3-Phenylcinnolines. II.[1] The Preparation of 4-Amino Derivatives

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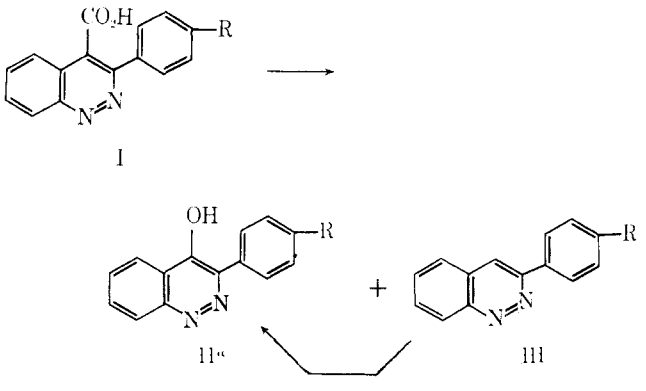
The development of methods for converting 3-phenylcinnoline-4-carboxylic acids into the 4-hydroxy and 4-chloro analogs led to the preparation of 4-amino compounds which were examined for pharmacological activity.

The availability of 3-phenylcinnoline-4-carboxylic acids[1,2] encouraged a search for a way to convert these acids to the 4-hydroxy or the 4-chloro derivatives from which 4-aminocinnolines might be prepared.[3] Along with several other methods, the fusion of the potassium salt in a manner similar to the preparation of phenols from sulfonic acids[4] was attempted and gave a small (5%) yield of 3-phenyl-4-cinnolinol (II).[5] The suggestion that this reaction might involve an oxidative mechanism[6] led to the use of cupric oxide with much improved results, and finally empirical conditions were developed for preparative use; a few representative experiments are shown in Table I.

TABLE I



a, R = H
b, R = Cl
c, R = OCH_3
d, R = OH

Run	Starting material, g	Product	Yield, %	Mp, °C[a]	Other products, %
1	Ia, 100	IIa	62	260–264	IIIa, 6
2[b]	IIIa, 3.0	IIa	9	268–270	IIIa, 74
3	Ib, 10	IId	4	234–245	
4	Ic, 6.1	IId	8	250–253	IIIc,[d] 10

[a] Although the hydroxy form is written here, nmr evidence similar to that described by J. M. Bruce, P. Knowles, and L. S. Besford, *J. Chem. Soc.*, 4044 (1964), for 4-cinnolone indicates that the 4-keto form predominates. [b] Purified: IIa, mp 268–270° (lit.[5] mp 268–270°); IId, mp 256–258°. [c] Treated for the same length of time as run 1; not exothermic. [d] See ref 1.

In a typical run (see Experimental Section; run 1, Table I) little change except a small amount of decarboxylation occurs until about 270° where rapid gas evolution begins and the reaction becomes exothermic. Best yields were obtained by cooling immediately when gas evolution ceased. Efficient stirring is critical, and a small amount of water was found desirable. The large amount of starting material recovered from the apparently slower reaction of run 2 suggests that initial decarboxylation cannot be the principal route of run 1, but the appreciable yield of IIa shows that more than one path is available. The applicability of this reaction is severely limited by the strenuous conditions as is illustrated in runs 3 and 4. Although much milder (but longer) routes are available (see below),[3,5] at present this is the shortest path to 3-phenyl-4-cinnolinol and was used to prepare this intermediate which *via* the 4-chloro derivative was converted to the majority of compounds reported here.

The direct preparation in run 2 encouraged an examination of other reactions on 3-phenylcinnoline. Although it failed to react with N-bromosuccinimide or with $POCl_3$ (compare the reaction on N-oxides below), a few per cent reacted with *t*-butyl hypochlorite to give the 4-hydroxy compound which was also formed to a similar extent in an attempt to prepare the 4-aldehyde with dimethylformamide–phosphorus oxychloride.[7a] The direct oxidation of 8-nitrocinnoline to the 4-hydroxy derivative by several reagents has recently been reported[7b] (see below).

We also studied the preparation and rearrangements of 3-phenylcinnoline N-oxide since these might yield ring-substituted derivatives as do quinoline N-oxides.[8] When this work was started only the report[9] on the preparation and nitration of certain 4-phenyl- and 3,4-diphenylcinnoline N-oxides was available, but shortly afterwards a publication[10] arrived describing the preparation and assignment of structure of cinnoline and 4-methylcinnoline 1- and 2-oxides. Based on work prior to ours, this communication aided in the structure assignments below, and with later publications from these[11] and other Japanese authors[7b,12] disclosed results which are similar to some reported here.

(1) Paper I: H. S. Lowrie, *J. Med. Chem.*, **9**, 664 (1966).

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

(3) J. L. Jacobs, in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 136–185, and references therein.

