Synthesis of 4,10-Dihydro-4,10-dioxo-1*H*-[1]-benzopyrano[3,2-*b*]pyridine, 4,5-Dihydro-4,5-dioxo-1*H*-[1]-benzopyrano[2,3-*b*]pyridine and 1,5-Dihydro-1,5-dioxo-4*H*-[1]-benzopyrano[3,4-*b*]pyridine Derivatives from Aminobenzopyrones.

David T. Connor, Patricia A. Young, and Maximilian von Strandtmann*

Warner-Lambert/Parke-Davis, Pharmaceutical Research Division,
2800 Plymouth Road, Ann Arbor, Michigan 48106

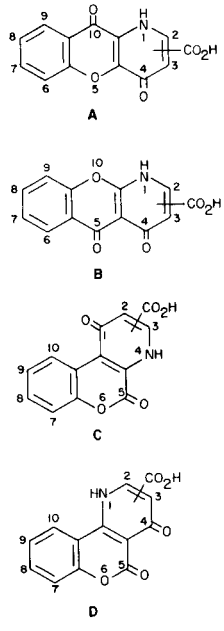
Received January 13, 1981

3-Aminochromone and 3-aminocoumarin were condensed with diethyl ethoxymethylenemalonate and with dimethyl acetylenedicarboxylate to give intermediates, which were thermally cyclized to give 4,10-dihydro-4,10-dioxo-1*H*-[1]-benzopyrano[3,2-*b*]pyridinecarboxylates and 1,5-dihydro-1,5-dioxo-4*H*-[1]-benzopyrano-[3,4-*b*]pyridinecarboxylates. 2-Aminochromone was converted to 4,5-dihydro-4,5-dioxo-1*H*-[1]-benzopyrano-[2,3-*b*]pyridinecarboxylate via an intermediate condensation product with diethyl ethoxymethylenemalonate. These esters were hydrolyzed to the corresponding carboxylic acids (**21**, **30**, **36**, **50**, and **60**). Attempts to prepare 4,5-dihydro-4,5-dioxo-1*H*-[1]-benzopyrano[4,3-*b*]pyridinecarboxylates from 4-aminocoumarin were unsuccessful.

J. Heterocyclic Chem., **18**, 697 (1981).

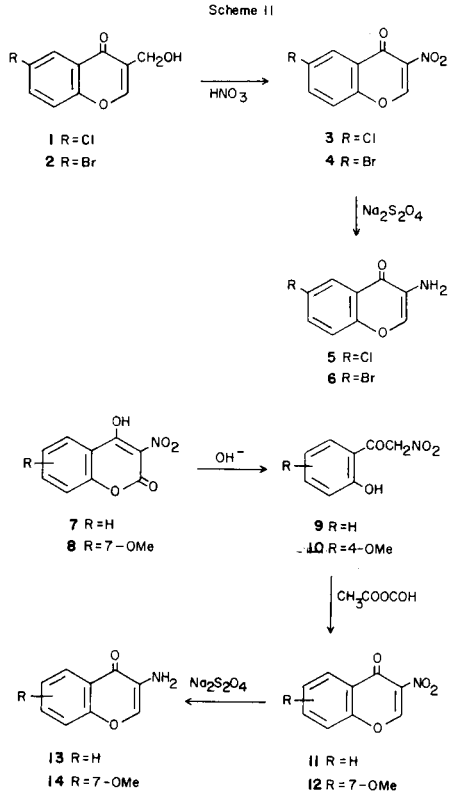
The discovery that disodium cromoglycate possesses prophylactic antiallergy activity (1,2) triggered an explosion in the field of chromone chemistry (3-6), which spilled over into xanthones (7-9), quinolones (10-12), and many related systems (13). Many compounds synthesized in these areas showed potent activity in the rat passive cutaneous anaphylaxis test. Also many fused pyridones are potent antibacterial agents (14).

Scheme I



Thus the various dihydrodioxobenzopyranopyridinecarboxylic acids shown in Scheme I were of interest as potential antiallergy agents. Also, alkylation of the nitrogen atoms in these molecules would lead to potential antibacterial agents. All of the carboxylic acids shown are novel compounds and when we started this work all of the ring systems were unknown (15).

