reserpine-induced ptosis. In these instances, apparently the stimulation mechanism is not of MAO inhibition origin.

Compounds IV and XII show significant ($P > 0.05$) increased sleeping times in mice. The control group had an average sleeping time of 11.7 ± 8.0 min. The animals receiving IV showed a sleeping time of 24.4 ± 5.0 min and those receiving XII showed 28.3 ± 2.4 min. These data correlated well with the data obtained in the ptosis-inhibition study, verifying the ptosis test that these two compounds have MAO inhibitory activity. Had the activity of these compounds been merely stimulatory, then a decreased sleeping time would have been observed.

In view of the mode and rate of administration of aqueous solutions of IV and XII, the effect on rabbit blood pressure and respiration was somewhat delayed in becoming apparent. After a 5-hr time lapse from the initial administration of IV at a dose level of 0.85 mmole/kg iv, there was an acute rise in blood pressure to a systolic level of 150 mm from a previous level of 110 mm. This pressure remained fairly steady for 2 hr after which time toxic manifestations were noted.

The respiratory rate showed a gradual increase over the entire period of observation from a level of 30/min after pentobarbital anesthesia to approximately 70/min after 3.5 hr even with additional pentobarbital. These data suggest central stimulatory activity sufficient to reverse pentobarbital depression. Indeed, once the stimulatory effects become apparent, the animal required an additional total dose of 46 mg/kg of pentobarbital in order to maintain the anesthetized state.

The results of the EEG study showed that at the dose level of 180 mg/kg ($T + 5$ hr) bundled spiking could be observed. At this time, the animal was tested for response to pain and deep tendon reflexes. The negative results indicated that the faster EEG activity was probably not due to light anesthesia.

Changes observed in the EKG were not uncommon for animals under anesthesia for this period of time and showed no myocardial damage or cardiotropic activity.

Similar intravenous administration of XII at 1.35 mmoles/kg did not show the type of response analogous to IV. Further research on this is in progress.

Acknowledgment.—The authors wish to thank Mrs. J. Rim for her technical assistance and Mr. G. Johnson, Mr. D. Calley, and Miss M. Golaz for their help in the biological evaluation of the compounds.

3-Phenylcinnolines. I. Some Reactions and Derivatives of 3-Phenylcinnoline-4-carboxylic Acids

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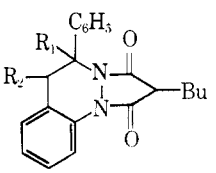
A series of amide, hydrazide, and ester derivatives of the title acids and two phenylbutazone analogs of 3-phenylcinnoline were prepared. These were examined for pharmacological activity.

In a continued search for less toxic analogs of phenylbutazone, the report of lower toxicity of its benzyl analog[1] and the ready availability of 3-phenylcinnoline-4-carboxylic acid[2] led initially to the preparation of the "benzyl-bridged"[3] analogs,[4] Ia and Ib, and of derivatives of this acid for general pharmacological testing. Later, the development of methods[5] for converting this acid to the 4-chloro analog from which cinnolines vaguely analogous to chloroquine might be prepared, and the discovery of the hypotensive activity of certain 4-aminocinnolines encouraged an expansion of the series.



Ia, $R_1 + R_2 = —$
b, $R_1 = R_2 = H$

The starting materials (Chart I and Table I) were prepared by a slight modification of the procedures of Baumgarten and Furnas[2] (see Experimental Section). Attempts to extend this synthesis were only partially successful; under the conditions used, a reasonable variation of substituents appears to be feasible on the phenyl of the aldehyde portion of the hydrazones II, but several attempts to use other aldehydes such as acetaldehyde, phenylacetaldehyde, or isonicotinaldehyde were unsuccessful. Further, substituents in the phenylhydrazine ring of II appear to be limited to those which allow mild conditions for the Friedel–Crafts reaction: methyl (IIf and IIg) went well as was reported by Baumgarten and Furnas for IIf,[2] but fluoro (II, R′ = F; R = H) would not allow cyclization to the isatin.[5] In a single experiment with the methoxyhydrazone IIh a low yield of slightly impure acid (IVh) was obtained after rearrangement. Since

(1) J. Büchi, J. Ammann, R. Lieberherr, and E. Eichenberger, *Helv. Chim. Acta*, **36**, 75 (1953).

(2) H. E. Baumgarten and J. L. Furnas, *J. Org. Chem.*, **26**, 1536 (1961).

(3) The phenyl-bridged analogs have been prepared in several laboratories: H. S. Lowrie, *J. Med. Pharm. Chem.*, **5**, 1362 (1962), and references therein.

(4) The 4-phenyl isomer of Ia has recently been reported by (a) D. E. Ames, R. F. Chapman, and H. Z. Kucharska, *J. Chem. Soc.*, 5659 (1964); and (b) T. Wagner-Jauregg, F. Schatz, and U. Jahn [U. S. Patent 3,222,366 (1965); French Patent 1,393,596 (1965)] who prepared a series of related derivatives.

