infrared bands were at 10.59 (s), 11.53 (m), and 13.18 μ(s).

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.8; H, 5.12; N, 23.7. Found: C, 50.9; H, 5.14; N, 23.7.

9-(2′-Deoxy-α-D-ribofuranosyl)purine (**α-VII**) was prepared from crystalline α-III by the same procedure as for β-VII. The intermediate glass (93% yield) was again free of chlorine. After deacylation, and recrystallization of α-VII from acetonitrile, a 52% yield was obtained, m.p. 138–139°, $[\alpha]^{25}D$ +70.6 ± 1.0° (H_2O), $\lambda_{max}^{H_2O}$ 263 mμ (ε 7000), R_{Ad} same as β-VII. Characteristic infrared bands were at 10.2 (m) and 11.62 μ (m).

Anal. Found: C, 51.0; H, 5.03; N, 23.6.

6-Dimethylamino-9-(2′-deoxy-β-D-ribofuranosyl)purine (**β-VIII**).—Concurrent deacylation and amination of 0.250 g. (0.495 mmole) of β-III with 1.25 ml. of anhydrous dimethylamine in 10 ml. of methanol was performed by the procedure[18] for using methanolic ammonia. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in water, then extracted with chloroform. The aqueous phase containing the product and dimethylamine hydrochloride was stirred for 20 min. with 0.115 g. (0.495 mmole) of silver oxide, and the resulting silver chloride was removed by filtration. The filtrate was concentrated *in vacuo* to a sirup, ethanol was added and removed *in vacuo*, and the semisolid residue was crystallized from acetonitrile solution to form 74 mg. (54%) of β-VIII, m.p. 177.5–179.0°, $[\alpha]^{26}D$ −21.2 ± 0.3° (H_2O), $\lambda_{max}^{H_2O}$ 276 mμ (ε 17,950), R_{Ad} 2.2 in system A and 1.6 in system B.

Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.6; H, 6.13; N, 25.1. Found: C, 51.7; H, 6.39; N, 25.2.

6-Dimethylamino-9-(2′-deoxy-α-D-ribofuranosyl)purine (**α-VIII**) was obtained from α-III as a hygroscopic glass (87% yield), which was chromatographically homogeneous, by the same procedure as for β-VIII; R_{Ad} same as for β-VIII, $\lambda_{max}^{H_2O}$ 276 mμ (ε 17,150), $[\alpha]^{25}D$ +50.2 ± 0.7° (H_2O).

Anal. Found: C, 51.5; H, 6.89; N, 23.6.

Acknowledgment.—The authors are indebted to Dr. Peter Lim for infrared interpretations, to his staff for the optical rotations and paper chromatographic data, and to Mr. O. P. Crews for the preparation of intermediates.

The Cyclization of Dinitriles by Anhydrous Halogen Acids. A New Synthesis of Isoquinolines[1]

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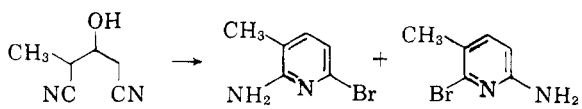
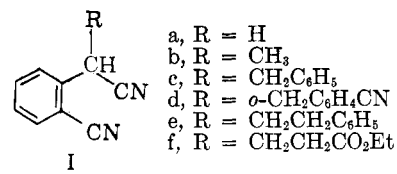
The action of anhydrous hydrogen chloride, bromide, and iodide, on a number of *o*-cyanobenzyl cyanides has been examined. While hydrogen chloride effects no cyclization, the other two acids afford 1-halo-3-aminoisoquinolines in excellent yield. Using this method, several polycyclic heterocycles were synthesized. In addition, a number of reactions of 1-bromo-3-aminoisoquinoline itself were studied.

In a recent study[2] of the action of hydrogen halides on 3-hydroxyglutaronitriles, we described a method for the facile preparation of simple 2-amino-6-halopyridines. In all but one case the dinitrile starting materials were symmetrical, and, in this instance, an equimolar mixture of the expected pyridines was obtained, *viz.*



We have continued these studies with an examination of other unsymmetrical dinitrile systems and an investigation of the applicability of this method of cyclization to the synthesis of isoquinoline derivatives. For these purposes, a series of α-substituted 2-cyanobenzyl cyanides were synthesized. 2-Cyanobenzyl cyanide (Ia, R = H) itself was prepared according to Gabriel and Otto,[3] while the simple alkyl derivatives Ib–d were made by the alkylation of Ia using the appropriate alkyl halide and sodium ethoxide in ethanol.[4–6] Besides these, alkylations were carried out with β-phenethyl iodide (β-phenethyl chloride caused no alkylation under the conditions used) and ethyl 3-bromopropionate to give the corresponding products, Ie and If, respectively.



a, R = H
b, R = CH_3
c, R = $CH_2C_6H_5$
d, R = *o*-$CH_2C_6H_4CN$
e, R = $CH_2CH_2C_6H_5$
f, R = $CH_2CH_2CO_2Et$

I

All attempts to alkylate Ia with ethyl chloroacetate failed. Of the catalyst systems used, sodium ethoxide in ethanol, triethylamine in tetrahydrofuran, sodamide in benzene, and potassium *t*-butoxide in *t*-butyl alcohol, none led to the desired product.