Scheme II

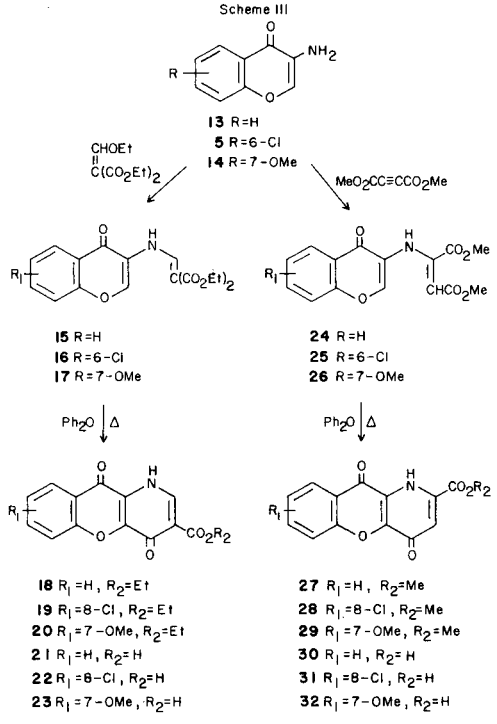


Aminobenzopyrones, such as 3-aminocoumarin, 4-aminocoumarin, 2-aminochromone, and 3-aminochromone, appeared to be attractive starting materials from which the target compounds could be synthesized by the routes shown in Schemes III to VI. 3-aminocoumarin

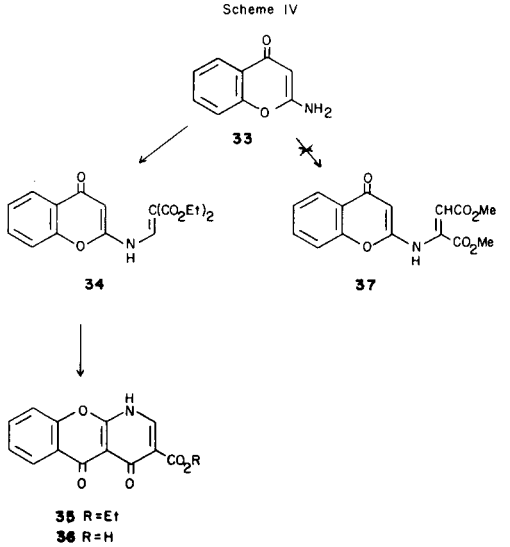
0022-152X/81/040697-06$02.25

(16), 4-aminocoumarin (17), and 2-aminochromone (18) are available by literature procedures. 3-Aminochromones, which had not been described in the literature when we started this work, were synthesized by the routes shown in Scheme II.