(5) Paper II: H. S. Lowrie, *J. Med. Chem.*, **9**, 670 (1966).

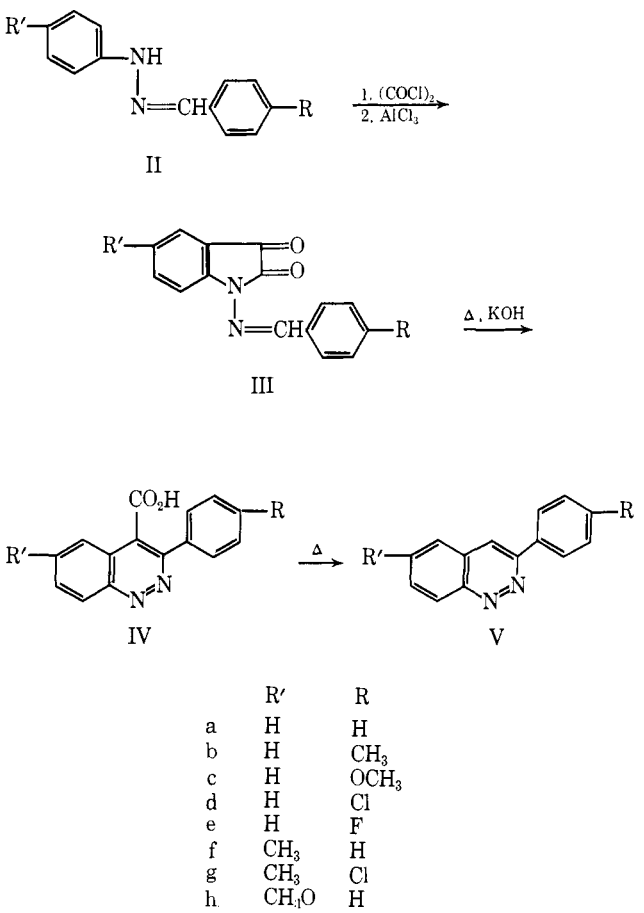
(6) The sequence was reported[2] unsuccessful with the corresponding chloro compound.

TABLE I

Structure[a]	Crystn solvent[b]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	R, % Calcd	R, % Found
IIIb	Ee	190–191	72.71	72.47	4.58	4.61	10.60	10.56		
IVb	A	207–208	72.71	72.65	4.58	4.63	10.60	10.45		
IIIc	Ee	173–175	68.56	68.36	4.32	4.37	10.00	9.94	11.07	11.28
IVc	Aa	249–250	68.56	68.54	4.32	4.39	10.00	10.04	11.07	10.85
Vc	Ee[c]	111–112	76.25	76.56	5.12	5.10			13.13	13.28
IIId	E	237–238	63.28	63.15	3.19	3.24	9.84	9.65		
IVd	A	210–211	63.28	63.61	3.19	3.35	9.84	9.69		
Vd	SKC	146.5–147.5	69.86	70.16	3.77	4.07	11.64	11.86	14.73	14.55
IIIe	Mc	223–224	67.16	66.98	3.38	3.76	10.45	10.68		
IVe	B	216–217	67.16	67.22	3.38	3.57	10.45	10.63	7.08	6.95
IIIf	Ee	150–151[d]					11.11	10.74		
IVf	B	222–223[d]					10.58	10.68		
Vf	M	139.6–140.3[d]					12.72	12.91		
IIIg[e]	Ee–SKB	147.5–148.5	68.71	68.77	5.35	5.46			14.49	14.69
IIIg	Ee	216–217					9.38	9.34	11.87	12.16
IVg	B	211–212	64.33	64.23	3.71	3.90	9.38	9.54		
Vg	M	185–186	70.72	70.97	4.35	4.59	11.00	11.01	13.92	14.01
IVh[f]	Aa	229–230	68.56	67.91	4.32	4.45	10.00	10.28		

[a] See Chart I. [b] Ee, ethyl ether; E, ethanol; SK (Skellysolve, see ref 20); A, acetone; Aa, acetic acid; Mc, methylene chloride; B, butanone; M, methanol; C, chloroform; Bz, benzene. [c] The principal contaminant after decarboxylation is the demethylated material which is best removed by extraction by dilute potassium hydroxide before crystallization. [d] Baumgarten and Furnas[2] give melting points of IIIf, 145–145.5°; IVf, 229–229.5°; Vf, 138.5–139.5°. [e] This hydrazone was prepared in refluxing Skellysolve L.[20] [f] In a single experiment the isatin was not obtained crystalline; the oil obtained by evaporation of the dried CH_2Cl_2 solution (see IIIa) was rearranged without purification.

CHART I



	R′	R
a	H	H
b	H	CH_3
c	H	OCH_3
d	H	Cl
e	H	F
f	CH_3	H
g	CH_3	Cl
h	CH_3O	H

the experimental variations are by no means exhausted, a further examination might broaden the usefulness of the reaction.[7]

For the acids IV in Table I, the solitary activity found in any of the tests[8–12] was the borderline[13a] anti-inflammatory[8] action of IVd.