In all of these reactions, concomitant addition of the reacting components to the sodium ethoxide solution was necessary for optimum yields. Attempts to preform the anion of 2-cyanobenzyl cyanide led to self-condensation. This had already

(1) This paper is to be regarded as Part III of the series, Polyfunctional Aliphatic Compounds.

(2) Francis Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, in press.

(3) S. Gabriel and R. Otto, *Ber.*, **20**, 2222 (1887).

(4) S. Gabriel, *ibid.*, **20**, 2499 (1887).

(5) S. Gabriel and T. Posner, *ibid.*, **27**, 2492 (1894).

(6) G. Eichelbaum, *ibid.*, **21**, 2679 (1888).

TABLE I

PREPARATION OF ISOQUINOLINES BY CYCLIZATION OF DINITRILES OF THE GENERAL STRUCTURE

R	Isoquinoline	Method	M.p., °C.	Cryst.,[a] from	Yield, %	Calcd. C	Calcd. H	Calcd. N	Calcd. Br	Calcd. I	Found C	Found H	Found N	Found Br	Found I
H	3-Amino-1-bromo-	A	153–154	PE/MC	66	48.5	3.2	12.6	35.8	...	48.6	3.4	12.4	35.6	...
H	3-Amino-1-iodo-	B	147.5–148	PE/MC	74	40.0	2.6	10.4	...	47.0	40.2	2.6	10.3	...	47.2
CH_3	3-Amino-1-bromo-4-methyl-	A	143–145	AC/PE	80	50.7	3.8	11.8	33.7	...	50.9	3.6	11.9	33.9	...
C_2H_5	3-Amino-1-bromo-4-ethyl-	A	152	EA/PE	92	52.6	4.4	11.2	31.8	...	52.4	4.7	11.1	31.8	...
$C_6H_5CH_2$—	3-Amino-1-bromo-4-benzyl-	A	161–162	MC/PE	88	61.4	4.2	8.9	25.5	...	61.2	4.1	8.9	25.5	...
$C_6H_5CH_2$—	3-Amino-1-iodo-4-benzyl-	B	175–176	MC/PE	52	53.3	3.6	7.8	...	35.3	53.7	3.7	7.8	...	35.1
$C_6H_5CH_2CH_2$—	3-Amino-1-bromo-4-phenethyl-	A	184–186	EA/PE	95	62.4	4.6	8.6	24.4	...	62.3	4.6	8.6	24.6	...
$C_6H_5CH_2CH_2$—	3-Amino-1-iodo-4-phenethyl-	B	151.5–152.5	MC/PE	80	54.6	4.0	7.5	...	34.0	54.4	4.0	7.4	...	34.2

[a] Solvent key: AC, acetone; EA, ethyl acetate; MC, methylene chloride; PE, petroleum ether (b.p. 30–60°).

II

III

been noted by Damerow[7] and Albahary[8] and structure II postulated[7] for the product, m.p. 270°.

This structure is supported by the presence of a band at 7.09 μ in the infrared spectrum. The latter we have found to be characteristic of many compounds having a —CH_2— group between an ethylenic group (or a benzene ring) and a nitrile. In addition to II we also isolated a second compound m.p. 225° which became the major product on prolonged boiling of Ia with alkoxide. This material showed bands at 4.46 and 4.49 μ (unsaturated nitriles), while amino group absorptions were evident at 2.90, 2.99, and 3.12 μ. On this basis, we consider that the second dimer is probably III, although a number of other structures are possible. Small amounts of other condensation products were also found in the reaction mixture but these were not investigated further.

The action of hydrogen bromide or iodide on the dinitriles (I) led to cyclization and afforded, in every instance, only one of the two possible isoquinolines, in excellent yield (Table I).

