aminopurine in 4 ml. of concd. hydrochloric acid and 12 ml. of water was heated under reflux for 10 min. During this time a flocculent yellow solid separated from the hot reaction mixture. After cooling to 0°, the mixture was filtered to give 0.46 g. (96%), m.p. 237–239° dec. Recrystallization from ethanol yielded small yellow needles, m.p. 243–245° dec., which were shown to be identical with an authentic sample of the hydrochloride of 4-benzalhydrazino-5-amino-6-methylmercaptopyrimidine by comparison of infrared spectra and by a mixture melting point determination.

Anal. Calcd. for $C_{12}H_{14}N_5SCl \cdot H_2O$: C, 46.0; H, 5.1; N, 22.4. Found: C, 45.8; H, 5.1; N, 22.9.

B. A mixture of 1.5 g. of 6-methyl-8-hydroxy-9-(*p*-nitrobenzal)aminopurine, 15 ml. of concd. hydrochloric acid and 15 ml. of water was heated under reflux for 4 hr. During this time *p*-nitrobenzaldehyde collected in the condenser and was recovered by recrystallization from ethanol. The reaction mixture was evaporated to dryness under reduced pressure and the residue triturated with cold 5% sodium hydroxide. Filtration removed 0.12 g. of brownish plates which were sublimed at 210°/0.05 mm. and then recrystallized from cellosolve to give golden plates, m.p. 307–308°, identical with an authentic sample of *p*-nitrobenzalazine prepared by the method of Curtius and Lublin.[15]

Anal. Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.4; H, 3.4; N, 18.8. Found: C, 56.4; H, 3.4; N, 18.4.

Acidification of the alkaline filtrate above yielded 0.85 g. of unchanged starting material.

6-Methyl-8-hydroxy-9-(p-ethylaminobenzyl)aminopurine (XVII). A mixture of 1.5 g. of 6-methyl-8-hydroxy-9-(p-nitrobenzal)aminopurine and 15 g. of Raney nickel in 150 ml. of absolute ethanol was stirred and heated under reflux for 4 hr. The hot reaction mixture was filtered, the collected catalyst extracted with boiling ethanol, and the combined filtrate and extract evaporated to dryness. Recrystallization of the residue from dilute ethanol yielded 1.1 g. (73%) of pale yellow needles, m.p. 225–226°.

(15) T. Curtius and A. Lublin, *Ber.*, **33**, 2460 (1900).

Anal. Calcd. for $C_{15}H_{18}N_6O$: C, 60.4; H, 6.0; N, 28.2. Found: C, 59.8; H, 5.7; N, 28.0.

1-(p-Nitrobenzal)amino-4-methyl-v-triazolo[d]pyrimidine. (XXX). To a rapidly stirred suspension of 2.0 g. of 4-(p-nitrobenzal)hydrazino-5-amino-6-methylpyrimidine in 20 ml. of water containing 2 ml. of concd. hydrochloric acid at room temperature was added, over the course of 20 min., a solution of 0.75 g. of sodium nitrite in 5 ml. of water. Stirring was continued for 1 hr. following addition of the sodium nitrite, and the reaction mixture was warmed to 60° for 15 min., cooled to 0°, and filtered. The collected solid was washed well with 5% sodium acetate solution followed by water and recrystallized from ethanol to give 1.1 g. (53%) of a yellow microcrystalline solid, m.p. 231–233° dec.

Anal. Calcd. for $C_{12}H_9N_7O_2$: C, 50.9; H, 3.2; N, 34.6. Found: C, 50.9; H, 3.3; N, 34.75.

1-Benzalamino-4-methylmercapto-v-triazolo[d]pyrimidine (XXXI). Nitrosation of 2.0 g. of 4-benzalhydrazino-5-amino-6-methylmercaptopyrimidine as described above yielded, after recrystallization of the crude product from ethanol, 1.65 g. (79%) of colorless needles, m.p. 176–177° dec. $\lambda_{max}^{C_2H_5OH}$ 269, 317 mμ; ε 18,000, 18,500.

Anal. Calcd. for $C_{12}H_{10}N_6S$: C, 53.3; H, 3.7; N, 31.1. Found: C, 53.5; H, 3.6; N, 31.6.

The following experiment is representative of hydrolysis attempts made with XXX and XXXI: A suspension of 10. g. of 1-benzalamino-4-methylmercapto-*v*-triazolo[d]pyrimidine (XXXI) in 40 ml. of 6*N* hydrochloric acid was steam distilled until no more benzaldehyde passed over (approximately 30 min). The reaction mixture was evaporated to dryness under reduced pressure, the residue treated with 5% sodium acetate solution and again evaporated to dryness. A cold-finger assembly was inserted into the reaction flask and the residue was sublimed at 0.05 mm. up to 180° (bath temperature) to give 0.24 g. of ammonium chloride contaminated with a trace of organic material of unknown composition. No identifiable material could be found in the sublimation residue.