Reduction of 3-phenylcinnoline with zinc dust and barium hydroxide[14a] yielded a dihydro derivative,[14b] undoubtedly the 1,4,[15] which tautomerized on reaction with butylmalonyl dichloride to yield the derivative Ia.[4a] Catalytic reduction furnished the corresponding tetrahydrocinnoline (Ib). The structures of these compounds are confirmed by the similarity of their infrared absorption spectra to those of other malonyl derivatives[3] and to that of phenylbutazone, and by their showing the expected nmr spectra.[15] Unfortunately, neither showed antiinflammatory activity[8,9] at the screening dose.[13a]

Reaction of the acids IV with thionyl chloride provided the acid chlorides VI which were treated as described below, and which were used to prepare the amides, hydrazides, and esters in Tables II–VI.

(7) The author wishes to acknowledge the excellent technical assistance of Mr. Richard J. Salzmann in the preparation of several of the compounds in Table I.

(8) Compounds were tested as inhibitors of yeast-induced foot edema in male, Badger rats (120 g). The minimal effective dose of phenylbutazone was 120 mg/kg subcutaneously, 175 mg/kg orally.

(9) We are indebted to Drs. F. J. Saunders and E. F. Nutting and their staff for the data from these tests in ref 8 and 10.

(10) Inhibition of cotton pellet induced granuloma growth was measured in adrenalectomized, male, Sprague–Dawley rats (200 g) for a 2-day period. A screening dose of 200 mg/kg/day orally was used. The minimal effective dose of phenylbutazone was 25 mg/kg/day orally.

(11) (a) Hypotensive activity: the decrease in mean pressure following injection of the test compound in the femoral vein was directly recorded from arterial cannulation of normal dogs anesthetized with pentobarbital sodium. The screening dose was 5 mg/kg. (b) Antiulcer activity: following intragastric administration of the test compound to male Charles River rats (250 g), inhibition was observed of ulceration induced by pyloric ligation as described by H. Shay, S. A. Kamarov, D. Meranque, M. Gruenstein, and H. Siblet, *Gastroenterology*, **5**, 43 (1945). (c) Diuretic activity: the diuresis produced in 5 hr by intragastric administration of the test compound in saline-primed, male, Sprague–Dawley rats (300 g) was compared with that of controls treated with hydrochlorothiazide.

(12) We are indebted to Dr. D. L. Cook and Mr. R. S. Jacobs and their staff for data from the tests in ref 11.

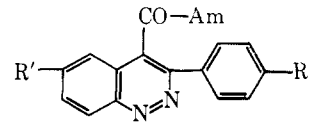
(13) (a) 80 mg/kg subcutaneously; (b) 320 mg/kg orally.

(14) (a) M. H. Duval, *Bull. Soc. Chim. France*, [4] **7**, 727 (1910). (b) This compound was obtained along with 3-phenylcinnoline by the $LiAlH_4$ reduction of 3-phenyl-4-cinnolinol: C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.*, 2858 (1959).

(15) L. S. Besford, G. Allen, and J. M. Bruce, *J. Chem. Soc.*, 2867 (1963).

TABLE II

AMIDES

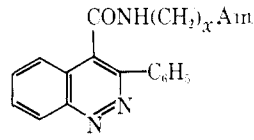


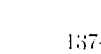
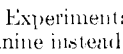
No.[a]	R	R'	Am	Crystn solvent[b]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	H	H	NH_2	E	272–273	72.27	72.50	4.45	4.22	16.86	16.57
2	Cl	H	NH_2	E	224–228	63.50	63.34	3.55	3.65	14.81	14.71
3	F	H	NH_2	E	236–237	67.41	67.46	3.77	4.01	15.72	15.75
4	CH_3	H	NH_2	E	266–267	72.98	72.94	4.98	4.96	15.96	15.88
5	OCH_3	H	NH_2	E	248–250	68.80	68.62	4.69	4.59	15.05	15.29
6	Cl	CH_3	NH_2	E	236–237	64.54	64.45	4.06	4.21	14.11	13.87
7	H	H	$NHCH_3$	M	209–212	72.98	73.05	4.98	4.96	15.96	15.78
8	H	H		Ee–SKA	160–162	75.22	75.42	5.65	5.78	13.85	13.67
9	H	H		M	173–175	75.68	75.48	6.03	5.97	13.25	13.14
10	H	H	$NHCH_2C_6H_5$	C	234–235	77.85	78.10	5.05	5.09	12.38	12.35
11	H	H	$NHCH(C_6H_5)_2$	M	214–215	80.94	80.77	5.09	5.05	10.11	9.95

[a] Compounds **2–6** were prepared as **1** in the Experimental Section. Compounds **7–9** and **11** were prepared as **10** in the Experimental Section but were crystallized from the solvent indicated. [b] See Table I, footnote *b*.