Scheme III

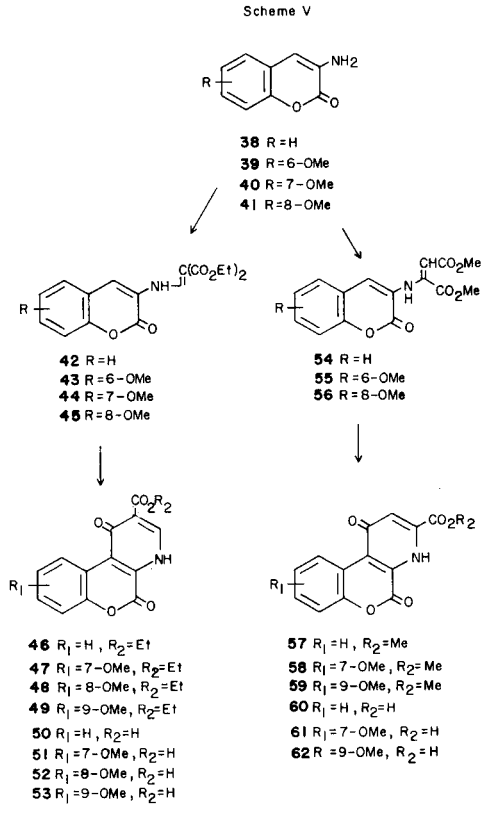


Scheme IV

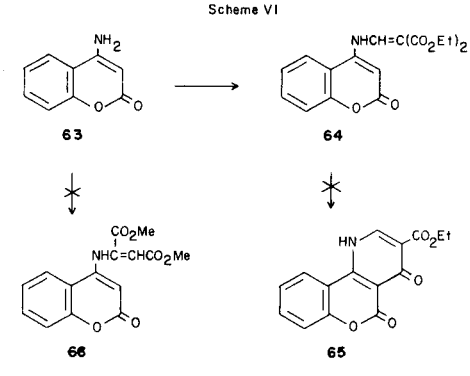


6-Chloro-3-nitrochromone (**3**) and 6-bromo-3-nitrochromone (**4**) were prepared by nitration (19) of the corresponding 3-hydroxymethylchromones (**1** and **2**). Reduction of the nitro groups with sodium dithionite gave the desired aminochromones, **5** and **6**. Nitration of 3-hydroxymethylchromones to give the corresponding 3-nitrochromones worked only when the aromatic ring was deactivated

Scheme V



Scheme VI



towards electrophilic substitution. Nitration of 3-hydroxymethylchromone failed to give a clean product. So a general synthesis of 3-nitrochromones was required. A general synthetic route to 3-nitrochromones is shown in Scheme II (**7** to **13**). Nitroketone (**9**) was prepared by the method of Huebner (20). While we were attempting to convert **9** to **11** with triethyl orthoformate and piperidine, a note (21) appeared describing the transformation of **9** to **11** using acetic formic anhydride. Thus nitrochromones, **11** and **12**, were prepared by this method and then reduced to aminochromones **13** and **14** with sodium dithionite.

Since we initiated this work, interest in the chemistry of 3-aminochromones has flourished. Contemporary with our initial disclosures (22-24) of the utilization of 3-aminochromones for the synthesis of antiallergy agents, addi-

Table I

3-Aminochromones

Compound	Mp °C	Solvent	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
5	184-186	acetone	90	$C_9H_6ClNO_2$	55.10	3.06	7.15	55.01	3.14	6.62
6	171-172	methanol	62	$C_9H_6BrNO_2$	45.00	2.50	5.83	44.86	2.65	5.73
13	117-122	[lit. (21) mp 126-128)	70	$C_9H_7NO_2$			(a)			
14	159-162	ethyl acetate	80	$C_{10}H_9NO_3$			(a)			

(a) These compounds were not obtained analytically pure.

Table II

Products from the Condensation of Amines with Diethyl Ethoxymethylenemalonate

Compound	Mp °C	Solvent	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
15	155-157	Ethyl acetate/Ethanol	63	$C_{17}H_{17}NO_6$	61.63	5.17	4.23	61.64	5.27	4.43
16	143-145	Ethyl acetate	68	$C_{17}H_{16}ClNO_6$	55.82	4.41	3.83	55.86	4.50	3.88
17	139-141	Ethyl acetate	34	$C_{18}H_{19}NO_7$	59.83	5.30	3.88	59.81	5.15	3.75
34	138-140	Ethyl acetate	91	$C_{17}H_{17}NO_6$	61.63	5.17	4.23	61.80	5.17	4.28
42	134-135	Hexane	89	$C_{17}H_{17}NO_6$	61.63	5.17	4.23	61.44	5.20	4.14
43	134-136	Ethyl acetate	68	$C_{18}H_{19}NO_7$	59.83	5.30	3.88	59.63	5.50	3.97
44	202-203	Ethyl acetate	36	$C_{18}H_{19}NO_7$	59.83	5.30	3.88	59.80	5.67	3.64
45	193-194	Ethyl acetate	99	$C_{18}H_{19}NO_7$	59.83	5.30	3.88	59.64	5.34	3.71
64	96-98	Hexane	53	$C_{17}H_{17}NO_6$	61.63	5.17	4.23	61.68	5.20	4.25

Table III

Products from the Condensation of Amines with Dimethyl Acetylenedicarboxylate

Compound	Mp °C	Solvent	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
24	155-157	Ethanol	58	$C_{15}H_{13}NO_6$	59.40	4.32	4.62	59.21	4.43	4.62
25	158-160	Ethyl acetate	80	$C_{15}H_{12}ClNO_6$	53.35	3.58	4.15	53.31	3.68	4.13
26	134-138	Ethyl acetate	38	$C_{16}H_{15}NO_7$	57.66	4.54	4.20	57.39	4.41	4.16
54	150-151	Ethyl acetate	91	$C_{15}H_{13}NO_6$	59.40	4.32	4.62	59.53	4.42	4.61
55	152-154	Ethyl acetate	39	$C_{16}H_{15}NO_7$	57.66	4.54	4.20	57.32	4.55	3.96
56	165-167	Ethyl acetate	81	$C_{16}H_{15}NO_7$	57.66	4.54	4.20	57.66	4.58	4.01

tional novel syntheses of 3-aminochromones have been reported (25-27). Also, the chemistry of 3-aminochromones has been investigated (28) and further examples of the use of 3-aminochromones as synthons for the synthesis of potential drugs have appeared (29, 30).

