[CONTRIBUTION FROM THE UNIVERSITY OF NEW MEXICO, LABORATORY OF PHARMACEUTICAL CHEMISTRY AND THE DEPARTMENT OF CHEMISTRY]

CINNOLINE CHEMISTRY. III. SUBSTITUTED 4-CINNOLYL-ACETONITRILES[1]

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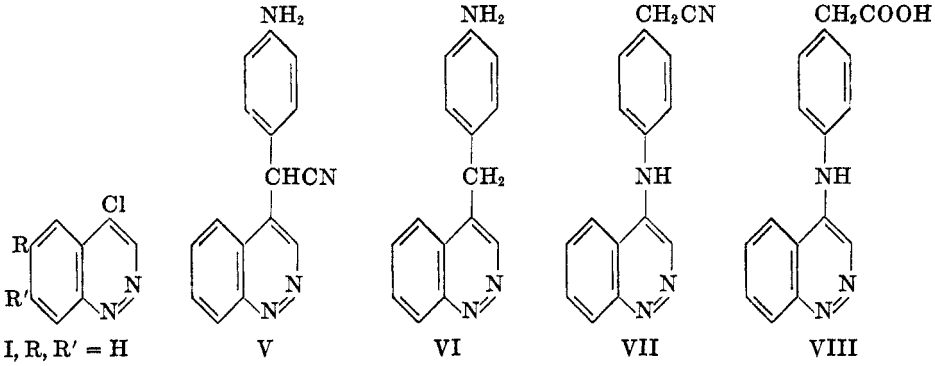
In this paper we wish to report an extension of the study (1) of the reaction of 4-chlorocinnolines with substituted phenylacetonitriles and other related acetonitriles. The present investigation has shown that the condensation between 4-chlorocinnoline (I) or 4-chloro-6,7-dimethoxycinnoline (II) and substituted acetonitriles is a general reaction, apparently limited only by the ability of the nitriles to form metal salt derivatives. In most of the condensations, sodium amide was a suitable base (Procedure A), the reaction being carried out in anhydrous benzene. However, in the case of 3,4-dimethoxyphenylacetonitrile and *p*-aminophenylacetonitrile it was necessary to prepare the potassium derivatives of the nitriles in liquid ammonia solution (Procedure B).

A series of eleven substituted acetonitriles was found to condense with I when sodium amide was employed as the condensing agent. A series of eight substituted acetonitriles was employed in the condensations with II when sodium amide was the condensing agent. The compounds obtained in these condensations are recorded in Tables I, II and III. The condensation of I and 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline is particularly interesting in view of the failure of I to condense with malononitrile (1).



I, R, R′ = H
II, R, R′ = OCH_3

V VI VII VIII

Previous attempts to prepare the sodio-derivative of 3,4-dimethoxyphenylacetonitrile (III) were not successful (1). Additional attempts in this investigation were not successful. It was found, however, that the potassio-derivative could be prepared by treating III with potassium in liquid ammonia. It is interesting to note that the potassio-derivative of III did not have the charac-

[1] For paper II in this series see *J. Org. Chem.*, **18**, 1706 (1953).

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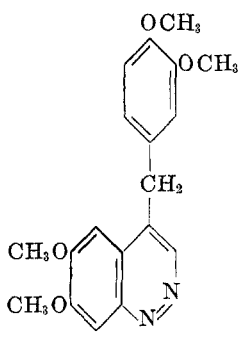
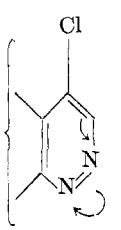
teristic red color of the sodio-derivatives of many other phenylacetonitriles studied. The potassio-derivative of III was condensed with I to give a 75% yield and with II to give an 86% yield of the respective condensation products. Attempts to prepare the sodio-derivative of *p*-aminophenylacetonitrile (IV) were not successful, however the potassio-derivative was readily prepared in liquid ammonia. This salt condensed with I to give a 71% yield of the condensation product. With II this salt condensed in small yield to give a compound for which a satisfactory analysis was not obtained, although it is believed that this compound is the desired α-(6,7-dimethoxy-4-cinnolyl)-*p*-aminophenylacetonitrile.

