[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES, UNIVERSITY OF LOUISVILLE]

2-Pyrones. XXI. Anilides, Esters, and Aziridine Derivatives of 2-Pyronecarboxylic acids

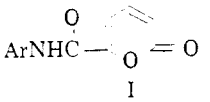
RICHARD H. WILEY AND C. L. DESILVA

Received March 5, 1956

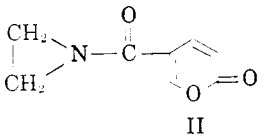
Several previously undescribed substituted amides, esters, and aziridine derivatives of 2-pyrone-6-carboxylic acid, coumalic acid, and isodehydroacetic acid have been characterized. Additional data supporting the assignment of the 5.75 μ (1740 cm^{-1}) infrared absorption band to the 2-pyrone carbonyl group are recorded and additional data defining the borderline tumor growth retardation effects observed in this series of compounds are given.

The recent report[1] that the tumor retardation properties of 6-mercaptopurine are antagonized by coenzyme A suggests that other possible coenzyme A antagonists be examined for tumor growth retradation effects. Since β-methylglutaconic acid and several closely related structures with the same carbon chain are known metabolites in the coenzyme A-catalyzed synthesis of cholesterol,[2,3,4] a continued exploration of 2-pyrone derivatives which are related to these metabolites is being conducted in our laboratories. In this note we wish to record the preparation and properties of some previously undescribed esters, anilides, and aziridino derivatives of isodehydroacetic acid, 2-pyrone-6-carboxylic acid, and coumalic acid.

2-Pyrone-6-carboxylic acid[5] has been converted through its acid chloride to a variety of N-substituted amides (I) using substituted anilides and



I

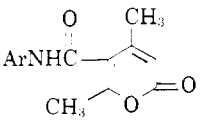


II

aminohetrocycles. The properties of these derivatives are listed in Table I. The acid chloride reacts with ethyleneimine in the presence of triethylamine[6] to give 1-(2-pyrone-6-carbonyl)aziridine. All of these derivatives show an absorption band at 5.75 ± 0.05 μ (1720–1750 $cm.^{-1}$) in the infrared characteristic of the 2-pyrone carbonyl. The amide I carbonyl absorption band appears at 5.9 μ (1690 $cm.^{-1}$) for the aziridine and at 5.95 μ (1680 $cm.^{-1}$) for the anilides. The anilides show two additional strong bands at 6.25 μ (1600 $cm.^{-1}$) and at 6.5 μ (1530 $cm.^{-1}$). Although within the range for the amide II carbonyl, these bands coincide with strong bands at 6.2 μ and 6.5 μ shown by 2-pyrone so that a definite assignment to these bands cannot be made with the available data.

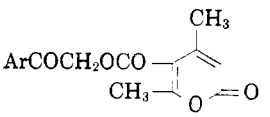
Coumalic acid has also been converted through its acyl chloride to the aziridine derivative (II) by reaction with ethyleneimine. Although the usual conditions of this reaction failed, a 60% yield of the product was obtained when the reaction was run at −30° and the product was recrystallized from ethyl acetate-ligroin at −20°. The infrared absorption spectrum for this compound shows strong absorption bands at 5.75 μ (1740 $cm.^{-1}$) characteristic of the 2-pyrone carbonyl and at 5.95 μ (1660 $cm.^{-1}$) characteristic of the amide carbonyl.

Isodehydroacetyl chloride[7] has been converted to a variety of N-substituted amides (III) listed in Table II by reaction with substituted anilines,



III

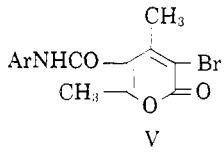
aromatic amines, and aminoheterocycles. The aziridine derivative was also prepared. Potassium isodehydroacetate was converted to the *p*-nitrobenzyl, phenacyl, *p*-bromo and *p*-phenyl phenacyl esters (IV). 3-Bromoisodehydroacetic



IV

acid, available in low yield by bromination of the acid,[8] was converted *via* its acid chloride to its anilide and 2,5-dimethoxyanilide (V). The infrared

(1) Biesele, *Annals N. Y. Acad. Sci.*, **60**, 228 (1954).
(2) Block, Clark, and Harary, *J. Biol. Chem.*, **211**, 687 (1954).
(3) Rudney, *J. Am. Chem. Soc.*, **76**, 2595 (1954); **77**, 1698 (1955).
(4) Rabinowitz, *J. Am. Chem. Soc.*, **77**, 1295 (1955); **76**, 5168, 3037 (1954).
(5) Wiley and Hart, *J. Am. Chem. Soc.*, **76**, 1942 (1954).
(6) Bestian, *Ann.*, **566**, 210 (1950).
(7) Wiley, Smith, and Bauer, *J. Am. Chem. Soc.*, **75**, 244 (1953).
(8) Buchner and Schroeder, *Ber.*, **35**, 790 (1902); Feist, *Ber.*, **26**, 747 (1893).