Having secured routes to our desired starting materials, the synthesis of the target compounds was commenced. 3-Aminochromone (**13**) was heated with diethyl ethoxymethylenemalonate to give **15**. The reaction was complete in four hours at 120°. 3-Aminocoumarin (**38**) behaved in a similar fashion. Both **13** and **38** reacted with dimethyl acetylenedicarboxylate at room temperature to give **24** and **54** respectively. 2-Aminochromone (**33**) reacted with diethyl ethoxymethylenemaloante to give **34**. This reaction was slower than the corresponding reactions with **13** and **38** requiring 16 hours at 130°. 4-Aminocoumarin (**63**) failed to react with diethyl ethoxymethylenemalonate at 130° and was heated at 180° for 24 hours to obtain **64**.

Table IV

Benzopyranopyridine Esters

Compound	Mp °C	Solvent	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
18	294-295	DMF	52	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	63.09	3.91	4.94
19	330-338	DMF	93	$C_{15}H_{10}ClNO_5$	56.35	3.15	4.38	56.36	3.23	4.68
20	277-280	DMF	64	$C_{16}H_{13}NO_6$	60.95	4.16	4.44	60.80	4.34	4.34
27	244-245	DMF	36	$C_{14}H_9NO_5$	61.99	3.34	5.16	61.73	3.36	5.11
28	300-305	DMF	88	$C_{14}H_8ClNO_5$	55.01	2.64	4.58	54.94	2.74	4.44
29	258-260	DMF	39	$C_{15}H_{11}NO_6$	59.80	3.68	4.65	59.65	3.73	4.75
35	174-175	DMF	83	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	63.11	3.87	4.90
46	284-285	DMF	99	$C_{15}H_{11}NO_5$	63.16	3.89	4.91	63.17	3.90	5.06
47	264-265	DMF	70	$C_{16}H_{13}NO_6 \cdot 1/2DMF$	59.85	4.67	5.82	59.93	4.58	5.49
48	295-296	DMF	84	$C_{16}H_{13}NO_6$	60.95	4.16	4.44	61.25	4.18	4.21
49	253-254	DMF	90	$C_{16}H_{13}NO_6$	60.95	4.16	4.44	60.66	4.16	4.57
57	225-227	DMF	93	$C_{14}H_9NO_5$	61.99	3.34	5.16	62.06	3.49	5.07
58	268-272	DMF	77	$C_{15}H_{11}NO_6$	59.80	3.68	4.65	59.74	3.98	4.72
59	245-250	DMF	75	$C_{15}H_{11}NO_6$	59.80	3.68	4.65	59.44	3.75	4.56

Table V

Benzopyranopyridine Carboxylic Acids

Compound	Mp °C	Solvent	Yield %	Formula	Analysis Calcd. C	H	N	Found C	H	N
21	>330 (dec)	DMF	94	$C_{13}H_7NO_5$	60.71	2.74	5.45	60.61	2.94	5.73
22	325-327	DMF	87	$C_{13}H_6ClNO_5$	53.54	2.07	4.80	53.25	2.18	4.81
23	318-219	DMF	82	$C_{14}H_9NO_6$	58.54	3.16	4.88	58.35	3.27	4.89
30	>290 (dec)	DMF	72	$C_{13}H_7NO_5$	60.71	2.74	5.45	60.60	3.01	5.74
31	290-320 (dec)	DMF	81	$C_{13}H_6ClNO_5$	53.54	2.07	4.80	53.26	2.22	4.76
32	253-254	DMF	42	$C_{14}H_9NO_6$	58.54	3.16	4.88	58.89	3.59	5.27
36	335-340	DMF	93	$C_{13}H_7NO_5$	60.71	2.74	5.45	60.51	2.74	5.43
50	295-300 (dec)	DMF	59	$C_{13}H_7NO_5$	60.71	2.74	5.45	60.25	2.79	5.29
51	330-335	(a)	97	$C_{14}H_9NO_6$	58.54	3.16	4.88	58.16	3.19	4.88
52	300-305	(a)	94	$C_{14}H_9NO_6 \cdot 1/4H_2O$	57.63	3.26	4.80	57.35	3.47	4.64
53	320-325	DMF	90	$C_{14}H_9NO_6$	58.54	3.16	4.88	58.36	3.29	4.82
60	265-268	DMF/Methanol	65	$C_{13}H_7NO_5$	60.71	2.74	5.45	60.31	2.80	5.38
61	290-295	(a)	72	$C_{14}H_9NO_6$	58.54	3.16	4.88	58.42	3.35	4.84
62	265-270	(a)	80	$C_{14}H_9NO_6 \cdot 1/4H_2O$	57.63	3.26	4.80	57.89	3.16	4.80