(4) P. Karrar, "Organic Chemistry," 2nd English ed, Elsevier Publishing Co., Inc., New York, N. Y., 1946, p 410.

(5) We sincerely thank Professor W. E. Noland for sending us an authentic sample of this compound: W. E. Noland and D. A. Jones, *J. Org. Chem.*, **27**, 342 (1962).

(6) We are indebted to Dr. H. L. Dryden, Jr., for this suggestion.

(7) (a) F. T. Tyson and J. T. Shaw, *J. Am. Chem. Soc.*, **74**, 2273 (1952); (b) I. Suzuki, T. Nakashima, and N. Nagasawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 713 (1965).

(8) A. R. Katritzky, *Quart. Rev.* (London), **10**, 395 (1956).

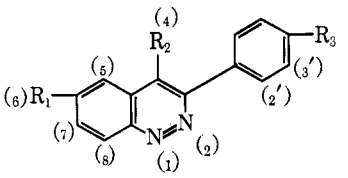
(9) C. M. Atkinson and J. C. E. Simpson, *J. Chem. Soc.*, 1649 (1947).

(10) M. Ogata, H. Kano, and K. Tori, *Chem. Pharm. Bull.* (Tokyo), **10**, 1123 (1962).

(11) (a) K. Tori, M. Ogata, and H. Kano, *ibid.*, **11**, 681 (1963); (b) M. Ogata, H. Kano, and K. Tori, *ibid.*, **11**, 1527 (1963).

(12) (a) I. Suzuki, T. Nakashima, and T. Itai, *ibid.*, **11**, 268 (1963); (b) I. Suzuki and T. Nakashima, *ibid.*, **12**, 619 (1964); (c) I. Suzuki, T. Nakashima, N. Nagasawa, and T. Itai, *ibid.*, **12**, 1090 (1964).

TABLE II[a]

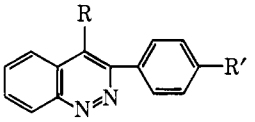


No.	R_1	R_2	R_3	Chemical shift,[b] cps H_2'	H_3'	H_4	H_5	H_6	H_7	H_8	R_1	R_3	Apparent coupling constant (cps) $J_{2',3'}$	$J_{7,8}$
1	H	H	H			490 s[c]				508–523				
2	H	H	Cl	493 d	452 d	488 s	——465–478——			507–523			9	
3	H	H	OCH_3	492 d	423 d	481 s	——458–472——			503–523		232 s	9	
4	CH_3	H	H			478 s[c]	448 s[c]	X	452 d	502 d	151 s			10
5	CH_3	H	Cl	488 d	448 d	478 s	460 s	X	448 d	504 d	153 s		9	10
6	H	H	H 1-oxide	|———		(466 s[c])			435–490–	507–527				
7	H	H	H 2-oxide	|———		(486[c])			444–480	——|				
8	H	H	Cl 1-oxide	481 d	447 d	470[c]	|—450–480[c]—			508–527			9	
9	H	H	OCH_3 1-oxide	477 d	417 d	|———	445–460		———|	503–521		229 s	9	
10	H	$CO_2C_2H_5$	H	|———		X	——430–490		———|	510–528				
11	H	$CO_2C_2H_5$	H 1-oxide	|———		X	——440–500		———|	517–535				

[a] See ref 22. [b] s, singlet, and d, doublet, refer to the appearance of the principle peak(s) for a particular proton. In several cases these were split (1 or 2 cps) by other coupling. [c] Tentative.

TABLE III

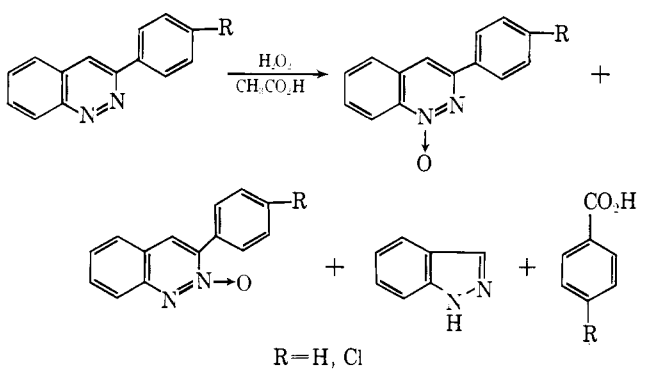
MISCELLANEOUS DERIVATIVES



No.	R	R'	Crystn solvent[a]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	R and/or R', % Calcd	R and/or R', % Found
1[b]	CO_2H	OH	E	239–240	67.66	67.42	3.79	4.20	10.52	10.27		
2[c]	OH	OH	E-T	256–258	70.58	70.38	4.23	4.48	11.76	11.74		
3[d]	H	OCH_3 1-oxide	M	165–169	71.41	71.69	4.80	5.00	11.11	11.29	12.30[g]	12.36
4[e]	Cl	Cl	A	138–140	61.11	61.30	2.93	3.13	10.19	10.16	25.77[h]	26.05
5[e]	Cl	OCH_3	SKB	130–141	66.54	66.51	4.10	4.09	10.35	10.42	13.10[h]	13.40
6[f]	$CO_2C_2H_5$	H 1-oxide	SKA	90–92	69.37	69.60	4.80	4.88	9.52	9.41		