The hydrolysis of α-(4-cinnolyl)-*p*-aminophenylacetonitrile (V) with 50% sulfuric acid gave a compound which analytical data indicates is 4-(*p*-aminobenzyl)cinnoline (VI). It appears that if the compound to which structure V has been assigned were the isomeric secondary amine (VII), the hydrolysis product in 50% sulfuric acid would be the corresponding substituted phenylacetic acid (VIII). This is not consistent with the analytical data for VI or with the inability of this compound to dissolve in alkali. However, attempts to demonstrate the presence of a primary aromatic amino-group have not been entirely satisfactory.

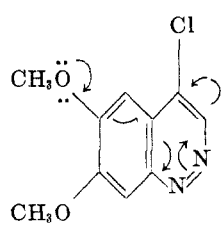
α-(6,7-Dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile (X) was converted into α-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetamide (XI) in good yield in concentrated sulfuric acid solution at room temperature. Attempts to prepare the papaverine analog (XII) from either X or XI by a variety of hydrolytic conditions were unsuccessful. Alternate synthetic routes to XII are being investigated.



XII



XIII



XIV

It has been noted that in contrast to 4-chlorocinnoline (I) which is a skin irritant and rather unstable, 4-chloro-6,7-dimethoxycinnoline (II) is completely stable at room temperature. There is also a surprising disparity between the colors and the solubilities of the two compounds. While I is yellow in color and is highly soluble in alcohols and in benzene at room temperature, II is nearly pure white in color when crystalline and it is only moderately soluble in boiling ethanol or in boiling benzene. On the basis of the relative stabilities of these two compounds, it might be expected that II would be the less reactive. Theoretical

considerations suggest that II should be less reactive than I toward nucleophilic attack at the 4-position. In both of the 4-chlorocinnolines, the activity of the chlorine atom is the result of a decreased electron density at the 4-carbon atom which is caused by the basic nitrogen atom in the 1-position (Structure XIII). A methoxyl group in the 6-position of the cinnoline ring can inhibit in part the normal electron shift in the hetero ring by contributing electrons along a conjugated path to the 4-position (Structure XIV). The methoxyl group in the 7-position should have no marked influence upon the 4-position.

In the instances in which the same substituted acetonitriles were condensed with both I and II, the yield was usually smaller with II.

Acknowledgement. The authors wish to express their appreciation to the Upjohn Company for financial support during the course of this investigation. We wish to express our appreciation to Drs. M. E. Speeter and D. I. Weisblat for their helpful suggestions.

EXPERIMENTAL

All melting points were taken with the Anschutz thermometers at total immersion, thus no stem correction was necessary, except where noted.

2-Amino-4,5-dimethoxyacetophenone. An improved procedure is described for the preparation of this compound based on the method of Simpson (2). A solution of 20 g. (0.089 mole) of 2-nitro-4,5-dimethoxyacetophenone in 230 ml. of glacial acetic acid and 100 ml. of water was heated to the boiling point. To this was added 30 g. (0.54 gram-atom) of iron powder (Mallinckrodt-reduced by hydrogen. No other iron was as satisfactory) at such a rate that a vigorous evolution of hydrogen was maintained. The addition required 40 minutes, after which the reaction mixture was refluxed and stirred for an additional four hours. Then 200 ml. of distillate was removed after refluxing, and 100 ml. of water was added and another 100 ml. of distillate was removed. The reaction mixture was poured onto about 400 g. of crushed ice and a yellow crystalline solid separated. After filtration and washing with water it amounted to 10.2 g. The filtrate produced an additional 4.4 g. upon ether extraction giving a total yield of 84% of amine melting at 81–103°. Although the melting range was large, only a trace of material was insoluble in 5% hydrochloric acid, and this material was suitable for the preparation of the 4-hydroxy-6,7-dimethoxycinnoline in high yield. The above procedure was carried out several times with consistently high yields.