(a) These compounds were too insoluble for recrystallization.

Amines, **33** and **63**, failed to react with dimethyl acetylenedicarboxylate. These results reflect the reduced basicity and nucleophilicity of the amino groups in **33** and **63** compared to those in **13** and **38**. Amines, **13** and **38** behave as normal aryl amines. The amino groups in **33** and **63** are deactivated by conjugation with their respective carbonyl groups and behave as vinylogous amides.

Compounds, **15, 24, 34, 42,** and **54**, cyclized in refluxing diphenyl ether to give the desired tricyclic esters **18, 27, 35, 46,** and **57**. Methyl esters, **24** and **54**, cyclized faster than ethyl esters, **15** and **42**, based on cessation of methanol or ethanol evolution. The reactions were worked up as soon as methanol or ethanol evolution stopped. If the reactions were allowed to proceed for longer times, some decomposition took place. Compound **64** was recovered unchanged after 30 minutes in refluxing diphenyl ether. Extended reaction times gave tar.

Esters, **18, 35, 46,** and **57**, were hydrolyzed to the corresponding acids, **21, 36, 50,** and **60** with 5*N* hydrochloric acid at 100°. Ester, **27**, was converted to acid, **30**, with 1*N* sodium hydroxide at room temperature.

Thus 3-aminochromones, 2-aminochromones, and 3-aminocoumarins were useful synthons for the elaboration of benzopyranopyridines **A, B,** and **C** respectively,

but 4-aminocoumarin could not be converted to compounds to type D.

An account of the biological properties of these compounds will be the subject of a forthcoming publication from this laboratory.

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. Nmr spectra were recorded on a Perkin-Elmer R-12-B spectrometer at 60 MHz and a Varian EM 390 at 90 MHz with TMS as internal standard. Infrared spectra were recorded on a Beckman IR-18A spectrometer and a Beckman IR-9 spectrometer. Ultraviolet spectra were recorded on a Beckman DK-I spectrometer and on a Cary 118 spectrometer.

General Procedure for the Reduction of 3-Nitrochromones to 3-Aminochromones with Sodium Dithionite.

Sodium dithionite (0.115 mole) was added to a suspension of the 3-nitrochromone (0.037 mole) in water (80 ml) and absolute ethanol (30 ml). The reaction mixture was refluxed under nitrogen for three hours, concentrated at reduced pressure, and filtered. The product was washed with water. Recrystallization (Table I) gave analytically pure material.

General Procedure for the Condensation of Amines with Diethyl Ethoxymethylenemalonate.

A mixture of amine (0.01 mole) and diethyl ethoxymethylenemalonate (0.016 mole) was heated at 120-180° for from four to 24 hours under nitrogen. The reaction mixture was cooled and filtered. The product was washed with ethyl acetate. Recrystallization (Table II) gave analytically pure material. Compounds prepared by this method with typical spectral data include:

Diethyl{[(4-oxo-4*H*-[1]-benzopyran-3-yl)amino]methylene}propanedioate (**15**).

The compound **15** had uv (ethanol): max 284 (20,400) and 320 (27,680); ir (nujol): 3095 (NH), 1675 and 1642 cm^{-1} (CO); nmr (dimethylsulfoxide): δ 10.59 (d, 1, J = 14 Hz, NH), 8.91 (s, 1, C_2-H), 8.39 (d, 1, J = 14 Hz, N-CH), 8.3-7.3 (m, 4, ArH), 4.19 (m, 4, CH_2), and 1.27 (m, 6, CH_3).