PRINCETON, N. J.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Reaction of Nitriles with *o*-Aminonitriles: A Convenient Synthesis of Fused 4-Aminopyrimidines[1a,b]

EDWARD C. TAYLOR AND ALAN L. BORROR[2]

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The base-catalyzed condensation of various aromatic and heterocyclic *o*-aminonitriles with nitriles to give 4-aminoquinazolines, 4-aminopyrazolo(3,4)pyrimidines, 4-aminopyrido(2,3-d)pyrimidines, and 6-aminopurines (adenines) is described. The scope, limitations, mechanism, and synthetic utility of this reaction are discussed.

A number of examples of the base-catalyzed dimerization of *o*-aminonitriles, leading to fused 4-aminopyrimidine heterocycles, have been reported recently from this Laboratory.[3–5] The reaction may be illustrated by the dimerization of 2-amino-5-nitrobenzonitrile (I) in methanolic ammonia to give 2-(2-amino-5-nitrophenyl)-4-amino-6-nitroquinazoline (II). It was suggested[3] that this reaction proceeds by initial condensation of the amino group of one molecule of the *o*-aminonitrile

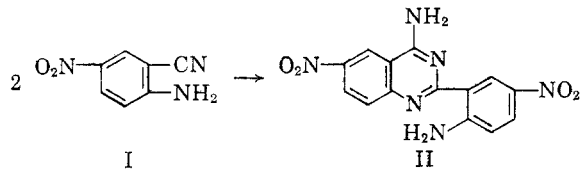
(1) (a) This work was supported in part by a research grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service. (b) Presented in part before the Division of Organic Chemistry at the 2nd Delaware Valley Regional Meeting of the ACS, Philadelphia, Pa., in February, 1960, and before the Hauptversammlung der Deutschen Chemischen Gesellschaft, Stuttgart, in April, 1960.

(2) du Pont predoctoral fellow, 1958–1959; Parke, Davis and Co. Fellow in Chemistry, 1959–1960: NIH Summer Fellow, 1960.

(3) E. C. Taylor, R. J. Knopf, and A. L. Borror, *J. Am. Chem. Soc.*, **82**, 3152 (1960).

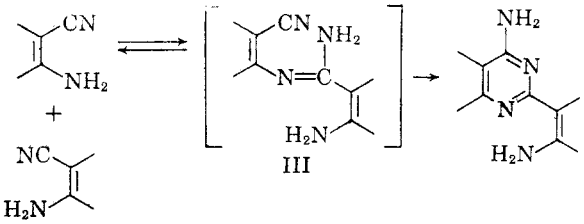
(4) E. C. Taylor, A. J. Crovetti, and R. J. Knopf, *J. Am. Chem. Soc.*, **80**, 427 (1958).

(5) E. C. Taylor and N. W. Kalenda, *J. Am. Chem. Soc.*, **78**, 5108 (1956).



I II

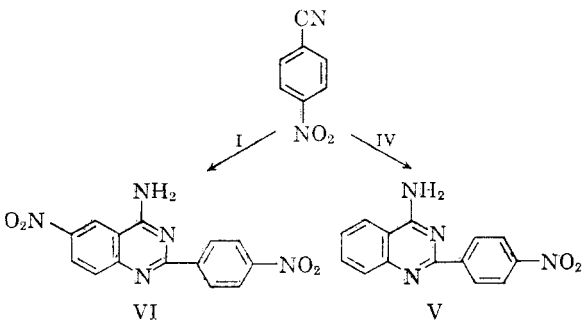
with the nitrile group of a second molecule to give an intermediate amidine (III) which then undergoes a second, but intramolecular, amine-nitrile condensation to give the observed product. A six- rather than an eight-membered ring dimer is formed because of the participation in the final ring closure of the more basic of the two amine functions of the intermediate III. It was suggested that



III

the undoubtedly unfavorable equilibrium reaction between starting materials and the intermediate amidine III is shifted irreversibly to the right by conversion of III into the highly aromatic, insoluble, and extremely stable 4-aminopyrimidine system (*i.e.*, II).

As neither 2-aminobenzonitrile (IV) nor 2-amino-5-bromobenzonitrile underwent dimerization under similar conditions, it was concluded[3] that the critical factor determining dimerization was the ability of the nitrile group to undergo nucleophilic attack rather than the basicity of the attacking amino group. It was thus predicted that 2-aminobenzonitrile (IV), precisely because it did *not* dimerize, should readily undergo mixed condensations with more reactive nitriles. In fact, IV reacted with 4-nitrobenzonitrile to give 2-(4-nitrophenyl)-4-aminoquinazoline (V) in good yield.