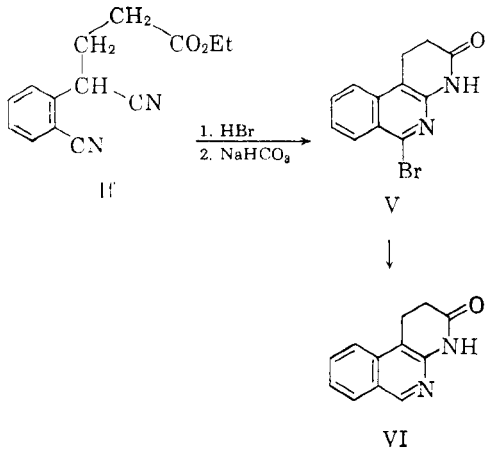
I IV

The structure of the simplest product (IV, R = H) was confirmed by hydrogenation over palladium in the presence of potassium hydroxide. This gave 3-aminoisoquinoline, the physical constants of which, and those of its picrate, were in excellent agreement with the values published for these compounds.[9] The action of nitrous acid on the reduced material gave the known alkali-soluble 3-hydroxyisoquinoline.[10]

By contrast, treatment of Ia with hydrogen chloride in ether followed by neutralization of the reaction mixture led to the recovery of starting material, a result in keeping with earlier work.[2]

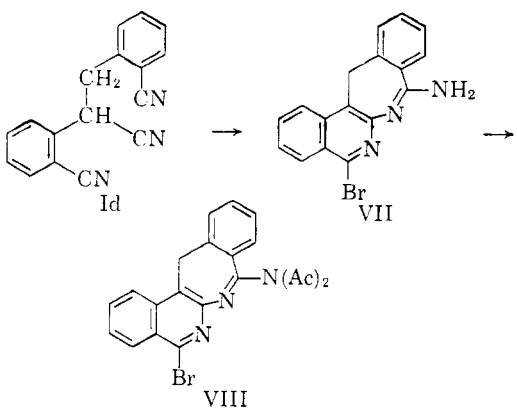
It seems most probable that the direction of cyclization observed with Ia is followed in all cases examined, especially since If afforded excellent yields of the tricyclic substance V, directly, when treated with hydrogen bromide.

(7) F. Damerow, *Ber.*, **27**, 2232 (1894).
(8) J. M. Albahary, *ibid.*, **29**, 2392 (1896).
(9) C. E. Teague and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).
(10) H. E. Baumgarten, W. F. Murdock, and J. E. Dirks, *J. Org. Chem.*, **26**, 803 (1961).

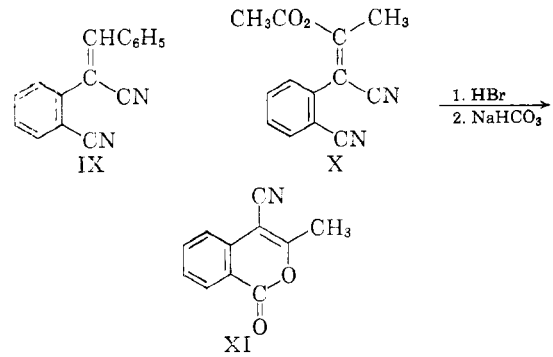


The infrared spectrum of the latter showed bands at 3.15, 3.27, and 5.87 μ consistent with this assignment. Hydrogenation of V in the presence of base gave VI in 66% yield.

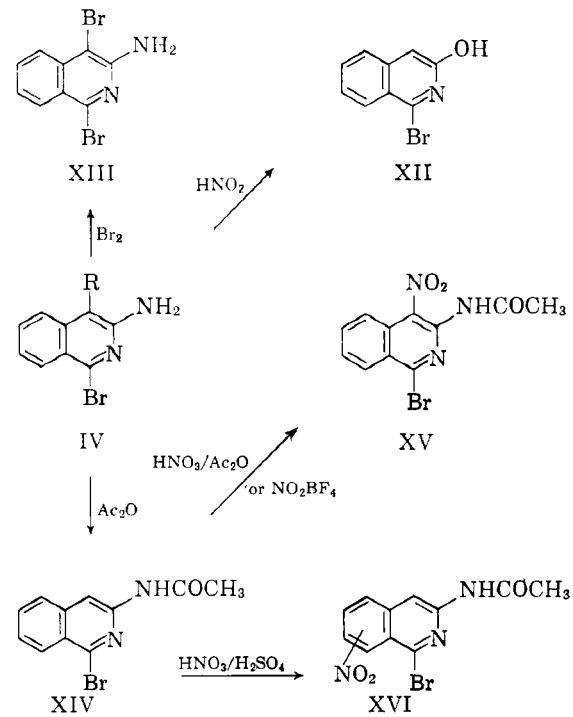
Reaction of the trinitrile, Id, with hydrogen bromide led, after neutralization, to an amorphous white powder which could not easily be crystallized and which showed no nitrile band in the infrared spectrum. In the 3-μ region, the absorptions present were characteristic of an amino group while from 6–7 μ a multiplicity of bands suggested an isoquinoline nucleus and a $\diagdown C{=}N{-}\diagup$ group. Acetylation of this substance afforded a material whose infrared spectrum showed no absorption for NH but strong bands at 5.80 and 5.88 μ characteristic of an imide group. Structures VII and VIII representing derivatives of a novel polycyclic system are therefore assigned to the cyclization product and its bisacetyl derivative.