[a] E, ethanol; T, toluene; Bz, benzene; M, methanol; A, acetone; SK, Skellysolve;[24] B, butanone; Ee, ethyl ether; Mc, methylene chloride; Ae, ethyl acetate; W, water. [b] Prepared by demethylation of 3-(4-methoxyphenyl)-4-cinnolinecarboxylic acid[1] in refluxing 48% HBr. [c] See Experimental Section. [d] Prepared as 3-(4-chlorophenyl)cinnoline 1-oxide using *m*-chloroperbenzoic acid (B).[c] [e] Prepared as 4. [f] Prepared as 3-(4-chlorophenyl)cinnoline 1-oxide using H_2O_2 (A).[c] [g] OCH_3. [h] Cl.

Oxidation of 3-phenylcinnoline with H_2O_2 in acetic acid[9] gave by crystallization about 50–60% yields of a mixture of the 1- and 2-oxides, principally the 1 isomer. Chromatography of the mother liquors furnished 6% of the 1-oxide, 3% of the 2-oxide, and 9% of indazole. Using 3-(4-chlorophenyl)cinnoline gave similar results and in each case the benzoic acid corresponding to the 3-phenyl group was isolated from the basic extract of the reaction mixture. Better yields were obtained using *m*-chloroperbenzoic acid, and the substituted-phenyl oxides of Tables II and III were best prepared with this reagent.



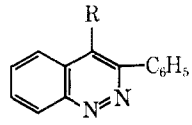
R=H, Cl

Suzuki, *et al.*,[7b] recently reported that similar oxidations of 5- and of 8-nitrocinnolines gave the corresponding indazoles along with the expected N-oxides and as noted, 4-hydroxy-8-nitrocinnoline. Our failure to isolate 3-phenyl- or 3-(4-chlorophenyl)indazole appears to rule out phenyl migration in this ring contraction and, coupled with the isolation of the corresponding benzoic acids, suggests that loss of the 3 carbon is one pathway in this oxidation.

Starting material was recovered on treating 3-phenylcinnoline 1-oxide with acetic anhydride, acetyl chloride, or *p*-toluenesulfonyl chloride. Thionyl chloride with this, or with the corresponding 3-(4-chlorophenyl) derivative, gave a complex mixture of chlorinated products; in the latter case a small quantity of 3-(4-chlorophenyl)-4-cinnolinol was isolated after hydrolysis of the reaction mixture. Using $POCl_3$, 3-phenyl-4-chlorocinnoline was obtained from either the 1- or the 2-oxide. Several recent reports[11b,12a,c] have described the similar rearrangement of the 1-oxides of

TABLE IV

AMINOCINNOLINES

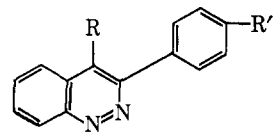


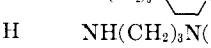
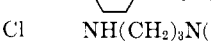
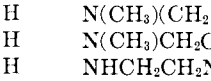
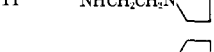
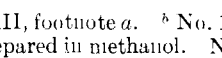
No.	R	Crystn solvent[a]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1[b]	$NHCH_2C_6H_5$	Ee	141–142	81.00	81.19	5.50	5.57	13.50	13.19
2	$NHCH_2CH_2C_6H_5$	Bz	145–146	81.20	81.41	5.89	5.93	12.91	13.14
3[c]		M	166.5–167.5	78.86	79.00	6.62	6.62	14.52	14.67
4[d]	$NHCH_2CH_2OH$	M–Bz	144–145	72.43	72.67	5.70	5.80	15.84	15.96
5[e]	$NHC_6H_4OCH_3$-*p*	Ee–SKB	150–151	77.04	77.19	5.23	5.39	12.84	13.03
6[e]	$NHC_6H_4CO_2CH_3$-*o*	M	163–165	74.35	74.18	4.82	5.04	11.84	11.65
7[e]	$NHCH_2CH_2OCH_2CH_2OH$	Bz	112–113	69.88	70.07	6.19	6.10	13.58	13.64
8[f]	$NHNH_2 \cdot HCl$	M–Ee	209–210	61.65	61.29	4.80	4.80	20.54	20.42

[a] Table III, footnote *a*. [b] See Experimental Section. [c] Prepared as **1**. [d] Prepared as **1**, but CH_2Cl_2 was used instead of ether for the second extraction. [e] Prepared as **5**, but the reaction mixture was diluted with CH_2Cl_2, washed with dilute base, dried,[25a] and evaporated *in vacuo*. The residue was crystallized as shown. [f] Prepared as **1**, using 95% hydrazine in THF, and converted to the hydrochloride in ethanol–ether.