VI V

The dependence of the course of the condensation reaction on the proclivity of the participating nitrile group to undergo nucleophilic attack was clearly demonstrated by the observation that a mixture of 2-amino-5-nitrobenzonitrile (I) and 4-nitrobenzonitrile yielded exclusively the product of mixed condensation, 2-(4-nitrophenyl)-4-amino-6-nitroquinazoline (VI); none of the dimer (II) was formed.

In the present paper we have attempted to delineate the scope and limitations of this mixed condensation reaction leading to fused 4-aminopyrimidine heterocycles. Extension of the reaction to heterocyclic *o*-aminonitriles has led to new and useful synthetic routes to 4-aminopyrazolo(3,4-d)-pyrimidines and to adenines.

The reaction of 2-aminobenzonitrile (IV) with other nitriles was first studied. With a slight molar excess of benzonitrile in methanolic ammonia in a sealed tube, and under rather severe conditions (twenty hours at 200°), 2-phenyl-4-aminoquinazoline (VII) was formed in 39% yield. No reaction occurred in refluxing methanol in the presence of sodium methoxide, but when the condensation was carried out in the same medium at 150° in a sealed tube, VII was formed in comparable yield. Although alkoxides in refluxing ethanol can also be used to catalyze mixed condensation reactions between *o*-aminonitriles and nitriles, the method suffers from the disadvantage that side reactions can occur involving the participating nitrile. For example, it has been reported that 4-nitrobenzonitrile is reduced by sodium ethoxide[6] and undergoes nucleophilic displacement of the nitro group with sodium methoxide.[7] In addition, nitriles bearing an active hydrogen can undergo Thorpe condensations in the presence of alkoxides.[8]

2-Aminobenzonitrile (IV) reacted with a large excess of acetonitrile in methanolic ammonia to give 2-methyl-4-aminoquinazoline (VIII) in 26% yield. Considerably reduced yields were obtained in the presence of diminished amounts of acetonitrile. The structure of this product, and also of 2-phenyl-4-aminoquinazoline (VII) formed as mentioned above, was assigned on the basis of analysis, the absence of a nitrile function (infrared), examination of the ultraviolet spectrum, and by analogy with the reaction of IV with *p*-nitrobenzonitrile, which was previously shown to give V.[3] 2-Aminobenzonitrile failed to react with 4-methoxybenzonitrile, 4-aminobenzonitrile or *o*-nitrobenzonitrile, even under forcing conditions.

2-Amino-5-bromobenzonitrile also undergoes mixed condensations with nitriles. Heating with a slight molar excess of benzonitrile in methanolic ammonia at 190° gave 2-phenyl-4-amino-6-bromoquinazoline (IX) in 31% yield, and the use of 4-nitrobenzonitrile gave 2-(4-nitrophenyl)-4-amino-6-bromoquinazoline (X) in 44% yield. In both cases the products separated in a high state of purity from the reaction mixture and were thus readily separated from the soluble, unchanged starting materials.

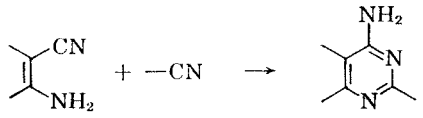
(6) W. Reinders and W. E. Ringer, *Rec. trav. Chim.*, **18**, 326 (1899).

(7) W. E. Ringer, *Rec. trav. Chim.*, **18**, 330 (1899).

(8) V. Migrdichian, *The Chemistry of Organic Cyanogen Compounds*, Reinhold, New York, 1947, p. 285.

TABLE I

FUSED 4-AMINOPYRIMIDINES



o-Amino-nitrile	Nitrile	Product	Solvent	Time, Hr.	Temp.	Recryst. Solvent	M.P.	Yield, %	Formula	Calcd., % C	H	N	Found, % C	H	N	Ultraviolet Spectra (0.1*N* HCl) λ_{max} (mμ)	Log ϵ
2-Amino-benzo-nitrile	Benzonitrile	2-Phenyl-4-amino-quinazoline (VII)	[a]	20	200	Aq. C_2H_5OH	145.5–146.5	39	$C_{14}H_{11}N_3$	76.0	5.0	19.0	76.0	5.0	19.3	253, 310	4.32, 4.00
2-Amino-benzo-nitrile	Acetonitrile	2-Methyl-4-amino-quinazoline (VIII)	[a]	24	210	H_2O	228–229	26	$C_9H_9N_3$	67.9	5.7	26.4	67.9	6.1	26.6	309, 315–322 (sh)	3.88, 3.76
2-Amino-5-bromo-benzo-nitrile	Benzonitrile	2-Phenyl-4-amino-6-bromo-quinazoline (IX)	[a]	20	190	Aq. C_2H_5OH	224–226	31	$C_{14}H_{10}N_3Br$	56.0	3.3	14.0	55.8	3.5	13.8	267.5, 326	4.45, 3.96
2-Amino-5-bromo-benzo-nitrile	4-Nitro-benzo-nitrile	2-(4-Nitro-phenyl)-4-amino-6-bromo-quinazo-line (X)	[a]	4	190	$C_2H_5OC_2H_4OH$	283–285	44	$C_{14}H_9BrN_4O_2$	48.7	2.6	16.2	48.7	2.4	16.0	237, 278, 320–330 (sh)	4.35, 4.43, 4.06
2-Amino-nicotino-nitrile	Nicotino-nitrile	2-(3-Pyridyl)-4-amino-pyrido-(2,3-d)-pyrimidine (XI)	[a]	5	200	Sublimed	312–314	56	$C_{12}H_9N_5$	64.6	4.1	31.4	64.65	4.25	31.5	265, 366	4.33, 3.98
			C_2H_5OH/ C_2H_5ONa	6	reflux	O		50									
3-Amino-4-cyano-pyrazole	3-Amino-4-cyano-pyrazole	4-Amino-6-[4-(3-amino-pyrazyl)]-pyrazolo-(3,4-d)-pyrimidine (XVI)	[a]	20	200	aq. CH_3SCH_3	334–338	63.5	$C_8H_8N_8$[b]	44.4	3.7	51.8	45.8	4.5	50.3	294	4.25