TABLE III

AMINOALKYL AMIDES

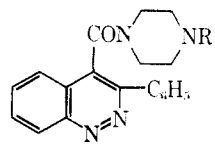


No.[a]	*x*	Am	Crystn solvent[b]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	3	$N(CH_3)_2$	Me–SKB	127–128	71.83	72.05	6.63	6.58	16.76	16.58
2	3		A	179–180	70.92	70.62	6.99	6.94	17.98	17.58
3	2	$N(CH_3)_2$	Ee–SKA	137–139	71.22	70.96	6.29	6.23	17.49	17.37
4	2	$N(n\text{-}C_3H_7)_2$	SKB	109–110	73.37	73.56	7.50	7.62	14.88	14.97
5	2		A–SKB	130–131	69.59	69.62	6.12	6.18	15.46	15.36

[a] Compounds **2** and **3** were prepared as **1** in the Experimental Section but were crystallized from the solvent indicated. Compounds **4** and **5** were prepared as **1** but using 2 moles of amine instead of pyridine as an acid acceptor. In work-up, the residue after evaporation of the washed reaction mixture was crystallized (omitting the acid extraction) from the solvent indicated. [b] See Table I, footnote *b*.

TABLE IV

PIPERAZINE AMIDES

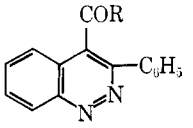


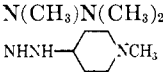
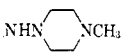
No.[a]	R	Crystn solvent[b]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	$H\cdot C_4H_4O_4$[c]	M	186–187	63.58	63.47	5.10	5.33	12.90	12.85
2	CH_3	Me–SKB	184–185	72.27	72.18	6.07	6.02	16.86	16.95
3	CH_2CH_2OH	M–Ee	125–127	69.59	69.83	6.12	6.14	15.46	15.13
4	NH_2	M–Ee	164–167	68.45	68.27	5.74	5.84	21.01	20.93
5	$NHCOCH_3$	Bz–Ee	181–182	67.18	66.82	5.64	5.66	18.66	18.72

[a] Compound **2** was prepared as **1**, Table III; **3** as **1** in the Experimental Section; **4** was treated as 1, Table III, and was worked up as **4**, Table III. Compound **5** was prepared from **4** and acetic anhydride in methylene chloride, and was worked up as **4**, Table III. [b] See Table I, footnote *b*. [c] Maleic acid salt.

Several attempts were made to prepare the 4-benzoyl derivatives VIII (Chart II). The Friedel–Crafts reaction in benzene using VIa gave a low yield of the intramolecular cyclization product VIIa (the presence of VIIIa cannot be excluded), which was better prepared in carbon disulfide. Reaction of VIc in benzene gave principally VIIIc along with VIIc, prepared in erratic yields in chlorobenzene. Reaction of the ester IX with phenylmagnesium bromide afforded, along with starting material and biphenyl, two products: a small amount of the 1-phenyl ester XI, which probably arose from 1,2 addition of the Grignard to the azo

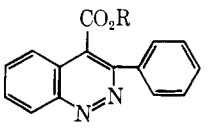
TABLE V
HYDRAZIDES

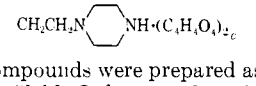


No.[a]	R	Crystn solvent[b]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	$NHNH_2$	Bz	198–200	68.17	68.17	4.58	4.65	21.20	21.03
2	$NHN{=}C(CH_3)_2$	A	201–203	71.03	70.86	5.30	5.54	18.41	18.16
3	$NHN(CH_3)_2$	M	237–240	69.84	69.68	5.52	5.53	19.17	19.12
4	$N(CH_3)N(CH_3)_2$	M	191–194	70.56	70.24	5.92	5.94	18.29	18.07
5		A	223–226	69.78	69.92	6.41	6.22	19.38	19.44
6		A–SKB	216–218	69.14	69.11	6.09	6.11	20.16	20.28

[a] Compound **1** was prepared as **5** in the Experimental Section but, on making the hydroxide extract neutral, the product crystallized. It was filtered off, dried, and recrystallized from benzene. Compound **2** was prepared from **1** by refluxing in, then crystallizing from, acetone. Compound **3** was prepared as **5**, but the hydroxide extraction was omitted. The residue on evaporation was stirred with ether, filtered off, and crystallized as indicated in the table. Compounds **4** and **6** were prepared as **3**.