Diethyl{[(4-oxo-4*H*-[1]-benzopyran-2-yl)amino]methylene}propanedioate (**34**).

The compound **34** had uv (ethanol): max 248 (1,100) and 330 (41,500): ir (nujol): 3100 (NH), 3200 (NH), 1700, 1655, and 1635 cm^{-1} (CO); nmr (deuteriochloroform): δ 11.4 (d, 1, J = 12 Hz, NH), 8.5 (d, 1, J = 12 Hz, N-CH), 8.4-7.3 (m, 4, ArH), 5.95 (s, 1, C_3-H), 4.35 (m, 4, CH_2), and 1.4 (t, 6, CH_3).

Diethyl {[(2-oxo-2*H*-[1]-benzopyran-3-yl)amino]methylene}propanedioate (**42**).

The compound **42** had uv (ethanol): max 268 (5600) and 360 (39,200); ir (nujol): 3100 (NH), 1710 and 1650 cm^{-1} (CO); nmr (deuteriochloroform): δ 12 (d, 1, J = 12 Hz, NH), 8.4 (d, 1, J = 12 Hz, N-CH), 7.7-7.2 (m, 5, ArH), 4.3 (m, 4, CH_2), and 1.4 (m, 6, CH_3).

Diethyl{[(2-oxo-2*H*-[1]-benzopyran-4-yl)amino]methylene}propanedioate (**64**).

This compound **64** had uv (ethanol): max 225 (10,800) and 320 (32,800); ir (nujol): 3250 (NH), 1732, 1700, and 1670 cm^{-1} (CO); nmr (deuteriochloroform): δ 11.1 (d, 1, J = 12 Hz, NH), 8.7 (d, 1, N-CH), 7.7 (s, 1, C_3-H), 7.9-7.2 (m, 4, ArH), 4.38 (m, 4, CH_2), and 1.42 (m, 6, CH_3).

General Procedure for the Condensation of Amines with Dimethyl Acetylenedicarboxylate.

A mixture of amine (0.02 mole) and dimethyl acetylenedicarboxylate (0.03 mole) in methanol (50 ml) was stirred at room temperature for from 24 to 48 hours. The product was filtered off and washed with methanol. Recrystallization (Table III) gave analytically pure material. Compounds prepared by this method with typical spectral data include:

Dimethy-2-[(4-oxo-4*H*-[1]-benzopyran-3-yl)amino]-2-butenedioate (**24**).

The compound **24** had uv (ethanol): max 238 (16,540) and 314 (18,400); ir (nujol): 3240 (NH), 1738, 1668, and 1643 cm^{-1} (CO); nmr (deuteriochloroform): δ 9.43 (bs, 1, NH), 8.2 (d, 1, ArH), 7.94 (s, 1, C_2-H), 7.7-7.2 (m, 3, ArH), 5.62 (s, 1, vinyl), and 3.75 (s, 6, CH_3).

Dimethyl-2-[(2-oxo-2*H*-[1]-benzopyran-3-yl)amino]-2-butenedioate (**54**).

The compound **54** had uv (ethanol): max 350 (25,600); ir (nujol): 3200 (NH), 1725, 1710 and 1680 cm^{-1} (CO); nmr (deuteriochloroform): δ 9.8 (bs, 1H, NH), 7.5-7.2 (m, 4, ArH), 6.95 (s, 1, C_4-H), 5.62 (s, 1, vinyl), 3.82 (s, 3, CH_3), and 3.75 (s, 3, CH_3).

General procedure for cyclization of the esters in diphenyl ether.

A solution of substrate (3.0 g) in diphenyl ether (50 ml) was refluxed under a Dean-Stark trap under nitrogen until the evolution of ethanol (or methanol) ceased (10 to 90 minutes). The reaction mixture was cooled and filtered. The product was washed with ethyl acetate and sucked dry. Recrystallization from dimethylformamide (Table IV) gave analytically pure material. Compounds prepared by this method with typical spectral include:

Ethyl 4,10-Dihydro-4,10-dioxo-1*H*-[1]-benzopyrano[3,2-*b*]pyridine-3-carboxylate (**18**).