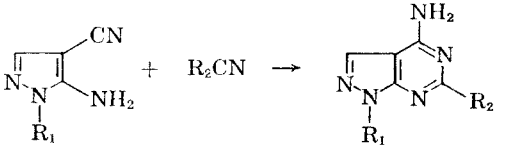
TABLE I (*continued*)

o-Amino-nitrile	Nitrile	Product	Solvent	Time, Hr.	Temp.	Recryst. Solvent	M.P.	Yield, %	Formula	Calcd. % C	H	N	Found, % C	H	N	Ultraviolet Spectra (0.1*N* HCl) λ_{max} (mμ)	Log ε
1-Methyl-4-cyano-5-amino-pyrazole	1-Methyl-4-cyano-5-amino-pyrazole	1-Methyl-4-amino-6-[4-(1-methyl-5-amino-pyrazyl)]-pyrazolo-(3,4-d)-pyrimidine (XVII)	[a]	20	200	Sublimed	255–257	41.5	$C_{10}H_{12}N_8$	49.2	4.95	45.9	49.4	5.2	45.9	222, 308	4.45, 4.24
1-Phenyl-4-cyano-5-amino-pyrazole	1-Phenyl-4-cyano-5-amino-pyrazole	1-Phenyl-4-amino-6-[4-(1-phenyl-5-amino-pyrazyl)]-pyrazolo-(3,4-d)-pyrimidine (XVIII)	[a]	20	200	aq. C_2H_5OH	255–257	43	$C_{20}H_{16}N_8$	65.1	4.4	30.4	65.4	4.5	30.6	235, 322	4.59, 4.32
1-Methyl-4-amino-5-cyano-imidazole	Benzonitrile	2-Phenyl-7-methyl-adenine (XX)	[a]	20	200	DMF	328–329	50	$C_{12}H_{11}N_5$	64.0	4.9	31.1	64.1	5.0	30.8	250, 276	4.38, 4.32

[a] Methanol/ammonia. [b] An analytically pure sample could not be obtained even after repeated recrystallizations followed by vacuum sublimation.