TABLE V

AMINOALKYLAMINOCINNOLINES



No.	R′	R	Crystn solvent[a]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	H	$NHCH_2CH_2N(C_2H_5)_2$	SKA	82–84	74.92	74.76	7.55	7.39	17.49	17.15
2	H	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	SKA	57–59	76.20	75.98	8.34	8.49	15.46	15.51
3	H		Bz–SKC	145–146	72.38	72.41	6.94	6.91	16.08	16.01
4[c]	H	$NH(CH_2)_3N(CH_3)_2 \cdot 2HCl$	M–Ee	204–206					14.77	14.73
5	H	$NHCH_2CH_2N(CH_3)_2$	SKB	105–107	73.94	74.25	6.90	6.94	19.16	19.07
6	H		SKB	103–105	76.63	76.66	7.83	7.57	15.54	15.67
7	Cl	$NH(CH_2)_3N(CH_3)_2$	Ee–SKB	118–119	66.95	66.97	6.21	5.92	16.44	16.52
8	H		Ee–SKB	138–140	75.87	76.01	7.28	7.28	16.86	16.90
9[d]	H	$N(CH_3)(CH_2)_3N(CH_3)_2 \cdot 2HCl$	M–Ee	214–216					14.24	14.57
10	H	$N(CH_3)CH_2CH_2N(CH_3)_2$	SKA	65–67	74.48	74.73	7.24	7.29	18.29	18.29
11	H	$NHCH_2CH_2NH_2 \cdot 2HCl$	M–Ee	255–257					16.61	16.60
12	H		SKB	82–84	75.44	75.44	6.96	6.86	17.60	17.89
13	H		Bz	168–170	68.45	68.72	5.74	5.83	21.01	21.09

[a] Table III, footnote *a*. [b] No. 1–4 were prepared as **1**, Table IV; **5–12** were prepared as **5**, Table IV. The hydrochlorides of **4**, **9**, and 11 were prepared in methanol. No. **13**, prepared as **6**, Table IV, crystallizes with 1 mole of benzene, mp 92–95°, which is lost by drying at 120° (0.5 mm) after grinding. [c] *Anal.* Calcd: Cl, 18.69. Found: Cl, 18.47. [d] *Anal.* Calcd: Cl, 18.03. Found: Cl, 17.99.

various cinnolines, but none have reported the corresponding reaction with the 2 isomers.

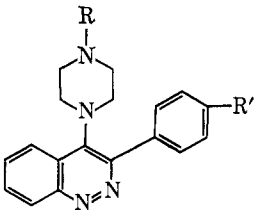
Although 4-chloro-3-phenylcinnoline would react with a large excess of a high-boiling amine (at about 150°) to give erratic yields of 4-amino derivatives, this method is unsuitable for sensitive (or valuable) amines and milder conditions were sought (compare ref 3, pp 168–170). The best of several solvents, dimethyl sulfoxide, at 95° gave good yields using more nearly equimolar amounts of reactants. The compounds in Tables IV–VI were prepared using these reactions.

Nmr spectroscopy was the principal method used to assign structure to the compounds reported here.[13,14] The appreciable downfield shift of the 8-H in cinnolines (between 505–525 cps, a complex multiplet) as compared with that of the other aromatic protons (at about 450–500 cps) was reported[10,11] essentially unchanged in the 1-oxides, but in the 2-oxides it was absent: the 8-H was hidden under the aromatic envelope. In order to verify that 3-phenyl substitution does not greatly alter the position of absorption of the 8-H, several of the compounds prepared in this and in the previous paper[1] were compared. The provisional

(13) We wish to thank Dr. R. H. Bible for extensive and continuing aid in the use and interpretation of nmr spectra.

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

TABLE VI
PIPERAZINYLCINNOLINES



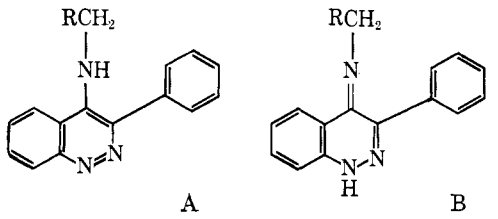
No.	R'	R	Crystn solvent[a]	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	H	CH_3	SKB	128–129	74.97	75.22	6.62	6.82	18.41	18.46
2	H	CH_2CH_2OH	Bz–SKB	174–176	71.83	71.86	6.63	6.71	16.76	16.92
3	H	H	Bz	171–173	74.45	74.54	6.25	6.23	19.30	18.90
4	H	C_6H_5	M	181–182	78.66	78.68	6.05	6.14	15.29	15.36
5	H	$CH_2C_6H_5$	SKB	110–111	78.92	79.00	6.36	6.60	14.73	14.72
6	H	NO	M	204–205	67.69	67.89	5.37	5.29	21.93	21.86
7	H	$COCH_3$	A–SKB	209–210	72.27	72.41	6.07	6.13	16.86	16.78
8	H	$CO_2C_2H_5$	Ae	128–129	69.59	69.73	6.12	5.97	15.46	15.46
9	Cl	CH_3	Ee–SKB	151–153	67.35	67.67	5.65	5.82	16.54	16.53
10	OCH_3	CH_3	Ee	156–157	71.83	71.92	6.63	6.57	16.76	16.57
11	H	COC_6H_4Cl-*p*	Ee	193–196	70.00	69.96	4.94	5.04	13.06	13.11