The compound **18** had uv (ethanol): max 242 (22,100), 257 (22,400), and 347 (7,400); i.r. (nujol): 3160 (NH), 1730, 1675, and 1632 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 9.41 (s, 1, C_2-H), 8.6-8.0 (m, 4, ArH), 4.80 (q, 2, CH_2), and 1.62 (t, 3, CH_3).

Methyl 4,10-Dihydro-4,10-dioxo-1*H*-[1]-benzopyrano[3,2-*b*]pyridine-2-carboxylate (**27**).

The compound **27** had uv (ethanol): max 242 (32,000), 260 (23,500), and 360 (7,100); i.r. (nujol): 3290 (NH), 1742, 1677, and 1638 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 8.5 (m, 1, ArH), 8.28 (s, 1, C_3H), 7.96 (m, 3, ArH), and 4.31 (s, 3, CH_3).

Ethyl 4,5-Dihydro-4,5-dioxo-1*H*-[1]-benzopyrano[2,3-*b*]pyridine-3-carboxylate (**35**).

This compound **35** had uv (ethanol): max 244 (35,000) and 336 (7,000); i.r. (nujol): 1695 and 1630 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 9.35 (s, 1, C_2-H), 8.7-7.6 (m, 4, ArH), 4.75 (q, 2, CH_2), and 1.62 (t, 3, CH_3).

Ethyl 1,5-Dihydro-1,5-dioxo-4*H*-[1]-benzopyrano[3,4-*b*]pyridine-2-carboxylate (**46**).

The compound **46** had uv (ethanol): max 274 (10,200), 350 (10,500), and 364 (10,500); ir (nujol): 1760 and 1735 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 9.55 (s, 1, C_3-H), 9.25 (d, 1, ArH), 8.2-7.5 (m, 3, ArH), 4.87 (q, 2, Ch_2), and 1.65 (t, 3, CH_3).

Methyl 1,5-Dihydro-1,5-dioxo-4*H*-[1]-benzopyrano[3,4-*b*]pyridine-3-carboxylate (**57**).

The compound **57** had uv (ethanol): max 246 (22,500) and 334 (9,000); ir (nujol): 3350 (NH), 1755 and 1730 cm^{-1} (CO); nmr (trifluoroacetic acid): δ 9.25 (d, 1, ArH), 8.5 (s, 1, C_2-H), 8.2-7.5 (m, 3, ArH), and 4.35 (s, 3, CH_3).

General Procedure for Hydrolysis of the Esters (Table IV) to give the Acids (Table V).

A suspension of the ester (0.037 mole) in 5*N* hydrochloric acid (170 ml) was stirred at 100° for 16 hours under nitrogen. The reaction mixture was cooled and filtered. The solid product was washed with water, with acetone, and sucked dry. Recrystallization (Table V) gave analytically pure material.

Procedure for Hydrolysis of Esters **27**, **28**, and **29** to Acids **30**, **31**, and **32**.

A suspension of the ester (0.0034 mole) in 1*N* sodium hydroxide solution (20 ml) was stirred at room temperature for 24 hours. The solid was filtered of, washed with water, with acetone, and suspended in 5*N* hydro-

chloric acid. The product was filtered off, washed with water, with acetone, and sucked dry. Recrystallization (Table V) gave analytically pure material.

Acknowledgement.

We thank S. England, E. Shoeb, R. B. Scott, C. Spurlock, F. A. MacKellar, R. E. Saville, and R. C. Greenough for spectral data and C. E. Childs and U. Zeek for microanalyses.

REFERENCES AND NOTES

(1) J. B. L. Howell and R. E. C. Altounyan, *Lancet*, **2**, 539 (1967).

(2) J. S. G. Cox, *Nature*, **216**, 1328 (1967).

(3) M. von Strandtmann, S. Klutchko, M. P. Cohen and J. Shavel, Jr., *J. Heterocyclic Chem.*, **9**, 171 (1972); S, Klutchko, M. P. Cohen, J. Shavel, Jr., and M. von Strandtmann, *ibid.*, **11** 183 (1974).