TABLE II

4-AMINOPYRAZOLO(3,4-d)PYRIMIDINES



R_1	R_2	Solvent	Time, Hr.	Temp.	Recryst. Solvent	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Ultraviolet Spectra (0.1N HCl) λ_{max} (mμ)	Ultraviolet Spectra (0.1N HCl) Log ϵ
H	3-Pyridyl	[d]	20	[f]	DMF	338–339 dec.	83	$C_{10}H_8N_6$	56.6	3.8	39.6	56.6	3.9	39.75	230, 264	4.32, 4.08
H	p-$NO_2C_6H_4$	[d]	20	[f]	DMF	360	83	$C_{11}H_8N_6O_2$	51.6	3.15	32.8	51.6	3.3	32.7	266, 282–294 (sh)	4.23, 4.18
H	$C_6H_5CH_2$	[d]	20	[f]	DMF	296–298	61.5	$C_{12}H_{11}N_5$	64.0	4.9	31.1	63.65	5.2	31.4	260	4.00
H	C_6H_5	[d]	20	[f]	Aq. DMF	275–277	69	$C_{11}H_9N_5$	62.55	4.3	33.2	62.2	4.35	33.6	242, 275	4.25, 4.18
H	CH_3[a]	[d]	24	[f]	Aq. DMF	300	77.5	$C_6H_7N_5$	48.3	4.6	47.0	48.6	4.9	46.7	259	3.95
CH_3	3-Pyridyl	[d]	20	[f]	DMF	262–263	71	$C_{11}H_{10}N_6$	58.4	4.5	37.15	58.5	4.6	37.3	233, 285–300 (sh)	4.37, 3.86
		[e]	3	[g]	DMF	262–263	80									
CH_3	p-$NO_2C_6H_4$	[d]	20	[f]	DMF	297–298	51	$C_{12}H_{10}N_6O_2$	53.3	3.7	31.1	53.7	4.1	30.9	226.5, 255, 306	4.34, 4.19, 4.09
CH_3	$C_6H_5CH_2$	[d]	20	[f]	Ethanol	206–207	71.5	$C_{13}H_{13}N_5$	65.25	5.5	29.3	65.5	5.6	29.0	222, 261	4.43, 3.99
CH_3	C_6H_5	[d]	20	[f]	Ethanol	199–200	59.5	$C_{12}H_{11}N_5$	64.0	4.9	31.1	64.0	5.2	31.3	241, 280	4.32, 4.13
		[e]	5	[g]	Ethanol	199–200	64									
CH_3	CH_3[b]	[d]	48	[f]	Aq. CH_3OH	260–261	65.5	$C_7H_9N_5$	51.5	5.6	42.9	51.7	5.75	43.0	259	3.93
C_6H_5	3-Pyridyl	[d]	20	[f]	Aq. DMF	239–240	71.5	$C_{16}H_{12}N_6$	66.65	4.2	29.15	66.7	4.5	28.9	239.5, 290–310 (sh)	4.54, 4.09
		[e]	3	[g]	Aq. DMF	239–240	91.5									
C_6H_5	p-$NO_2C_6H_4$	[d]	20	[f]	DMF	300–301	67	$C_{17}H_{12}N_6O_2$	61.4	3.6	25.3	61.7	3.65	25.3	243, 304	
C_6H_5	$C_6H_5CH_2$	[d]	20	[f]	Aq. DMF	220–221	57	$C_{18}H_{15}N_5$	71.7	5.0	23.2	71.5	4.9	23.3	239	4.52
C_6H_5	C_6H_5	[d]	20	[f]	Aq. DMF	224–225	71	$C_{17}H_{13}N_5$	71.3	4.6	24.4	71.3	4.7	24.3	245	4.47
		[e]	5	[g]	Aq. DMF	224–225	72									
C_6H_5	CH_3[c]	[d]	48	[f]	Aq. C_2H_5OH	246–248	73.5	$C_{12}H_{11}N_5$	64.0	4.9	31.1	63.75	5.2	30.8	238	4.41

[a] This compound has been reported (ref. 9) to melt above 300° and to have $\lambda_{max}^{0.1N\ HCl}$ 259 mμ, ϵ 8650. [b] This compound has been reported (ref. 9) to melt at 251–252° and to have $\lambda_{max}^{0.1N\ HCl}$ 260 mμ, ϵ 9450. [c] This compound has been reported (ref. 9) to melt at 287–289° and to have $\lambda_{max}^{0.1N\ HCl}$ 238 mμ, ϵ 25,200. However, upon rechecking (private communication) Professor Robins has found that his compound melts at 250°. Our sample and his were compared directly and found to be identical. [d] Methanol/ammonia. [e] Ethanol/sodium ethoxide. [f] 200°. [g] Reflux.

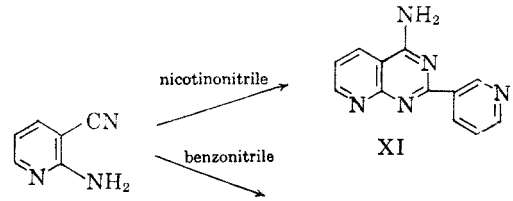
It was mentioned above that 2-amino-5-nitrobenzonitrile (I), which readily dimerizes to II under basic conditions, yielded only the product of mixed condensation (VI) when heated with a molar amount of 4-nitrobenzonitrile. This result was interpreted in support of the thesis that the initial condensation leading to the intermediate amidine III would take place with the more reactive of the two competing nitriles. It was thus of considerable interest to observe that the reaction of 2-amino-5-nitrobenzonitrile (I) with benzonitrile in methanolic ammonia at 190° led to the dimer II; no product of mixed condensation was isolated or detected. One must conclude that the nitrile group of I is more susceptible to nucleophilic attack than is benzonitrile.

Further evidence in support of these conclusions was afforded by the following experiment. An equimolar mixture of 2-aminobenzonitrile (IV) and 2-amino-5-nitrobenzonitrile (I) was allowed to compete for a molar quantity of 4-nitrobenzonitrile in methanolic ammonia at 190°. The only product formed was 2-(4-nitrophenyl)-4-amino-6-nitroquinazoline (VI). Thus, although the attacking amino group in 2-aminobenzonitrile is more basic than is the amino group in 2-amino-5-nitrobenzonitrile, consideration of the intermediate amidines formed reveals that intramolecular cyclization from the amidine derived from the latter nitrile should proceed much more readily than cyclization from the amidine derived from the former nitrile. Thus, the facility with which the nitrile group *in the o-aminonitrile* undergoes nucleophilic attack can determine not only whether dimerization or mixed condensation takes place, but also the course of competitive condensation reactions.