4-Hydroxy-6,7-dimethoxycinnoline, 4-chlorocinnoline, and *4-chloro-6,7-dimethoxycinnoline.* These compounds were prepared by the methods described by Castle and Kruse (1).

p-Fluorophenylacetonitrile. A solution of 24.5 g. (0.108 mole) of *p-fluorobenzyl* iodide and 9.1 g. (0.135 mole) of 96% potassium cyanide in 130 ml. of ethanol and 10 ml. of water was refluxed for ten hours, then the solution was evaporated to a small volume and some inorganic salt was removed by filtration. Water was added to the filtrate and an oil separated. The mixture was extracted with ether, the extract dried (sodium sulfate), and the ether evaporated. The residue was distilled at 85–87° at 0.1 mm. There was obtained 6.3 g. of the nitrile (43% yield).

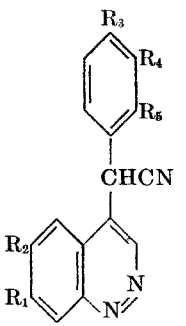
Anal. Calc'd for C_8H_6FN: C, 71.10; H, 4.47.
Found: C, 69.44; H, 4.49.

SYNTHESIS OF SUBSTITUTED α-(4-CINNOLYL)PHENYLACETONITRILES

Procedure A. This procedure was used for many of the nitriles whose properties are shown in Tables I and II. It is described by Castle and Kruse (1) and was used in this work with only minor variations. In some instances the desired nitrile was worked up in slightly different ways.

TABLE I

SUBSTITUTED α-(4-CINNOLYL)PHENYLACETONITRILES



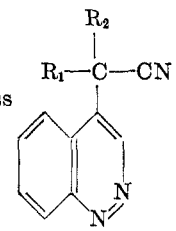
R_1	R_2	R_3	R_4	R_5	PROCEDURE	YIELD, %	M.P., °C.	FORMULA	ANALYSES				DESCRIPTION AND SOLVENT OF CRYSTALLIZATION
									Calc'd		Found		
									C	H	C	H	
H	H	F	H	H	A	65	170–172.8	$C_{16}H_{10}FN_3$	72.99	3.83	72.45	3.76	Orange-red needles, benzene[a]
H	H	Cl	H	H	A	61	177.6–178.4	$C_{16}H_{10}ClN_3$	68.70	3.60	68.75	3.68	Fibrous orange needles, benzene
H	H	Br	H	H	A	71	188.2–188.8	$C_{16}H_{10}BrN_3$	59.28	3.11	59.34	3.33	Orange needles, benzene
H	H	I	H	H	A	53	185.6–186.4	$C_{16}H_{10}IN_3$	51.35	2.69	51.73	2.67	Glistening orange-red needles, benzene
H	H	H	H	Cl	A	60	200.4–201.2	$C_{16}H_{10}ClN_3$	68.70	3.60	68.51	3.82	Small bright yellow needles, aq. ethanol
H	H	Cl	H	Cl	A	52	188–188.8	$C_{16}H_9Cl_2N_3$	61.16	2.89	61.21	2.92	Stubby golden needles, aq. ethanol
H	H	Cl	Cl	H	A	77	236.6–237.6	$C_{16}H_9Cl_2N_3$	61.16	2.89	61.41	2.91	Orange-gold platelets, ethanol