[a] Table III, footnote *a*. [b] No. 1 was prepared as 1, Table IV; **8** prepared in the same manner was chromatographed on alumina before crystallization. No. **2–4**, and **6** were prepared as **6**, Table IV; **5**, **9**, and **10** as **5**, Table IV. From **3** in CH_2Cl_2 was prepared **7** with acetic anhydride, and 11 with *p*-chlorobenzoyl chloride–triethylamine; each was worked up as **3**.

assignments in Table II refer to the approximate centers of the absorption bands, or to the approximate range of unresolved multiplets.

The 2′ and 3′ positions on the 3-phenyl ring were established by comparing coupling in the first three compounds; it was assumed that the *ortho* position (3′) to the chloro or methoxyl in **2** or **3** would be most shielded and appear at a higher field than the *meta*, or 2′ position. The positions of the 4-H were estimated by comparing each compound with the corresponding 4-chloro derivative (where available). The coupling pattern of **4** and **5** established the 5, 7, and 8 positions. In agreement with the observations on other cinnolines,[10,11] we then assign **6**, 8, and **9** as 1-oxides and **7** as 2-oxide. Comparing **1**, **10**, and **11**, the latter may also be assigned as the 1-oxide.

Although the amino structure, A, has generally been assigned over the imino form, B, for 4-alkylamino cinnolines,[3] we substantiated this assignment with nmr for several of the compounds in Tables IV and V by observing the expected change in the coupling pattern of the α-methylene hydrogens on deuterium exchange of the amino hydrogen.[15]



A B

Of the compounds in Table IV, only the hydrazine, 8, showed even borderline antiinflammatory activity[16–18a] but was inactive in adrenalectomized animals.[19]

The most interesting, **6**, inhibited ulceration in the Shay rat at 10 mg/kg, as did the **2** at 50 mg/kg.[20,21]

When **1** of Table V was found to have hypotensive action at screening doses,[20] several obvious variations shown in this table were prepared. The best, **5**, was active at about 1 mg/kg, but toxic side reactions in this series discouraged further exploration.[20,21] Although borderline antiinflammatory activity was also found in the series related to **5**, **2**, having the chloroquine side chain, was inactive at screening doses.[16,18]

The cyclic analog, **1** of Table VI, was found equally active to **5**, Table V, as a hypotensive, but all the variations shown in Table VI diminished this activity. Likewise, these piperazines generally were less active in the antiinflammatory tests. The best, **3**, was active[16] at screening levels[18] both subcutaneously and orally.

Experimental Section[22]

3-Phenyl-4-cinnolinol. A. From 3-Phenylcinnoline-4-carboxylic Acid (Table I).—In the best of several reactions (run

(15) For instance, **1**, Table V, the quartet centered at 292 cps changes to a triplet with same center on D_2O exchange, and the broad NH at 380 cps disappears; the same occurs for the quartet at 218 cps and NH at 300 of **2**, Table IV. Likewise, the doublet at 267 cps of **1**, Table IV, changes to a singlet (267 cps), and the NH at 310 disappears.

(16) Compounds were tested as inhibitors of yeast-induced foot edema in male, Badger, 120-g rats. The minimal effective dose of phenylbutazone was 120 mg/kg subcutaneously or 175 mg/kg orally.[17]

(17) We are indebted to Drs. F. J. Saunders and E. F. Nutting, and their staff for the data from these tests.

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

(19) 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.[17]

(20) (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 anesthesized 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 the test compound in saline-primed, male, Sprague–Dawley rats (300 g) was compared with that of controls treated with hydrochlorothiazide.

(21) We are indebted to Dr. D. L. Cook and Mr. R. S. Jacobs and their staff for data from the tests in ref 20.

(22) 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 in $CDCl_3$ solution.