(4) A. Nohara, *Tetrahedron Letters* 1187 (1974); A. Nohara, K. Ukawa and Y. Sanno, *Tetrahedron*, **30**, 3563 (1974); A. Nohara, H. Kuriki, T. Saijo, K. Ukawa, T. Murata, M. Kanno and Y. Sanno, *J. Med. Chem.*, **18**, 34 (1975).

(5) J. R. Bantick, H. Cairns, A. Chambers, R. Hazard, J. King, T. B. Lee and R. Minshull, *ibid.*, **19**, 817 (1976); R. A. Appleton, J. R. Bantick, T. R. Chamberlain, D. N. Harden, T. B. Lee and A. D. Pratt, *ibid.*, **20**, 371 (1977).

(6) G. P. Ellis in "Chromenes, Chromanones, and Chromones", G. P. Ellis, Ed., J. Wiley and Sons, Inc., New York, N.Y., 1977.

(7) J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks, A. P. Roszkowski, A. Van Horn and J. H. Fried, *J. Med. Chem.*, **15**, 1032 (1972); J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks and J. H. Fried, *ibid.*, **21**, 669 (1978).

(8) W. D. Jones, Jr., W. L. Albrecht, N. L. Munro and K. T. Stewart, *ibid.*, **20**, 594 (1977).

(9) A. C. Barnes, P. W. Hairsine, S. S. Matharu, P. J. Ramm and J. B. Taylor, *ibid.*, **22**, 418 (1979).

(10) D. P. Evans, D. J. Gilman, D. S. Thompson and W. S. Waring, *Nature*, **250**, 592 (1974).

(11) C. M. Hall, H. G. Johnson and J. B. Wright, *J. Med. Chem.*, **17**, 685 (1974).

(12) E. H. Erickson, L. R. Lappi, T. K. Rice, K. F. Swingle and M. Van Winkle, *ibid.*, **21**, 984 (1978); E. H. Erickson, C. P. Hainline, L. S. Lenon, C. J. Matson, T. K. Rice, K. F. Swingle and M. Van Winkle, *ibid.*, **22**, 816 (1979).

(13) S. C. Bell, R. J. Capetola and D. M. Ritchie in "Annual Reports in Medicinal Chemistry", Vol. 6, H-J Hess, Ed., Academic Press, New York, N.Y., 1979, p. 51.

(14) R. Albrecht in "Drug Research", Vol 21, E. Jucker, Ed., Birkhauser A G, Basel, 1977, p. 9.

(15) Synthesis of the 1,5-dihydro-1,5-dioxo-1*H*-1-benzopyrano[3,4-*b*]-pyridine ring system has been described. M. A. Khan and A. L. Gemal, *J. Heterocyclic Chem.*, **14**, 1009 (1977).

(16) F. W. Lynch, *J. Chem. Soc.*, **101**, 1758 (1912).

(17) V. A. Zagorevski and N. V. Dudykina, *Zh. Obshch. Khim.*, **32**, 2384 (1962).

(18) Y. Kawase and K. Sakashite, *Bull. Chem. Soc. Japan*, **35**, 1869 (1962).

(19) M. von Strandtmann and S. Klutchko, U.S. Patent 3,906,005 (1975).

(20) C. F. Huebner and K. P. Link, *J. Am. Chem. Soc.*, **67**, 99 (1945).

(21) G. J. P. Becket and G. P. Ellis, *Tetrahedron Letters*, 719 (1976).

(22) D. T. Connor, P. A. Young and M. von Strandtmann, U.S. Patent 4,046,769 (1977).

(23) D. T. Connor, P. A. Young and M. von Strandmann, U.S. Patent 4,066,655 (1978).

(24) D. T. Connor, P. A. Young and M. von Strandtmann, U.S. Patent 4,076,729 (1978).

(25) V. Szabo and L. Nemeth, *Magy. Kem. Foly.*, **83**, 429 (1977).

(26) V. Szabo and L. Nemeth, *ibid.*, **84**, 164 (1978).

(27) G. J. Becket, G. P. Ellis, and M. I. U. Trindade, *J. Chem. Res.*, 47 (1978).

(28) V. Szabo and L. Nemeth, *Magy. Kem. Foly.*, **84**, 494 (1978).

(29) Europe Patent 488 (1979) issued to CIBA GEIGY A G.

(30) Europe Patent 3-360 (1979) issued to CIBA GEIGY A G.