium hydroxide.[5] These

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[6] All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J. and all melting points were taken on a Fisher-Johns melting point assembly.

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