1, Table I) 100 g of 3-phenylcinnoline-4-carboxylic acid[1] and 200 ml of 50% KOH solution were dissolved in 400 ml of ethanol. This solution was mixed with 200 g of cupric oxide powder and 100 g of copper powder in 1000 ml of mineral oil in a 2-l. stainless steel,[23] round-bottom flask. While stirring very fast the suspension was heated rapidly: ethanol and water distilled from 95 to 200° (internal temperature; Dow silicone antifoam was added); the distillate was collected above 200°; 3-phenylcinnoline crystallized from it. At about 270° a mild exothermic reaction and gas evolution began: the rate of heating was slowed and finally stopped at 285°. The temperature rose to 300°: after a few minutes gas evolution ceased. The reaction was cooled by slowly filling a surrounding pan with water. The suspension was diluted with Skellysolve L[24] and filtered. The filtrate was combined with the distillate from above 200° and extracted with concentrated HCl. This was diluted with water, neutralized with dilute KOH, and extracted with ether. After drying,[25a] the solvent was evaporated and the residue crystallized from Skellysolve B;[24] yellow prisms, 5.2 g (6.3%), identical in all respects[26a] with 3-phenylcinnoline.

The solid obtained in the filtration above was dried and then extracted repeatedly with water and with dilute KOH by suspending and filtering. The combined filtrates were saturated with CO_2 and the solid which precipitated was filtered off and dried. It was dissolved in 4 l. of boiling butanone, stirred with activated charcoal, filtered, and concentrated by boiling to 1.5 l. The yellow powder which separated on cooling was filtered off and dried: 39.5 g (44.4%), mp 260–264°. Addition product melting at this point or above was obtained by reworking the mother liquor and totaled 15.7 g (17.7%).

A sample of this material was sublimed at 200–300° (0.2 mm), then crystallized from methanol; shiny, yellow-white plates, mp 268–270°, identical in all respects[26] with an authentic sample[5] of 3-phenyl-4-cinnolinol, mp 268–270°.

3-(4-Hydroxyphenyl)4-cinnolinol was isolated in the same way from runs 3 and 4, Table I, and is described in Table III, **2**.

B. From 3-Phenyl-4-chlorocinnoline.—A solution of 10.0 g of 3-phenyl-4-chlorocinnoline (see below) and 10 ml of 25% KOH solution was heated on a steam bath in 20 g of dimethyl sulfoxide for 24 hr. After diluting with water and neutralizing with dilute HCl, the mixture was filtered and the solid crystallized from butanone; yellow plates, 8.4 g, identical[26a] with authentic[5] 3-phenyl-4-cinnolinol.

C. From 3-Phenylcinnoline. (1).—A solution of 3.0 g of 3-phenylcinnoline[1] and 2.0 g of *t*-butyl hypochlorite in 100 ml of methylene chloride was allowed to stand 20 hr. After extracting with dilute KOH, the solution was dried,[25a] diluted with Skellysolve B,[24] and concentrated; 1.8 g of yellow needles separated, identical[26a] with starting material. The basic extracts were acidified, and the white powder was filtered and dried; 0.08 g (2.5%), mp 260–265°, undepressed by 3-phenyl-4-cinnolinol, which had an identical infrared spectrum.

(2).—A solution of 2.1 g of 3-phenylcinnoline[1] and 1.7 g of $POCl_3$ prepared in 20 ml of DMF was allowed to stand 3 days. After diluting with water, it was extracted with CH_2Cl_2 which was worked up as the previous example to give 1.7 g of starting material and 0.1 g of 3-phenyl-4-cinnolinol.

3-Phenylcinnoline 1- and 2-Oxides.—A solution of 6.0 g of 3-phenylcinnoline[1] and 5 ml of 30% H_2O_2 in 20 ml of glacial acetic acid was heated for 2 hr on a steam bath, then diluted to 120 ml with water and cooled to 0°. The oil which separated crystallized on standing; the supernate was decanted, and the solid was dissolved in ether and washed with dilute KOH. The ether layer after drying[25a] was concentrated to 150 ml and cooled; brown prisms, 3.9 g (60%), mp 130–135°, which nmr showed to be principally 1-oxide.

The basic extract above was acidified and extracted with ether. This was dried,[25b] concentrated, and diluted with Skellysolve B.[24] The powder obtained was recrystallized from ether–Skellysolve A;[24] 0.3 g (8%), white clusters, mp 118–120°, undepressed by authentic benzoic acid, which had an identical infrared spectrum.

The mother liquors from several larger runs were combined in benzene and chromatographed on alumina. Elution with increasing per cents of ethyl acetate–benzene, followed by combination of the fractions in a peak, and crystallization furnished principal products in this order: (15% ethyl acetate–benzene) fractions 3–7, 3-phenylcinnoline 1-oxide, 6%, yellow needles from methanol, mp 138–139° (after several recrystallizations); fractions 9–14, 3-phenylcinnoline 2-oxide, 3%, white flakes from methylene chloride–Skellysolve B,[24] mp 181–182°; (75% ethyl acetate–benzene) indazole, 9%, mp 147–148°, identical[26] with an authentic sample from Aldrich Chemical Co.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found for 3-phenylcinnoline 1-oxide, mp 138–139°: C, 75.92; H, 4.83; N, 12.78. Found for 3-phenylcinnoline 2-oxide, mp 181–182°: C, 75.84; H, 4.82; N, 12.71.