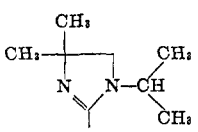
H	H	OCH_3	OCH_3	H	B	75	180.6–181.2	$C_{18}H_{15}N_3O_2$	70.81	4.95	70.37	5.11	Tiny bright orange needles, ethanol
H	H	NH_2	H	H	B	71	236.4–237.4	$C_{16}H_{12}N_4$	73.83	4.65	73.51	4.98	Deep red needles, ethanol
OCH_3	OCH_3	I	H	H	A	24	252.6–253.0 dec.	$C_{18}H_{14}IN_3O_2$	50.13	3.27	50.35	3.36	Tiny orange-red crystals, benzene
OCH_3	OCH_3	Cl	H	H	A	39	224.4–225.2 dec.	$C_{18}H_{14}ClN_3O_2$	63.63	4.15	63.40	4.10	Orange red crystals, benzene
OCH_3	OCH_3	Br	H	H	A	35	241.4–241.8 dec.	$C_{18}H_{14}BrN_3O_2$	56.26	3.67	55.98	3.64	Orange red microcrystalline powder, benzene
OCH_3	OCH_3	Cl	Cl	H	A	40	275.2–276.2 dec.	$C_{18}H_{13}Cl_2N_3O_2$	57.77	3.50	57.58	3.48	Brilliant orange needles, ethanol
OCH_3	OCH_3	H	OCH_3	H	A	64	222.2–223.2 dec.	$C_{19}H_{17}N_3O_3$	68.05	5.11	67.99	5.12	Red gold needles, ethanol
OCH_3	OCH_3	NH_2	H	H	B	—	206–207 uncorr.	$C_{18}H_{16}N_4O_2$	67.48	5.04	65.59[b]	5.47	Deep red needles, aq. ethanol
OCH_3	OCH_3	OCH_3	OCH_3	H	B	86	250–250.8	$C_{20}H_{19}N_3O_4$	65.65	5.24	65.65	5.33	Fine orange needles, ethanol

[a] The compound crystallizes from benzene in two forms, yellow plates, apparently a benzene solvate, which become orange-red needles upon complete drying in a vacuum. [b] A satisfactory analysis could not be obtained even after chromatography on alumina, however the constitution given appears the most logical.

TABLE II

SUBSTITUTED α-(4-CINNOLYL)ACETONITRILES

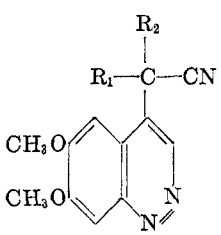


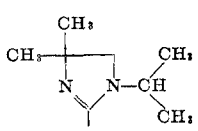
R_1	R_2	PROCEDURE	YIELD, %	M.P., °C.	FORMULA	ANALYSES				DESCRIPTION AND SOLVENT OF CRYSTALLIZATION
						Calc'd		Found		
						C	H	C	H	
Phenyl	Phenyl	A	20	186.2–186.8	$C_{22}H_{15}N_3$[a]	82.22	4.71	82.37	4.91	Pale yellow crystals, aq. ethanol
α-Naphthyl	H	A	58	224.0–224.8	$C_{20}H_{13}N_3$	81.34	4.44	81.17	4.52	Orange crystals, ethanol
β-Naphthyl	H	A	12	248.2–249.0	$C_{20}H_{13}N_3$	81.34	4.44	81.40	4.61	Dark golden needles, aq. ethanol
	H	A	83	207–208 uncorr.	$C_{18}H_{21}N_5$	70.33	6.89	70.25	7.02	Brilliant yellow needles, aq. ethanol

[a] N, Calc'd: 13.07; Found: 12.92.

TABLE III

SUBSTITUTED α-(6,7-DIMETHOXY-4-CINNOLYL)ACETONITRILES



R_1	R_2	PROCEDURE	YIELD, %	M.P., °C.	FORMULA	ANALYSES				DESCRIPTION AND SOLVENT OF CRYSTALLIZATION
						Calc'd		Found		
						C	H	C	H	
Phenyl	Phenyl	A	24	238.6–239.4	$C_{24}H_{19}N_3O_2$	75.57	5.02	75.45	5.10	Pale yellow crystals, ethanol
α-Naphthyl	H	A	53	247.2–248.0	$C_{22}H_{17}N_3O_2$	74.35	4.82	74.37	4.98	Tiny orange-gold crystals, ethanol
	H	A	—	242–243 dec. uncorr.	$C_{20}H_{25}N_5O_2$	65.37	6.86	65.09	6.75	Bright yellow crystals, Al_2O_3 chromatography, ethanol