V

data for the 3-bromoisodehydroacetanilides show absorption bands at 5.75–5.8 μ (1730–1740 cm.$^{-1}$) characteristic of the 2-pyrone carbonyl and at 6.0–6.1 μ (1640–1660 cm.$^{-1}$) characteristic of the Amide I absorption bands. Two or three additional strong absorption bands appear in the 6.2–6.5 μ region where the Amide II and pyrone bands overlap.

Representative examples of the compounds described in this paper have been evaluated by procedures described elsewhere,[9,10] but none of those thus far tested have shown significant activity in retarding the growth of tumors. We have commented briefly on the results of both weight[9] and diameter[10] ratio tests previously.[11] At this time we would add that, of additional materials studied in the interim, decamethylene diisodehydroacetate at rather high dose levels has been rated ±, −, − on the diameter ratio scale (Stock), and that the following weight ratio (Goodson) results have been observed: dodecyl 2-pyrone-6-carboxylate 0.42 (300 mg./kg.); trimethylene glycol bis 2-pyrone 6-carboxylate 0.69 (200 mg./kg.); ethylene glycol bis 2-pyrone-6-carboxylate 0.66 (300 mg./kg.); β-methylglutaconic anhydride 0.79 (30 mg./kg.); and diethylaminoethyl isodehydroacetate 0.76 (50 mg./kg.). The dodecyl ester and β-methylglutaconic anhydride were also tested at 500 mg./kg. and rated negative on the tumor diameter ratio scale. The authors wish to express their appreciation to Dr. Stock and Dr. Goodson for conducting these tests.

EXPERIMENTAL

Details of a typical preparation for each of the types of compounds will be given. Others were prepared by similar procedures except as noted.

2-Pyrone-6-carboxanilide (I, Aryl = phenyl). A solution of 1.5 g. (0.01 mole) of 2-pyrone-6-carbonyl chloride,[b] m.p. 72–73°, in 10 ml. of dry benzene was added to a solution of 2.0 g. (0.02 mole) of freshly distilled aniline in 10 ml. of dry benzene. After warming for 5 minutes the aniline hydrochloride was separated by washing with water. Evaporation gave a solid which was recrystallized from methanol to give 1.7 g. (80%) of the product, m.p. 158°.

The other anilides listed in Table I and Table II were prepared similarly. 3-Bromoisodehydroacetic acid, m.p. 156°, was prepared in 20% yield by the bromination of the acid in water solution[8] and was recrystallized from benzene. It was converted to the acid chloride in 80% yield.

TABLE I

2-PYRONE-6-CARBOXANILIDES

Ar of Formula I	M.P., °C.	Yield,[a] (%)	Nitrogen Analyses Calc'd	Found
C_6H_5	158	80	6.51	6.62
o-$CH_3C_6H_4$	128	85	6.11	6.22
p-$CH_3C_6H_4$	168	85	6.11	6.24
2,6-$(CH_3)_2C_6H_3$	149	80	5.76	5.85
o-$CH_3OC_6H_4$	158	85	5.71	5.72
2,5-$(CH_3O)_2C_6H_3$	186	80	5.09	5.26
m-ClC_6H_4	164	85	5.61	6.66
p-ClC_6H_4	214	90	5.61	5.88
p-$(CH_3)_2NC_6H_4$	226	70	10.85	10.73
p-$(C_2H_5)_2NC_6H_4$	156	75	9.78	9.90

[a] All were recrystallized from methanol.

The reaction of isodehydroacetyl chloride with 2-aminothiazole and 2-aminobenzothiazole gave recrystallizable solids, m.p. 240° and 190° respectively which contained 14.8% and 18.0% nitrogen respectively. Structural assignments in accord with these analyses have not been made.

Phenacyl isodehydroacetate (IV, Aryl = phenyl). A solution of 1.0 g. of phenacyl bromide in 10 ml. of ethanol was refluxed for one hour with a solution of 1.0 g. of potassium isodehydroacetate in 5 ml. of water. On cooling the solid ester precipitated. It was recrystallized from alcohol to give 1.35 g. (80%) of the ester. The other esters listed in Table II were prepared similarly.

1-(Isodehydroacetyl)aziridine. A solution of 4.3 g. (0.025 mole) of isodehydroacetyl chloride in 25 ml. of dry benzene was added dropwise to a solution of 1.0 g. (0.025 mole) of ethyleneimine and 2.5 g. (0.025 mole) of triethylamine in 100 ml. of dry benzene with stirring at 5°. After 30 minutes the precipitated triethylamine hydrochloride was separated and the remaining solution was evaporated at room temperature to give a white solid. Recrystallization from ether at −20° gives 3.5 g. (80%) of the product, m.p. 96°.

Anal. Calc'd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.81; H, 5.78; N, 6.88.