The action of hydrogen bromide on two other derivatives of Ia was examined. Attempts to cyclize IX[11] gave gummy products which could not be crystallized, while XI was obtained in 75% yield when X[12] was treated with hydrogen bromide. A related transformation was observed by Gabriel and Neumann,[12] who boiled the benzoylation product of Ia with concentrated hydrochloric acid and obtained 3-phenyl-4-cyanoisocoumarin.



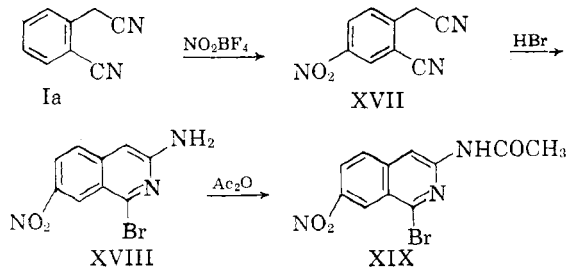
As simple 1,3-difunctional derivatives of isoquinoline of the type described above have not been available before, some of the reactions of IV (R = H) were examined.



Diazotization of 1-bromo-3-aminoisoquinoline, followed by heating, led to XII while bromination afforded XIII. The structure of XIII was supported by a band in its infrared spectrum at 13.35 μ, characteristic of the out-of-plane vibrations of four adjacent hydrogen atoms in an aromatic ring. Similar evidence was used to assign the structure XV to the product obtained from XIV by acetic anhydride–nitric acid nitration. Nitration using nitronium fluoroborate also led to XV, although some starting material was recovered in the one experiment tried. When XIV was nitrated with a nitric acid–sulfuric acid mixture, a mononitro derivative XVI, which appears to be substituted in

(11) S. Gabriel and G. Eschenbach, *Ber.*, **31**, 1578 (1898).
(12) S. Gabriel and A. Neumann, *ibid.*, **25**, 3563 (1892).

the benzene ring,[13] was obtained in very poor yield. The latter is not the 7-nitro derivative (XIX), as this was prepared unambiguously by the following sequence.[14]



The methods described in this paper for the preparation of isoquinoline compounds functionally substituted in the heteroring present many advantages over conventional methods. They are easy to carry out and give good yields on the cyclization step. 3-Aminoisoquinoline has been prepared previously[9] only by a tedious six-step process which leaves much to be desired,[15] while few other 3-aminoisoquinoline derivatives have been reported. Further studies on the cyclizations of these and other dinitriles will be presented in future papers.

Experimental

Melting points were determined on a Fisher–Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model No. 4-55 as films or as Nujol mulls. Hydrogen bromide (30–32%) in acetic acid was used as supplied by Eastman-Kodak.

Dimers of 2-Cyanobenzyl Cyanide (II) and (III).—A solution of 2-cyanobenzyl cyanide (4 g.) was added to sodium ethoxide (from 0.646 g. of sodium) in ethanol (60 cc.) and the mixture refluxed 3 hr., then allowed to stand overnight. The precipitate (1.68 g.) was removed by filtration and washed with water and methanol. Recrystallization of this material gave a first crop (0.668 g.) m.p. 273–274°. This recrystallized from ethanol afforded pure II, m.p. 274–276° (reported,[6,7] 270°). The infrared spectrum showed weak bands in the 3-μ region for $-NH_2$, while nitrile absorption was evident at 4.50 and 4.52 μ. Concentration of the mother liquors gave a second crop of material (0.916 g.) which, after repeated crystallization, gave the second dimer, m.p. 225°. Its infrared showed absorptions at 2.90, 2.99, 3.11 (NH_2), and at 4.46 and 4.49 μ (unsaturated nitriles).

Anal. Calcd. for $C_{18}H_{12}N_4$: C, 76.0; H, 4.3; N, 19.7. Found: C, 76.0; H, 4.2; N, 19.7.