3-(4-Chlorophenyl)cinnoline 1-Oxide. A. Using H_2O_2. In a similar manner to that above, 8.0 g of 3-(4-chlorophenyl)-cinnoline[1] furnished 4.1 g (48%) of the 1-oxide, yellow needles from benzene, mp 184–186°.

Anal. Calcd for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.53; N, 10.92; Cl, 13.81. Found: C, 65.55; H, 3.63; N, 10.86; Cl, 13.66.

p-Chlorobenzoic acid was isolated as above, 0.56 g (11%), mp 238–241°, undepressed by authentic material whose infrared spectrum was identical.

Chromatography of the mother liquor furnished 12% of the 1-oxide, mp 167–174°, and 0.32 g (8%) of indazole, mp 146–148°, identical[26a] with authentic material.

B. Using *m*-Chloroperbenzoic Acid.—To 61.5 g (0.255 mole) of 3-(4-chlorophenyl)cinnoline in 1.5 l. of CH_2Cl_2 was added portionwise 55 g (0.271 mole, 86% assay) of *m*-chloroperbenzoic acid; the heat of reaction warmed the solution slightly. After standing overnight the solution was washed with dilute NaOH, dried,[25b] and evaporated *in vacuo*. The yellow crystals obtained were converted without purification into the 4-chloro derivative using $POCl_3$: see below for 3-phenylcinnoline 1-oxide; CH_2Cl_2 was used instead of ether in extraction; see also Table III) in 80% over-all yield.

3-(4-Chlorophenyl)-4-cinnolinol.—A solution of 2.0 g of 3-(4-chlorophenyl)cinnoline 1-oxide in $SOCl_2$ was refluxed for 1 hr, then evaporated *in vacuo*. Attempts to crystallize a homogeneous material from the residue were unsuccessful. The various fractions were combined in 30% ethanol containing 2 g of KOH and this solution was refluxed for 1 hr. After diluting with water and boiling off the ethanol, the solution was cooled, washed with CH_2Cl_2, and acidified. The powder which separated was filtered off, dried (0.4 g), and crystallized from butanone. The yellow flakes obtained were sublimed, 250–330° (0.05 mm), and then crystallized from butanone; shiny white plates, 0.15 g, mp 329–330°.

Anal. Calcd for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.53; N, 10.92; Cl, 13.81. Found: C, 65.75; H, 3.83; N, 10.85; Cl, 13.84.

3-Phenyl-4-chlorocinnoline. A. From 3-Phenyl-4-cinnolinol.—The preparation of Schofield and Swain[27] using $POCl_3$ and PCl_5 was carried out on several batches of the 4-cinnolinol and furnished excellent yields of the 4-chloro intermediate. A sample was crystallized twice from Skellysolve B[24] for a reference standard: yellow needles, mp 120–121° (lit.[27] mp 119–120°).

Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; N, 11.64; Cl, 14.73. Found: C, 69.78; H, 3.79; N, 11.52; Cl, 14.77.

B. From 3-Phenylcinnoline 1-Oxide.—A solution of 0.90 g of the 1-oxide was refluxed in 10 ml of $POCl_3$ for 1.5 hr, the solvent was evaporated *in vacuo*, and the residue was worked up as above. Two crystallizations furnished 0.24 g of yellow needles identical[26] with those above.

C. From 3-Phenylcinnoline 2-Oxide.—Use of 0.50 g of the 2-oxide as in B furnished 0.27 g of material identical[26] with the chloro derivative in A. Acidifying the basic wash of the work-up gave a 0.068 g of a white powder, mp 265–269°, undepressed by authentic 3-phenyl-4-cinnolinol,[5] which had an identical infrared spectrum.

3-Phenyl-4-benzylaminocinnoline (Table IV, 1).—3-Phenyl-4-chlorocinnoline (3.0 g), 1.0 g of copper powder, and 20 g of benzylamine were refluxed under nitrogen for 20 min. After

(23) A copper flask serves equally well: glass is attacked, and the silica contaminates the product.

(24) Petroleum ether fraction: A, bp 28–38°; B, bp 60–71°; C, bp 86–100°; L, bp 91–126°.

(25) The organic layer was shaken with a saturated solution of NaCl, then filtered slowly through anhydrous (a) K_2CO_3 or (b) Na_2SO_4.

(26) (a) Melting point, mixture melting point, and infrared absorption spectrum; (b) nmr spectrum.