1-(2-Pyrone-6-carbonyl)aziridine. This compound was prepared by the procedure outlined above for the preparation of isodehydroacetyl aziridine. Recrystallization from warm benzene gave 75% of the product, m.p. 98°.

Anal. Calc'd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.13; H, 4.38; N, 8.35.

1-Coumalylaziridine (II). A solution of 1.0 g. (0.02 mole) of ethyleneimine and 2.4 g. (0.02 mole) of triethylamine in 50 ml. of dry ether was added to a solution of 3.7 g. (0.02 mole) of coumalyl chloride in 100 ml. of dry ether at −30°. After 30 minutes stirring the triethylamine hydrochloride was separated. Ligroin was added to the remaining solution which on standing at −20° deposited the product as white flakes. Recrystallization from ethyl acetate and ligroin at −20° gave 2.2 g. (60%) of white needles, m.p. 121°.

Anal. Calc'd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.46; H, 4.59; N, 8.36.

If the order of addition is reversed in this preparation, a procedure reported[6] to give good yields of the N-(2-chloroethyl)amide, a product, m.p. 119°, was obtained which was halogen free. The analytical data correspond to a product formed by addition of two molecules of water to coumalyl aziridine.

Anal. Calc'd for $C_8H_7NO_3 \cdot 2H_2O$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.94; H, 4.15; N, 6.88.

3-Nitro-4,6-dimethyl-2-pyrone.[12] Nitric acid (4.5 ml., *sp. gr.* 1.42) was added to a stirred solution of 6.2 g. (0.050 mole) of 4,6-dimethyl-2-pyrone in 75 ml. of 96% sulfuric

(9) Stock, *Current Research in Cancer Chemotherapy*, Report No. 3–55, p. 3 (1955).

(10) Goodson, Kodras, Palmer, Rowland, and Stone, *Cancer Research*, Suppl. No. 1, p. 45 (1953); Goodson, Barvick, Stone, Ibach, and Palmer, *Cancer Research*, Suppl. No. 2, p. 81 (1955).

(11) Wiley, Hart, Davis, and Smith, *J. Am. Chem. Soc.*, **76**, 4931 (1954).

(12) This compound was prepared by Albert J. Hart.

TABLE II

ISODEHYDROACETIC ACID DERIVATIVES

Ar of Formula II	M.P., °C.	Recryst.[a] from	Yield, (%)	Analyses[b] Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
(a) N-SUBSTITUTED ISODEHYDROACETAMIDES									
2,6-$(CH_3)_2C_6H_3$	170	A–P	50	—	—	5.16	—	—	5.36
2,5-$(CH_3O)_2C_6H_3$	147	M	40	63.36	5.65	—	63.27	5.65	—
$C_6H_5CH_2CH_2$	128	M	40	—	—	5.16	—	—	5.21
2-Pyridyl	237	M–E	35	—	—	11.47	—	—	11.35
2-Pyrimidyl[c]	233 dec.	M	30	58.77	4.52	—	58.71	4.43	—
(b) PHENACYL ESTERS									
Ar of Formula III									
C_6H_5	102	M	—	67.12	5.93	—	66.90	4.98	—
p-$NO_2C_6H_4$	115	M	—	52.63	3.59	—	52.45	3.69	—
p-$C_6H_5C_6H_4$	160	M–B	—	72.92	5.01	—	72.66	5.17	—
p-$NO_2C_6H_4CH_2$[d]	159	M	—	59.40	4.30	—	59.40	4.38	—
(c) 3-BROMOISODEHYDROACETANILIDES									
Ar of Formula IV									
C_6H_5	153	M	40	52.20	3.76	—	52.20	3.75	—
p-$CH_3OC_6H_4$	151	M	35	51.15	4.01	—	51.30	4.14	—
2,5-$(CH_3O)_2C_6H_3$	185	M	30	50.26	4.22	—	50.20	4.23	—

[a] A, ethyl acetate; P, petroleum ether; M, methanol; E, ether; B, benzene. [b] N, nitrogen; C, carbon; H, hydrogen. [c] This compound was prepared by Albert J. Hart. [d] p-Nitrobenzyl ether.

acid at 0–5°. After two hours the solution was poured onto ice to precipitate the crude product. The aqueous solution was extracted with ether to obtain an additional quantity of crude product. The two fractions were combined and recrystallized from benzene-petroleum ether to give 1.0 g. (12%) of plates, m.p. 108°.

Anal. Calc'd for $C_7H_7NO_4$: N, 8.28. Found: N, 8.12.

The infrared absorption data were obtained using potassium bromide pellets in a Baird double beam recording infrared spectrometer.

Acknowledgment. The authors wish to express their gratitude for grants received from the Damon Runyon Fund and the National Cancer Institute of the U. S. Public Health Service which provided partial support for this research, and for a Fulbright Travel Grant held by one of us (CLD).

LOUISVILLE 8, KENTUCKY