We believe that the following conclusions can be drawn concerning the reaction of aromatic *o*-aminonitriles with nitriles on the basis of the experiments thus far discussed: (1) the reaction is favored by the presence of electron-withdrawing substituents in the participating nitrile; (2) electron-withdrawing substituents in the *o*-aminonitrile promote dimerization, and in such cases mixed condensations are possible only with second nitriles of greater reactivity; (3) provided dimerization does not occur, the mixed condensation is also favored by electron-withdrawing substituents in the *o*-aminonitrile; and (4) bulky *o*-substituents in the participating nitrile can prevent reaction.

Despite the fact that the yields of the mixed condensation products in the above examples were not high, the ease of isolating products from unreacted starting materials and the simplicity of the reaction would seem to make it attractive enough as a synthetic route to 4-aminoquinazolines to warrant further investigation.

As it has been shown in the case of the aromatic *o*-aminonitriles discussed above that those *o*-aminonitriles which undergo dimerization readily react in mixed condensations only with very reactive nitriles, while *o*-aminonitriles undergoing dimerization with difficulty are correspondingly less selective in undergoing mixed condensations with other nitriles, it was anticipated that similar orders of reactivity would be observed with heterocyclic compounds. This proved to be the case. Thus, 2-aminonicotinonitrile reacted with nicotinonitrile in methanolic ammonia at 200°, or in refluxing ethanol in the presence of sodium ethoxide, to give only 2-(3-pyridyl)-4-aminopyrido(2,3-d)-pyrimidine (XI), the product of mixed condensation. None of the dimer of 2-aminonicotinonitrile (XII)[4] was formed. On the other hand, when a



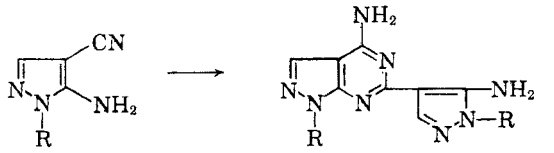
XI

XII

mixed condensation of 2-aminonicotinonitrile with benzonitrile was attempted under similar conditions, the only product isolated was XII. Similarly, the dimerization of 4-amino-5-cyano-2-methylpyrimidine could not be suppressed even in the presence of a large excess of benzonitrile; clearly the nitrile group of benzonitrile is less reactive than the pyrimidine nitrile, in spite of the presence in the latter of an *o*-situated amino group. One must conclude that the synthetic usefulness of mixed condensation reactions of the above type with *o*-aminonitriles which dimerize readily is indeed limited to very reactive participating nitriles.

In agreement with earlier work,[4] 3-amino-4-cyanopyrazole (XIII), 1-methyl-4-cyano-5-aminopyrazole (XIV), and 1-phenyl-4-cyano-5-aminopyrazole (XV) were recovered unchanged after prolonged refluxing in ethanol in the presence of sodium ethoxide, indicating the presence in these compounds of relatively unreactive nitrile groups. It has now been found, however, that treatment with methanolic ammonia at 200° afforded in each case a high-melting, insoluble, yellow compound which did not contain a nitrile group (infrared), and which was isomeric with the starting material. Although the compounds were too insoluble to permit a molecular weight determination, examination of the ultraviolet spectra confirmed the presence in each case of a bicyclic ring system, and it was apparent that dimerization to the 4-aminopyrazolo(3,4-d)pyrimidines XVI–XVIII had occurred under these forcing conditions.

In contrast to the difficulty experienced in dimerizing these compounds, and in agreement with predictions based on the considerations outlined above, it was found that mixed condensations with a wide variety of nitriles took place to give the 4-aminopyrazolo(3,4-d)pyrimidines given in Table II. A slight molar excess of the participating

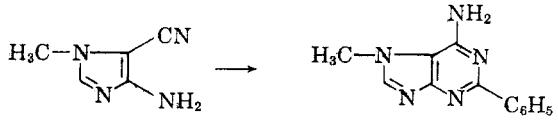


XIII. R = H
XIV. R = CH_3
XV. R = C_6H_5

XVI. R = H
XVII. R = CH_3
XVIII. R = C_6H_5

nitrile was used in most cases; with acetonitrile, however, a large excess was required to insure good yields. The products usually crystallized directly from the reaction mixtures in a state of high purity. The use of sodium ethoxide in refluxing ethanol rather than methanolic ammonia gave variable results. Good yields of the 2-phenyl- and 2-(3-pyridyl) derivatives were obtained with 1-methyl- (XIV) and 1-phenyl-4-cyano-5-aminopyrazole (XV) when condensations with benzonitrile and nicotinonitrile were carried out under these conditions, but no reaction with either nitrile took place with 4-amino-5-cyanopyrazole (XIII). This may be due to the fact that sodium ethoxide, as a stronger base, can abstract a proton from XIII to give a resonance-stabilized anion in which the most nucleophilic center may no longer be the 4-amino group, and in which the nitrile group is deactivated as a result of delocalization of the negative charge of the anion. Attempted condensations of XIV and XV with benzylcyanide in the presence of sodium ethoxide gave poor yields of the corresponding 4-benzyl derivatives, probably because benzylcyanide readily undergoes a Thorpe condensation in this medium.[8]