(27) K. Schofield and T. Swain, *J. Chem. Soc.*, 2393 (1949).

cooling, the mixture was diluted with ether, washed several times with dilute KOH, and then extracted with dilute HCl. The acid extracts were separated (a suspension of the hydrochloride may form) and made alkaline, and the organic base was extracted with ether. This solution was dried[25a] and evaporated; the residue was crystallized as shown.

3-Phenyl-4-(4-methoxyphenylamino)cinnoline (Table IV, 5).—A solution of 4.8 g (0.02 mole) of 3-phenyl-4-chlorocinnoline and 4.8 g (0.04 mole) of *p*-anisidine in 20 g of dimethyl sulfoxide was heated on a steam bath for 16 hr. After cooling, the solution was diluted with ether and worked up as in the previous example.

N-Monoalkyl-β-alkylcinnamamides as Sedatives

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A series of N-monoalkyl-β-alkylcinnamides has been prepared and tested for sedative action in hyperirritable rats. Several polymethoxylated derivatives in this series showed pronounced sedative action.

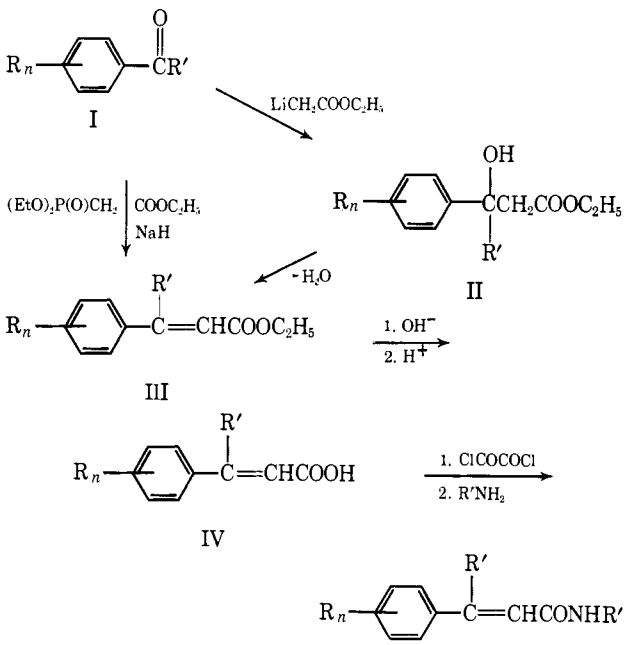
The sedative properties of carboxylic acid amides have been studied extensively.[1] Cinnamamides have likewise received considerable attention, but studies seem to have been confined almost exclusively to derivatives with either no substitution at the α,β-carbon atoms or with substitution at the α-carbon only.[2-9] Relatively little work has appeared in the literature concerning the sedative effects of the β-alkylcinnamamides.[2]

Lott and Christiansen[2] showed that the greatest hypnotic activity among the cinnamamides studied was obtained from β-methylcinnamamide. We have investigated numerous analogs of β-methylcinnamamide, together with higher β-alkyl substitutions, for the purpose of defining the structural modifications that could enhance the sedative effects of this class of compounds.

The preparation of β-alkylcinnamamides proceeded from appropriately substituted alkyl aryl ketones (I). A few of the intermediate cinnamic acids were prepared by a Hauser condensation[10] of ethyl lithoacetate with alkylphenyl or halophenyl methyl ketones (I), followed by dehydration of the hydroxy esters II and saponification to the acids IV. This procedure applied to polymethoxylated ketones was successful only if the usual dehydration agent, phosphorus oxychloride, was replaced by formic acid. The yield, however, was low (10%). As a consequence of poor over-all yields by this route, the Wadsworth–Emmons modification[11] of the Wittig reaction using triethyl phosphonoacetate and sodium hydride was chosen as an alternate method. It in general gave quite satisfactory yields and was employed for most of the acids prepared in this study.

The phosphonate modification of the Wittig reaction favors formation of the *trans* isomer.[12,13] Because of the apparent homogeneity of most of the products from the phosphonate condensation, the acids were converted without purification to amides as indicated in Chart I. The use of thionyl chloride alone or oxalyl chloride in chloroform to make polymethoxylated cinnamoyl chlorides led to cinnamamides that were difficult to purify. Conditions found to be successful were treatment of the acids with oxalyl chloride in benzene and conversion of the crude acid chlorides to cinnamamides.

CHART 1



In one preparation of 3,4,5-trimethoxy-β-methylcinnamic acid through the modified Wittig reaction, the product, even when recrystallized several times, still contained about 3% β,γ-unsaturated acid as

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(2) W. A. Lott and W. G. Christiansen, *J. Am. Pharm. Assoc.*, **23**, 788 (1934).

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(10) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

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(12) L. Horner, H. Hoffmann, H. Wippel, and G. Klahre, *Ber.*, **92**, 2499 (1959).

(13) D. H. Wadsworth, O. E. Schupp, E. J. Seus, and J. A. Ford, *J. Org. Chem.*, **30**, 680 (1965).