Ethyl 4-Cyano-4-(2-cyanophenyl)butyrate (If).—To a solution of potassium (0.95 g.) in *t*-butyl alcohol (50 ml.) there was added a mixture of 2-cyanobenzyl cyanide (4 g.) and ethyl 3-bromopropionate (5.5 g.) dropwise during 5 min. The reaction mixture was refluxed for 1.5 hr. and the solvent removed by distillation. The resulting sirup was dissolved in methylene chloride, washed with water, and dried over anhydrous sodium sulfate. The extract was then percolated through a column of neutral alumina (30 g.). The initial fractions eluted from the column contained traces of starting material and ethyl acrylate. These were quickly followed by fractions containing a pale yellow sirup (3.89 g.). This material could not be induced to crystallize. Further chromatography of a small sample of this material did not seem to improve its purity.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.8; N, 11.6. Found: C, 70.0; H, 5.8; N, 12.0. Nitrile and saturated ester absorptions were evident in the infrared at 4.45 and 5.78 μ, respectively.

2-(2-Cyanophenyl)-4-phenylbutyronitrile (Ie).—Sodium hydride (0.675 g.) was suspended in dry ether (100 ml.) and ethanol (1.3 g.) added. The mixture was refluxed overnight and then a solution of 2-cyanobenzyl cyanide (4.0 g.) and 2-iodoethylbenzene (6.52 g.) in a minimum quantity of ether added dropwise to the reaction mixture. After refluxing for 20 hr., the ether was partially removed by distillation. The remaining solution washed with water and sodium thiosulphate solution and dried over anhydrous sodium sulfate. Removal of the organic solvent left a dark red-brown syrup. This was dissolved in a 3:1 mixture of benzene and petroleum ether (b.p. 30–60°) and absorbed on a column of alumina (40 g.). Elution of the column with this solvent mixture gave a pale yellow sirup which largely crystallized on standing at −25°. Crystallization of this material from ethyl acetate–petroleum ether (b.p. 30–60°) gave the desired product (2.5 g.) m.p. 60–62°. A sample prepared for analysis had m.p. 62–64°.

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.9; H, 5.7; N, 11.4. Found: C, 82.7; H, 5.7; N, 11.6. Nitrile absorption was evident at 4.42 (weak) and 4.46 μ in the infrared spectrum.

Further elution of the column with more polar solvents led to small quantities of the dimers of 2-cyanobenzyl cyanide.

Cyclization of the Dinitriles. Method A.—The dinitrile was suspended or dissolved in 10–20 times its weight of dry ethyl ether, and cooled in an ice bath. Dry hydrogen bromide was then bubbled through the mixture for 30 min. to 1 hr. until precipitation of the hydrogen halide salt appeared complete. The total reaction mixture was poured into an excess of sodium hydrogen carbonate solution. The crude 1-halo-3-aminoisoquinoline was separated by filtration and subsequently recrystallized from the appropriate solvent.

Method B.—The dinitrile was dissolved in a minimum of acetic acid (or if liquid used neat) and added dropwise with stirring and cooling to a solution of hydrogen halide in acetic acid (~ 3 equivalents). Stirring was continued until separation of the hydrohalide salt was judged complete. This was then separated by filtration and added to an excess of sodium hydrogen carbonate solution. Isolation of the isoquinoline derivative was then accomplished as in method A.

3-Aminoisoquinoline.—3-Amino-1-bromoisoquinoline (0.5 g.) in ethanol (40 ml.) containing potassium hydroxide (0.3 g.) was hydrogenated over a 10% palladium-on-charcoal catalyst (50 mg.). Absorption of one equivalent of hydrogen was complete at room temperature and pressure in 15 min. Isolation of the product by filtration, dilution with water, and extraction with methylene chloride led to a pale yellow solid (0.278 g.). Recrystallization from benzene afforded pure 3-aminoisoquinoline m.p. 178–179° (reported[9] 178°). The picrate prepared in the usual way was obtained as yellow crystals, m.p. 262–264° (reported[9] 261°).

6-Bromo-1,2-dihydrobenzo(*c*)(1,8)naphthyridin-3(4*H*)-one (V).—Hydrogen bromide was bubbled through a solution of ethyl 4-cyano-4-(2-cyanophenyl)butyrate (If; 3.89 g.) in ether (50 ml.) for 2.5 hr. The reaction mixture was poured into water containing only enough sodium hydrogen carbonate to keep the solution slightly acid. The precipitate (3.14 g.) m.p. 198–204°, was removed by filtration and recrystallized from ethanol to yield the pure material, m.p. 204°. Its infrared spectrum showed bands at 3.16, 3.29 (NH), and 5.89 μ (amide).

Anal. Calcd. for $C_{12}H_9BrN_2O$: C, 52.0; H, 3.2; Br, 28.9; N, 10.1. Found: C, 51.9; H, 3.1; Br, 28.8; N, 10.0.

(13) Protonation of the heterocyclic ring nitrogen by the strong acid medium probably inhibits nitration at the 4-position.