Procedure B. This procedure is illustrated with the synthesis of α-(4-cinnolyl)-3,4-dimethoxyacetonitrile. A suspension of potassium amide in liquid ammonia was prepared by the addition of 3.1 g. (0.08 gram-atom) of potassium metal to 500 ml. of liquid ammonia to which a small amount of ferric nitrate had been added. To this suspension was added with continuous stirring 14.0 g. (0.08 mole) of 3,4-dimethoxyphenylacetonitrile. After this mixture was stirred for 30 minutes, 6.1 g. (0.037 mole) of 4-chlorocinnoline was added whereupon the grey mixture became deep red. This mixture was stirred for four hours, during which time the ammonia evaporated. Approximately 400 ml. of water was added and then 10 ml. of conc'd hydrochloric acid was added to effect hydrolysis of the potassium salt. The orange solid which formed was filtered, washed with water, and dried. After crystallization from ethanol there was obtained 8.1 g. (75%) of the desired compound. After two crystallizations from ethanol, tiny bright orange needles were obtained, m.p. 180.6–181.2°. Analytical data is given in Table I.

Essentially the same procedure was used for the other compounds which are indicated in the tables.

4-(p-Aminobenzyl)cinnoline. A solution of 1.0 g. of α-(4-cinnolyl)-*p*-aminophenylacetonitrile in 14 ml. of 50% sulfuric acid was refluxed for four hours. The solution was poured on ice and neutralized with ammonium hydroxide. The yellow solid obtained gave 0.58 g. (64%) of glistening yellow needles (m.p. 176–177° uncorr.) after crystallization from benzene.

Anal. Calc'd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57.

Found: C, 76.72; H, 5.46.

α-(6,7-Dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetamide. A solution of 5.0 g. of α-(6,7-dimethoxy-4-cinnolyl)-3,4-dimethoxyphenylacetonitrile in 50 ml. of concentrated sulfuric acid was allowed to stand at room temperature for six hours. After the solution was poured on ice and neutralized with ammonia, a white solid separated. After crystallization from ethanol, the colorless fibrous needles (2.4 g., 46%) melted at 250–252° (uncorr.).

Anal. Calc'd for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52.

Found: C, 62.38; H, 5.32.

4-(p-Aminobenzyl)-6,7-dimethoxycinnoline. By the procedure above for 4-(*p*-aminobenzyl)cinnoline, 0.5 g. (69%) of pale yellow crystals, m.p. 175.8–177° was obtained after crystallization from benzene from 0.9 g. of α-(6,7-dimethoxy-4-cinnolyl)-*p*-aminophenylacetonitrile. Although the analysis was not satisfactory, it did not change on furthur purification.

Anal. Calc'd for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80.

Found: 68.27; H, 5.87.

SUMMARY

The condensation of 4-chlorocinnoline and 4-chloro-6,7-dimethoxycinnoline with substituted phenylacetonitriles and other closely related acetonitriles was studied and shown to be a general reaction. Generally sodium amide was a suitable condensing agent, however in a few instances potassium in liquid ammonia was required.

Some of the acetonitriles were hydrolyzed to the corresponding acetamides. Some of the acetonitriles were hydrolyzed and decarboxylated to the corresponding 4-benzylcinnolines. Attempts to prepare 4-(3,4-dimethoxybenzyl)-6,7-dimethoxycinnoline, a papaverine analog, were unsuccessful.

Twenty-three of the cinnolines described in this investigation have not previously been described in the literature.

ALBUQUERQUE, N. M.

REFERENCES

(1) CASTLE AND KRUSE, *J. Org. Chem.*, **17**, 1571 (1952).
(2) SIMPSON, *J. Chem. Soc.*, 94 (1946).