Although insufficient material precluded a corresponding investigation of the reaction of 1-methyl-4-amino-5-cyanoimidazole (XIX) with nitriles, it was found that the reaction with benzonitrile in methanolic ammonia at 200° gave 2-phenyl-7-methyladenine (XX) in 50% yield. The reaction would thus appear to be similarly applicable to the synthesis of purines from imidazole *o*-aminonitriles.



XIX + C_6H_5CN

XX

Several of the 1-(un)substituted 4-amino-6-methylpyrazolo(3,4-d)pyrimidines reported in Table II were previously described by Cheng and Robins[9] by a five-step sequence from the corresponding 1-(un)substituted 4-cyano-5-aminopyrazole. The one-step synthesis described here thus represents a considerable improvement both in simplicity and in versatility over the previously available method for the preparation of these physiologically interesting purine analogs.

(9) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 191 (1958).

EXPERIMENTAL[10]

5-Bromo-2-nitrobenzamide. To a cooled solution of 1.7 g. of potassium nitrate in 15 ml. of concd. sulfuric acid was added portionwise and with stirring 3.25 g. of 3-bromobenzamide[11] so that the temperature of the reaction mixture did not exceed 35°. The resulting pale yellow solution was stirred at room temperature for 1.5 hr. and then poured carefully over 250 g. of crushed ice. The pale yellow solid which separated was collected by filtration and washed well with water; yield, 3.18 g., m.p. 172–175°. Recrystallization from ethanol gave 2.05 g. (52%) of pale cream needles, m.p. 185–186°.

Anal. Calcd. for $C_7H_5BrN_2O_3$: C, 34.3; H, 2.1; N, 11.4. Found: C, 34.1; H, 2.3; N, 11.5.

5-Bromo-2-nitrobenzonitrile. To a cooled solution of 20.9 g. of 5-bromo-2-nitrobenzamide in 50 ml. of pyridine was added dropwise and with stirring 15.3 g. of phosphorus oxychloride over a period of 45 min. The reaction mixture was then stirred for an additional 15 min. and poured over crushed ice. The solid which separated was collected by filtration and recrystallized from ethanol to give 13.5 g. (70%) of pale yellow crystals, m.p. 117–119°.

Anal. Calcd. for $C_7H_3BrNO_2$: C, 37.1; H, 1.3. Found: C, 36.9; H, 1.3.

2-Amino-5-bromobenzonitrile. To a well stirred suspension of 20 g. of mossy tin in 22.5 ml. of 25% hydrochloric acid was added in small portions 7.7 g. of 5-bromo-2-nitrobenzonitrile, care being taken so that the temperature did not exceed 35°. After 5 hr., the reaction mixture was diluted with water to a total volume of 60 ml. and decanted from unchanged tin. The resulting partial suspension was made basic by the addition of 120 ml. of 15% sodium hydroxide and extracted several times with 50-ml. portions of ether. The combined ether extracts were dried over potassium carbonate, evaporated under reduced pressure and the solid residue recrystallized from carbon tetrachloride to give 4.0 g. (60%) of yellow crystals, m.p. 92–94°. Vacuum sublimation at 90°/0.5 mm. gave white needles, m.p. 95–96°.

Anal. Calcd. for $C_7H_5BrN_2$: C, 42.7; H, 2.5. Found: C, 43.0; H, 2.7.

Condensation of o-aminonitriles with nitriles (see Tables I and II). The *o*-aminonitrile, nitrile, and appropriate solvent were placed in a glass liner and sealed within a steel hydrogenation bomb. The reaction mixture was then heated as specified (with shaking), and the product was isolated either by direct filtration of the cooled reaction mixture or by evaporation under reduced pressure followed by recrystallization of the residue from the specified solvent.