(14) Attempts to prepare XVII by the action of potassium cyanide on 2-cyano-4-nitrobenzyl bromide led only to deeply colored solutions, from which no product could be isolated.

(15) H. E. Baumgarten and J. E. Dirks, *J. Org. Chem.*, **23**, 900 (1958).

1,2-Dihydrobenzo(*c*)(1,8)naphthyridin-3(4*H*)-one (VI).—A solution of V (2.8 g.) in ethanol (250 cc.) containing sodium acetate (0.82 g.) was hydrogenated over a palladium-on-charcoal catalyst (0.3 g.; 10% palladium) until hydrogen uptake ceased (1.1 equiv.). The product separated during the hydrogenation. Acetone was added and the reaction mixture heated to effect solution of the organic precipitate. The catalyst was removed by filtration and the filtrate concentrated to give VI in 66% yield (1.3 g.), m.p. 268–270°. The pure material was obtained by recrystallization from a large volume of methanol m.p. 270–271°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.7; H, 5.1; N, 14.1. Found: C, 72.9; H, 5.0; N, 13.9.

8-Amino-5-bromo-13*H*-benzo[*e*]isoquinolin[3,4-*b*]azepine (VII) and Its N,N-Diacetyl Derivative (VIII).—Hydrogen bromide was bubbled for 3 hr. through a solution of 1,2-bis-(2-cyanophenyl)propionitrile (0.6 g.) in a 1:1 mixture of ether and methylene chloride (40 ml.). The reaction mixture was poured into excess sodium hydrogen carbonate solution, and the precipitate was removed by filtration (0.78 g.), m.p. ∽ 328°. Attempted recrystallization of this material from a large number of solvents proved difficult because of its insolubility. Its infrared spectrum showed bands in the 3-μ region typical for NH_2 and at 6.20, 6.30, and 6.45 μ (isoquinoline nucleus). In view of this, the bulk of the material was heated with acetic anhydride (4 ml.) and pyridine (1 ml.). After 1 hr. the reaction mixture was poured into 20% aqueous sodium acetate and the precipitate (0.7 g.) removed by filtration. Three recrystallizations from large volumes of ethyl acetate gave pure VIII m.p. 252–255° (sinters 230°, darkens 245°). Its infrared spectrum showed bands at 5.82 and 5.91 μ characteristic of an imide group, but absorptions for NH in the 3-μ region were completely absent.

Anal. Calcd. $C_{21}H_{16}BrN_3O_2$: C, 59.7; H, 3.8; Br, 18.9; N, 10.0. Found: C, 59.8; H, 3.9; Br, 18.8; N, 9.9.

4-Cyano-3-methylisocoumarin (XI).—Hydrogen bromide was bubbled through a solution of X (1.0 g.) in ether–benzene for 2 hr. The reaction mixture was then poured into aqueous sodium hydrogen carbonate solution and the resulting biphasic liquid was filtered to remove a small amount of suspended solid. The organic layer was separated and dried (Na_2SO_4). Removal of the solvent afforded 4-cyano-3-methylisocoumarin which, after recrystallization from methanol, had m.p. 142° (0.6 g.). Its infrared spectrum showed significant absorption at 4.46 and 5.71 μ.

Anal. Calcd. for $C_{11}H_7NO_2$: C, 71.4; H, 3.8; N, 7.6. Found: C, 71.0; H, 3.8; N, 7.6.

1-Bromo-3-hydroxyisoquinoline (XII).—3-Amino-1-bromoisoquinoline (1.3 g.) was dissolved by heating in 6 *N* sulphuric acid (75 cc.), then cooled in an ice bath. A solution of sodium nitrite (0.3 g.) in water was added slowly, and the reaction mixture stirred several hours at 0°, then allowed to come to room temperature. The solid which had separated was filtered, dried, dissolved in ethyl acetate, and percolated through a small alumina column (10 g.). The eluate yielded a pale yellow solid which after repeated crystallization afforded XII in small yield, m.p. 179–181°.

Anal. Calcd. for C_9H_6BrNO: C, 48.2; H, 2.7; Br, 35.7; N, 6.3. Found: C, 48.0; H, 2.4; Br, 35.8; N, 6.4.

3-Amino-1,4-dibromoisoquinoline (XIII).—To a solution of 3-amino-1-bromoisoquinoline (0.45 g.) in acetic acid (10 ml.) there was added bromine in carbon tetrachloride (21 ml.; 0.1 *M* in bromine). Some precipitation of solid occurred during the reaction, but on completion of the addition the mixture was poured into sodium acetate solution. Removal of the product by filtration, followed by drying and crystallization of the crude solid (0.6 g.) from ethyl acetate, led to pure XIII, m.p. 193–194°, in long yellow needles.