TABLE VI
ESTERS



No.[a]	R	Crystn solvent[b]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	$(CH_2)_3N(CH_3)_2 \cdot C_4H_4O_4$[c]	A	153–155	63.85	64.07	5.58	5.46	9.31	9.13
2		E	150–151	59.20	59.17	5.30	5.61	9.21	9.25

[a] These compounds were prepared as **1**, Table III; the maleic acid salts of the crude products were crystallized from the solvent indicated. [b] See Table I, footnote *b*. [c] Maleic acid salt.

bond, followed by tautomerization[15] to the 4-H derivative; and the dihydro ester Xa, formed by reduction by the Grignard. A related ester (Xb) was isolated in low yield in an attempt to prepare the primary hydrazide (see related hydrazides, Table V) from methylhydrazine in refluxing butanol; hydrazines are known to cause reduction of azo bonds under similar conditions.[16]

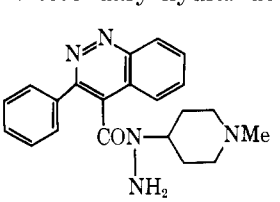
The structure of the dihydro ester Xa is derived from the infrared and nmr spectra. A single, D_2O-exchangeable proton is seen at 2.9 μ and at 485 cps, respectively. The carbonyl band at 5.77 μ and the ethoxy pattern in the nmr (quartet centered at 245 cps integrating for two protons, triplet at 65 cps, three protons) establish the ester. The 4-hydrogen occurs as a single peak, one proton, at 308 cps. Nine aromatic hydrogens are seen as complex multiplets from 400 to 480 cps. These data rule out the isomeric structures, 1,2-dihydro, 1-aminoindole, or 3,4-dihydro, and are in agreement with similar data on other 1,4-dihydrocinnolines.[15]

The same arguments apply to the butyl ester Xb which shows the same 4-H absorption and the expected aliphatic absorption in going from ethyl to butyl in the nmr spectrum. The 1-phenyl derivative XI differs only by the lack of an exchangeable hydrogen and by an increased absorption in the nmr due to the five phenyl protons.

Borderline[13] antiinflammatory activity[8] was found in 3-phenylcinnoline-4-carboxamide (1) and encouraged an extension of this series, shown in Table II. Unfortunately, only the N-benzyl analog (**10**) showed even equal subcutaneous activity, and both were inactive in adrenalectomized animals.[9,10] The series showed no interesting activity in other screening tests.[11b,c,14] (These amides were too insoluble to allow intravenous injection for the hypotensive test.[11a])

Table III shows aminoalkyl amides. The most interesting activity found at screening levels was hypotensive[11a,12] for **1** and **2**, and antiinflammatory[8,13] for **4**. By contrast, the best activity shown for the piperazine amides of Table IV was antiulcer[11b] at 10 mg/kg by **1**.

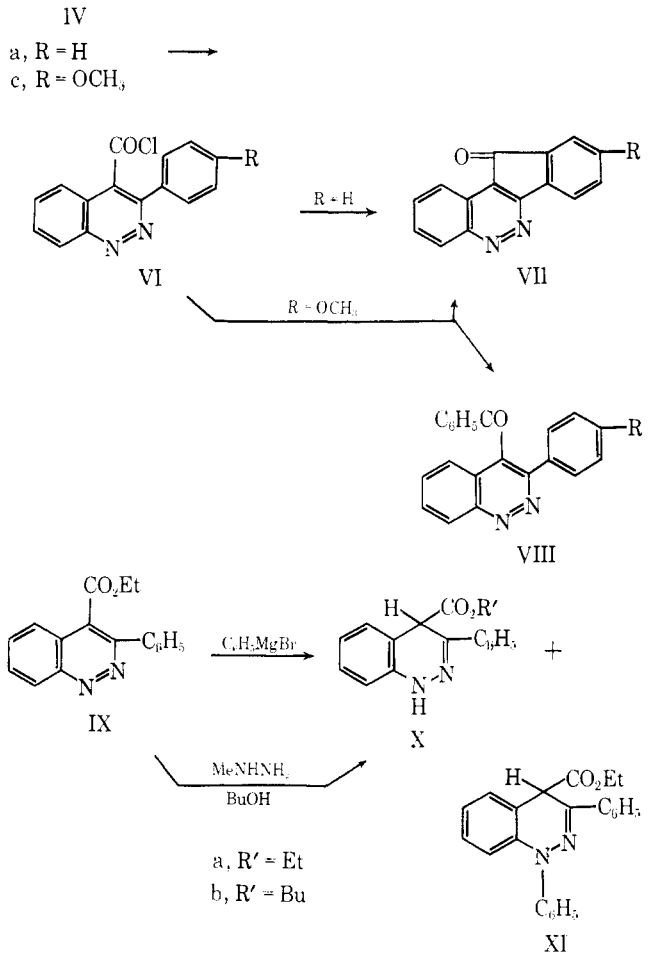
The primary hydrazides (-CONHN=) of Table V were soluble in dilute potassium hydroxide but were precipitated by addition of carbon dioxide. This behavior was used to separate **5**, formed in 50% yield, from the isomeric secondary hydrazide XII in the reaction of 1-methyl-4-hydrazinopiperidine and the acid chloride VIa. The best activity of these compounds was that of **2** in the antiinflammatory test,[8,13a] while of the esters in Table VI was that of **2** in this test.[8,13]



XII

(16) S. Kubota, T. Akita, and T. Yokoshima, *J. Pharm. Soc. Japan*, **78**, 1194 (1958).