Anal. Calcd. for $C_9H_6Br_2N_2$: C, 35.8; H, 2.0; N, 9.3; Br, 52.9. Found: C, 35.6; H, 2.0; N, 9.2; Br, 52.8.

3-Acetamino-1-bromoisoquinoline (XIV).—Acetylation of 3-amino-1-bromoisoquinoline (0.6 g.) with acetic anhydride (8 ml.) in pyridine (4 ml.) was accomplished in 1.5 hr. at room temperature. Isolation of the product in the usual manner led to XIV in 98% yield (0.7 g.), m.p. 275°. One recrystallization from a large volume of ethanol provided the pure acetyl derivative m.p. 278°. Its infrared spectrum showed absorption typical for an acetamino group at 5.95 μ.

Anal. Calcd. for $C_{11}H_9BrN_2O$: C, 49.8; H, 3.4; Br, 30.1; N, 10.6. Found: C, 49.7; H, 3.4; Br, 29.9; N, 10.4.

3-Acetamino-1-bromo-4-nitroisoquinoline (XV).—a. 3-Acetamino-1-bromoisoquinoline (0.53 g.) was suspended in acetic anhydride (8 ml.) and cooled in an ice bath. To this was added a mixture of nitric acid (1 ml.) in acetic anhydride (2 ml.). The mixture was allowed to warm to room temperature, stirred for 5 hr., then poured into saturated sodium hydrogen carbonate solution. The resulting suspended solid was extracted with methylene chloride. Isolation in the usual way, followed by crystallization from methanol, led to yellow needles, of XV (0.3 g.), m.p. 235–240° (dec. sinters at 225°). Its infrared spectrum showed bands at 6.59, 7.69 μ (nitro group), and at 13.04 μ.

Anal. Calcd. for $C_{11}H_8BrN_3O_3$: C, 42.6; H, 2.6; Br, 25.8; N, 13.6. Found: C, 42.6; H, 2.6; Br, 26.0; N, 13.5.

b. When XIV (1.0 g.), suspended in *ca.* 30 ml. of tetramethylene sulfone-nitromethane (1:1) was treated with nitronium fluoroborate (0.5 g.) in tetramethylene sulfone for 24 hr. at room temperature, 0.35 g. of XV was removed by filtration of the reaction mixture. Pouring the filtrate into a large volume of water resulted in the recovery of 0.5 g. of the starting material. The nitro compound prepared in this way was identical by infrared spectrum and melting point with that prepared by method a.

1-Bromo-3-acetamino-x-nitroisoquinoline (XVI).—1-Bromo-3-acetaminoisoquinoline (1.3 g.) was dissolved in 20 ml. of concentrated sulfuric acid with heating. Addition of excess nitric acid to the ice-cold reaction flask was accompanied with a great deal of foaming. After 2 hr., a small amount of a solid product was removed by filtration. The infrared spectrum of this compound was similar but not identical with that of XV. The analytical sample was prepared by recrystallization from large volumes of ethanol, m.p. 262–265°.

Anal. Calcd. for $C_{11}H_8BrN_3O_3$: C, 42.6; H, 2.6; Br, 25.8; N, 13.6. Found: C, 42.5; H, 2.6; Br, 26.0; N, 13.6. Its infrared spectrum showed no strong bands in the 11–13-μ region.

2-Cyano-4-nitrobenzyl Cyanide XVII.—To a solution of 2-cyanobenzyl cyanide (3.5 g.) in tetramethylene sulfone (20 ml.), cooled to 5°, there was added over 20 min. nitronium fluoroborate (3.2 g.) in the same solvent (50 ml.). After the addition was complete, the mixture was warmed to 60° for 1 hr., then allowed to stand at room temperature for 3 days. The product was isolated by pouring the reaction solution onto crushed ice, stirring for 1 hr., and removing the dark yellow solid (2.6 g.) by filtration. One crystallization from methylene chloride–ether (charcoal) served to give the pure nitro compound with good recovery, m.p. 117–118°. It showed bands at 6.54 and 7.42 μ characteristic of a nitro group.

Anal. Calcd. for $C_9H_5N_3O_2$: C, 57.8; H, 2.7; N, 22.5. Found: C, 57.5; H, 2.6; N, 22.3.

1-Bromo-3-amino-7-nitroisoquinoline (XVIII) and Its N-Acetyl Derivative (XIX).—To a solution of 2-cyano-4-nitrobenzyl cyanide (1.6 g.) dissolved in acetic acid was added with stirring 30% hydrogen bromide in acetic acid (excess). After stirring for 60 hr. at room temperature, the reaction mixture was poured into a solution of dilute sodium acetate. The resulting dark red needles were removed by filtration tion (1.8 g.). Recrystallization from large volumes of ethanol afforded the pure material, m.p. 225–230° (sintering), whose infrared spectrum had characteristic $-NH_2$ absorption at 2.91, 3.02, and 3.13 μ and nitro bands at 6.40 and 7.50 μ.

Anal. Calcd. for $C_9H_8BrN_3O_2$: C, 40.3; H, 2.3; Br, 29.8; N, 15.7. Found: C, 40.1; H, 2.1; Br, 29.8; N, 15.8.

Treatment of XVIII in the usual way with acetic anhydride–pyridine (1 hr. on the steam bath) afforded XIX in 60% yield as yellow needles. Recrystallized from dimethylformamide m.p. 291–293° dec.

Anal. Calcd. for $C_{11}H_8BrN_3O_3$: C, 42.6; H, 2.6; Br, 25.8; N, 13.6. Found C, 42.4; H, 2.9; Br, 25.7; N, 13.7.

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The Reaction of Trifluoroacetonitrile with Aliphatic Diamines[1,2]

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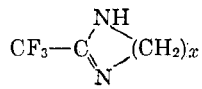
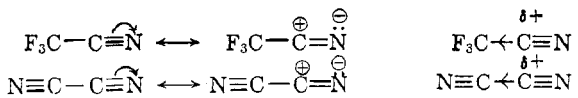
Trifluoroacetonitrile reacts with aliphatic diamines to yield carboxamidines, $CF_3C(=NH)NH(CH_2)_xNH(HN=)CCF_3$, and where $x = 2$, 3, or 4 cyclic compounds as well.



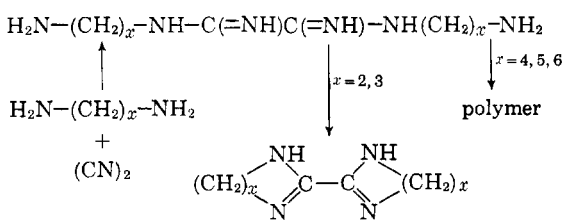
N,N-Dialkylaminoalkylenediamines produce substituted trifluoroacetamidines.

Recent work has indicated a similarity in chemical action of the —CN group in cyanogen and that in trifluoroacetonitrile.[3-6] This has been interpreted as the result of the electron-withdrawing effects of the NC— and CF_3— groups, which enhance the electrophilic character of the CN carbon involved in a resonance hybrid:



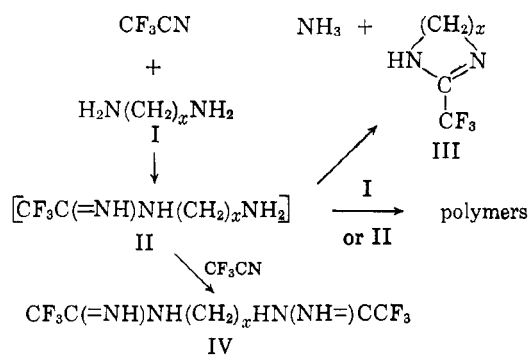
Obviously, in the case of cyanogen, a third resonance structure ($\overset{\oplus}{N}{=}C{=}C{=}\overset{\ominus}{N}$) must reduce somewhat the electrophilicity of the carbon in question and may explain the slower reaction rate observed in some cases.[6]

Extensive studies have been made of the reaction of cyanogen with aliphatic diamines.[7,8] The reaction takes place in two steps. First an oxamidine is formed; then, depending upon the number of carbon atoms in the chain, either an intramolecular reaction results in cyclization or an intermolecular reaction results in polymerization:



No reaction in which cyanogen attacks both NH_2 groups of the diamine is observed.

This investigation has shown that substitution of trifluoroacetonitrile for cyanogen results in a similar sequence of reactions, but introduces a new factor, attack on the second NH_2 group by a second molecule of trifluoroacetonitrile. This presumably is the result of the strong positive character of the reacting $C^{\oplus}$.



The fate of the intermediate (II) depends upon the value of x and, for a particular x, the conditions employed.

Ethylenediamine ($x = 2$).—(1) Ethane-1,2-bis-(trifluoromethyl)carboxamidine (IV. $x = 2$) was isolated when ethylenediamine was added to a solution of trifluoroacetonitrile in ether. (2) 2-Trifluoromethylimidazoline (III. $x = 2$) resulted when either (a) the nitrile was distilled into pure ethylenediamine or into a mixture of the diamine

(1) From the thesis submitted by Roland N. Johnson in partial fulfillment of requirements for the M.A. degree, June 1962.

(2) This work was supported in part by National Science Foundation Grant, G 9922.

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