CHART II



Experimental Section[17]

The preparations below illustrate the modifications of the procedures of Baumgarten and Furnas.[2]

N-Benzylideneaminoisatin (IIIa).—To 126 g (1.0 mole) of oxalyl chloride in 1.5 l. of refluxing CH_2Cl_2 was added dropwise in 2 hr with stirring 196 g (1.0 mole) of benzaldehyde phenylhydrazone dissolved in 2.0 l. of CH_2Cl_2. The solution was stirred and refluxed 2 hr more, then 450 g (3.4 moles) of $AlCl_3$ was added portionwise but rapidly, and the mixture was stirred overnight. It was decomposed by pouring on ice, the organic layer was separated, washed with dilute HCl, dried first by shaking with a saturated solution of NaCl and then by filtering slowly through Na_2SO_4, and concentrated to 1 l. Upon dilution with 2 l. of ethanol and cooling to 0°, red prisms separated.[18] These were filtered and dried; yield 174 g (70%), mp 145–150°.[19] An additional 24 g (10%) of less pure material, mp 130–145°, was obtained by concentrating the mother liquor *in vacuo* to 500 ml. All this material was sufficiently pure for conversion to the acid. A portion of the first crop was recrystallized from a large volume of ether to yield orange needles, mp 149.5–150°.[19]

Small portions of these isatins were best crystallized from ether since refluxing in higher boiling solvents as ethanol was found to cause slow decomposition.

3-Phenylcinnoline-4-carboxylic Acid (IVa).—To 1 l. of 50% KOH was added 155 g of the combined crops from the previous experiment. The suspension was heated with occasional shaking to reflux on a hot plate for 30 min, then diluted carefully to 4 l. with boiling water. The tar which did not dissolve while boiling was skimmed off, and the solution was stirred with activated charcoal, filtered, and acidified with concentrated HCl to pH 4. After cooling to room temperature the yellow powder was filtered off, washed well with water, and dried; 150 g (97%), mp 224–224.5° (with gas evolution, and depending somewhat on the rate of heating). A sample was recrystallized from ethanol: yellow prisms, mp 224–225°.[19]

3-Phenylcinnoline (Va).—Twenty grams of IVa was melted and heated in an oil bath until gas evolution ceased, then distilled at 0.1–0.5 mm. Crystallization from 60 ml of methanol afforded yellow prisms, 14.4 g (87%), mp 120–121°. Recrystallization from Skellysolve C[20] furnished fine yellow needles, 13.0 g, mp 120.5–121.5°.[19]

1,4-Dihydro-3-phenylcinnoline.—Under an atmosphere of nitrogen, 1.4 g of 3-phenylcinnoline, 5.0 g of barium hydroxide octahydrate, and 5.0 g of zinc dust were stirred and refluxed for 4 hr in 150 ml of ethanol and 50 ml of water. The mixture was filtered hot, and the filtrate was saturated with CO_2, filtered, and concentrated until cloudy. On cooling, yellow plates separated, 0.85 g, mp 152–153° (sealed under N_2).

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 81.01; H, 5.82; N, 12.92.

1,2-Butylmalonyl-1,2-dihydro-3-phenylcinnoline (Ia).—To 0.80 g of 1,4-dihydro-3-phenylcinnoline and 0.80 ml of pyridine in 60 ml of CH_2Cl_2 at −80° was added 0.80 g of α-butylmalonyl dichloride. The solution was allowed to warm to room temperature and stand overnight. After diluting with CH_2Cl_2, the solution was washed well with dilute HCl and dried by shaking with a saturated solution of NaCl and filtering through Na_2SO_4. The residue obtained by evaporation of the filtrate *in vacuo* was dissolved in 10% K_2CO_3, washed with ether, stirred with activated charcoal, and the mixture was filtered. The oil which separated on acidification to pH 2 was extracted with ether, which was dried as above, and concentrated. After addition of Skellysolve A[20] and cooling, 0.45 g of yellow rosettes were obtained: mp 95–96°; $\lambda_{max}^{CHCl_3}$ (μ) 5.72, 5.82 (C=O). The nmr ($CDCl_3$) showed one vinyl proton (singlet) at 333 cps, and the α-malonyl hydrogen as a triplet at 185 cps.

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 76.02; H, 6.21; N, 8.11.

1,2-Butylmalonyl-1,2,3,4-tetrahydro-3-phenylcinnoline (Ib).—Using 50 mg of 5% Pd–C as catalyst, 323 mg of Ia was reduced in 10 ml of acetic acid at 25° under hydrogen at 1 atm pressure. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue crystallized on stirring with ether; after diluting with Skellysolve A,[20] the crystals were filtered off and recrystallized from 10 ml of ether at −10°; clear prisms, 80 mg; mp 128–130°; $\lambda_{max}^{CHCl_3}$ (μ) 5.70, 5.84 (C=O). The nmr spectrum ($CDCl_3$) integrated for one proton as a quartet at 360 cps (3-H), and 3 protons (one α-H, two 4-H) as superimposed multiplets between 180 and 210 cps.

Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.81; H, 6.69; N, 8.31.

3-Phenylcinnoline-4-carbonyl Chloride (VIa).—The acid IVa (30 g) was suspended in 200 ml of $SOCl_2$ and refluxed 2 hr until dissolved. After evaporating the solvent *in vacuo*, the residue was stirred with 500 ml of Skellysolve A.[20] The yellow powder obtained on filtering and drying *in vacuo* was sufficiently pure for further reaction. A portion was recrystallized from Skellysolve B;[20] yellow needles, mp 139–142°.

Anal. Calcd for $C_{15}H_9ClN_2O$: C, 67.05; H, 3.38; Cl, 13.20. Found: C, 67.09; H, 3.35; Cl, 13.24.

11H-Indeno[1,2-c]cinnolin-11-one (VIIa).—In the best of several runs, 53 g (0.4 mole) of $AlCl_3$ was added portionwise with stirring to a refluxing solution of 50.0 g (0.193 mole) of VIa in 800 ml of CS_2. After 1 hr the clear supernate was decanted, and the residue was decomposed with ice and extracted with chloroform. This extract was washed three times with dilute HCl and once with dilute KOH, then dried by shaking with a saturated solution of NaCl and filtering through anhydrous K_2CO_3. On concentrating the solution to 200 ml and cooling, orange needles separated which were filtered off and dried, 20.0 g (45%), mp 291–292°. Additional less pure crops totaling 13.7 g (30%) were obtained from the mother liquor.

(17) All melting points are corrected and were taken in a Hershberg apparatus. Microanalysis were performed by the Microanalytical Department under Dr. R. T. Dillon. Infrared spectra were recorded on a Beckman IR 4. Nmr, recorded on a Varian A-60, is given in cycles per second (cps) of downfield shift from tetramethylsilane as an internal reference standard.

(18) Alternatively, the methylene chloride solution may be evaporated *in vacuo* to dryness and the residue stirred with ether to induce crystallization.

(19) For the purified compounds, Baumgarten and Furnas[2] give melting points of IIIa, 148–149°; IVa, 224–224.5°; Va, 118.5–119°.

(20) Petroleum ether fraction: A, bp 28–38°; B, bp 80–71°; C, bp 86–100°; E, bp 91–126°.

Anal. Calcd for $C_{15}H_8N_2O$: C, 77.57; H, 3.47; N, 12.06. Found: C, 77.63; H, 3.69; N, 12.02.

3-(4-Methoxyphenyl)-4-benzoylcinnoline (VIIIc) and 9-Methoxy-11H-indeno[1,2-*c*]cinnolin-11-one (VIIc).—A mixture of 3.0 g of VIc and 2.6 g of $AlCl_3$ was stirred in 150 ml of benzene for 21 hr. After decomposition with ice, washing with acid and base, and drying as in the previous example, the solution was evaporated and the residue in benzene was chromatographed on alumina. Elution with 5% ethyl acetate–benzene, followed by recrystallization from ethanol of the first fractions, yielded VIIIc as yellow prisms, mp 165.5–166.5°, λ_{max}^{KBr} 6.0 μ (C=O), and VIIc in later fractions as red needles, mp 214–215°, λ_{max}^{KBr} 5.8 μ (C=O), in a ratio of about 6:1.

Anal. of VIIIc. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23; OCH_3, 9.12. Found: C, 77.61; H, 4.81; N, 8.36; OCH_3, 9.24.

Anal. of VIIc. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68; Found: C, 73.11; H, 3.78; N, 10.61.

Ethyl 3-Phenylcinnoline-4-carboxylate (IX).—A solution of 48.0 g of VIa in 1 l. of ethanol was refluxed 1 hr, then evaporated *in vacuo*. The residue in methylene chloride was washed with dilute K_2CO_3, the solution was dried (see VIIa), and the solvent was evaporated *in vacuo*. Crystallization from ethyl acetate–Skellysolve C[20] afforded 41.0 g (77%) of yellow prisms, mp 85–90°. An analytical sample was recrystallized from methanol, mp 92–93°.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.06; H, 5.10; N, 9.91.

Ethyl 1,3-Diphenyl-1,4-dihydrocinnoline-4-carboxylate (XI) and Ethyl 3-Phenyl-1,4-dihydrocinnoline-4-carboxylate (Xa).—To 20.6 g (0.074 mole) of IX dissolved in 1.5 l. of anhydrous ether was added dropwise with stirring 18.1 g (0.1 mole) of phenylmagnesium bromide in 50 ml of ether. After stirring 2 hr, the solution was decomposed with water and washed first with dilute HCl and then with dilute KOH. It was dried (see VIIa) and evaporated. Chromatography of the residue (27 g) on silica and elution furnished the principal products in this order: biphenyl (4.7 g, eluted with 20% benzene–Skellysolve B[20]), XI (1.3 g, 75% C_6H_6–Skellysolve B[20]), Xa (6.4 g, 100% C_6H_6), IX (starting material, 10.2 g, 5% ethyl acetate–benzene). XI was crystallized from Skellysolve B;[20] tan clusters, mp 111–112°.

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; N, 7.86. Found: C, 76.97; H, 5.65; N, 8.23.

Xa was crystallized from ether–Skellysolve A;[20] white blades, mp 82–84°.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.91; H, 5.64; N, 10.13.

Butyl 3-Phenyl-1,4-dihydrocinnoline-4-carboxylate (Xb).—A solution of 11.5 g (0.04 mole) of IX and 12 g (0.3 mole) of methylhydrazine in 70 ml of butanol was refluxed 15 hr. The residue after evaporation *in vacuo* was stirred with ether, and the yellow powder was filtered off and dried; 5.3 g, mp 160–165°. Repeated recrystallization from methanol and from ethanol failed to yield a homogeneous product.

The ether filtrate was evaporated and the residue was chromatographed on silica. Elution with benzene gave first (along with starting material later) crystalline fractions which when recrystallized from Skellysolve B[20] formed 0.42 g of white needles, mp 64–66°.

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09; mol wt, 308.37. Found: C, 73.78; H, 6.41; N, 9.03; mol wt, 309.

3-Phenylcinnoline-4-carboxamide (Table II, 1).—To 2.7 g of VIa in 300 ml of butanone was added 10 ml of concentrated NH_4OH, and the solution refluxed 1.5 hr. After evaporation of the solvent *in vacuo*, the residue was stirred with dilute NaOH, and the solid was filtered off, washed well with water, and then with a small amount of methanol. Crystallization twice from ethanol afforded 1.6 g of yellow prisms described in Table II.

3-Phenylcinnoline-4-(N-benzyl)carboxamide (Table II, 10).—To a solution of 5.3 g (0.05 mole) of benzylamine in 150 ml of CH_2Cl_2 was added slowly a solution of 4.6 g (0.017 mole) of VIa in 50 ml of methylene chloride. The solution stood overnight. It was diluted with CH_2Cl_2, washed with dilute HCl, dilute KOH, and water, and then dried (see VIIa). The residue obtained by evaporation of the solvent *in vacuo* was crystallized from chloroform, yielding 4.4 g of white needles described in Table II.

3-Phenylcinnoline-4-[N-(3-dimethylaminopropyl)]carboxamide (Table III, 1).—To a solution of 3.0 g (0.03 mole) of 3-dimethylaminopropylamine and 3.0 ml (0.022 mole) of pyridine in 150 ml of methylene chloride was added slowly a solution of 5.4 g (0.02 mole) of VIa in 50 ml of CH_2Cl_2. After standing overnight, the solution was diluted with CH_2Cl_2 and washed well with dilute KOH. It was dried (as VIIa) and evaporated *in vacuo*. The residue was dissolved in dilute HCl, which was washed with ether and then made basic with dilute KOH. The suspension was extracted with CH_2Cl_2 which was dried and evaporated. Crystallization of the residue from methylene chloride–Skellysolve B[20] afforded 4.0 g of yellow flakes described in Table III.

3-Phenyl-4-(1-piperazinylcarbonyl)cinnoline (Table IV, 1).—A solution of 26.9 g (0.1 mole) of VIa in 500 ml of butanone was added dropwise with stirring in 1 hr to 25 g (0.3 mole) of piperazine dissolved in 150 ml of butanone. After stirring 1 hr the piperazine monohydrochloride was filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in dilute HCl, which was filtered to remove a small amount of solid and then worked up as in the preparation above of **1**, Table III. The maleic acid salt of the product was prepared in methanol and is described in Table IV.

1-(3-Phenylcinnoline-4-carbonyl)-2-(1-methyl-4-piperidinyl)-hydrazine (Table V, 5).—A solution of 10.8 g (0.04 mole) of VIa in 100 ml of methylene chloride was added dropwise with stirring to 13.0 g (0.10 mole) of 1-methyl-4-hydrazinopiperidine[21] dissolved in 200 ml of CH_2Cl_2. After standing 2 days the solution was washed with a 5% K_2CO_3 solution, then extracted with 10% KOH. This extract was neutralized to pH 7 and extracted with methylene chloride, which was dried (as VIIa) and evaporated *in vacuo*. Crystallization of the 7-g residue from acetone yielded 4.8 g of shiny, pale yellow plates, described in Table V.

(21) A. Ebnöther, E. Jucker, A. Lindenmann, E. Rissi, R. Steiner, R. Süess, and A. Vogel, *Helv. Chim. Acta*, **42**, 533 (1959).