2-(4-Nitrophenyl)-4-amino-6-nitroquinazoline (VI). A mixture of 0.71 g. of 2-aminobenzonitrile, 0.98 g. of 2-amino-5-nitrobenzonitrile, 0.89 g. of 4-nitrobenzonitrile, and 25 ml. of methanolic ammonia was placed in a glass liner which was sealed within a steel hydrogenation bomb and then heated at 185° for 2 hr. The cooled reaction mixture was filtered and the collected solid washed with ethanol and dried to give 0.91 g. of a yellow solid, m.p. 298–301°. Evaporation of the filtrate, cooling, and extraction of the collected solid with boiling water produced an additional quantity (0.12 g.) of a

(10) The microanalyses were performed by Dr. Joseph F. Alicino, Metuchen, N. J., and the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(11) O. Folin, *Am. Chem. J.*, **19**, 328 (1897).

yellow solid, m.p. 280–290°. Both samples were shown to be slightly impure 2-(4-nitrophenyl)-4-amino-6-nitroquinazoline by comparison of infrared spectra with the spectrum of an authentic sample[8] m.p. 303–304°, and by subsequent recrystallization to give pure material. Cooling of the water extract above yielded 0.1 g. of 2-amino-5-nitrobenzonitrile, m.p. 204–206°, identical with an authentic sample.[12]

PRINCETON, N. J.

(12) H. Ph. Baudet, *Rec. trav. chim.*, **43**, 707 (1924).

[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, THE ORTHO RESEARCH FOUNDATION]

Piperidylquinolizidines Derived from Sparteine

HENRY BADER[1a]

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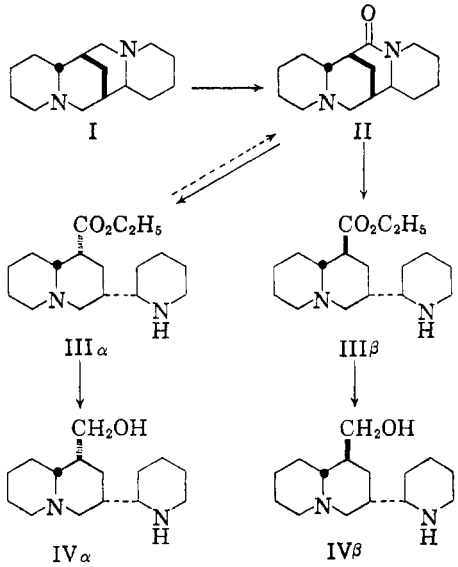
Through the hydrolytic cleavage of *l*-oxysparteine 1α- and 1β-carbethoxy-3α-(2′-piperidyl)quinolizidine (IIIα and IIIβ) were obtained, and from these were derived various other 1-substituted 3α-(2′-piperidyl)quinolizidines. Several different approaches to the synthesis of the 1-unsubstituted 3α-(*N*-methyl-2′-piperidyl)quinolizidine (XI) are described; one of these, utilizing a Curtius degradation, proved successful.

The known oxytocic properties of sparteine (I) prompted an investigation of simpler piperidylquinolizidines which can be derived from it through an opening of its ring C.



This class of compounds, very little known when the present work was initiated, has in the meantime received attention from several workers,[4–6,9,19] most of whom have used fully synthetic routes. The alternative approach followed in this work, namely using *l*-sparteine as the starting material, had the advantage of being able to produce individual steroisomers rather than diastereoisomeric pairs. The preparation of the starting material, *l*-oxysparteine (II), in satisfactory yield required some modification of the conditions hitherto mentioned in the literature. Although Schöpf[1b] claimed a 95% yield of the crystalline lactam after one-half minute of oxidation of sparteine with potassium ferricyanide, in our hands these conditions produced only 15% of oxysparteine. Clemo, Morgan, and Raper[2] obtained a 35% yield after five hours of reaction at room temperature. In our experience the best yield (60%) was obtained after three hours at 55–60°.

l-Oxysparteine was hydrolyzed with concentrated hydrochloric acid at 180° during twenty-four hours, following Orechoff's procedure for the hydrolysis of its *d*-isomer, oxypachycarpine.[3] The resulting amino acid was converted into its ethyl ester, which was separated by chromatography into the two isomeric esters IIIα and IIIβ. Regardless of the reaction time, there was always an appreciable amount of oxysparteine recovered. This proved to be attributable, not to incomplete hydrolysis, but to reformation of the original amide from the less stable of the two isomeric amino esters. In fact, the ester which was obtained in lower yield (10–13%) could be completely reconverted into oxysparteine by slow distillation at 130°, and even a very rapid distillation produced an appreciable amount of the lactam. Merely standing at room temperature for one month was sufficient to induce an 18–20% conversion of this isomer into oxysparteine, as judged by the alteration in its infrared spectrum. The other isomer showed no tendency to recyclise. This difference between the two isomers can only be ascribed to a difference in the orientation of the carbethoxy group, which in the unstable isomer must be *cis* to the piperidyl substituent, as it is in oxysparteine. The carbethoxy group of this isomer is therefore α-oriented (IIIα).

The other isomer, obtained in 35–65% yield, could be distilled or stored indefinitely without undergoing conversion to oxysparteine. Its carbethoxy group is therefore *trans* to the piperidyl substituent, or β-oriented (IIIβ). Its formation is,

(1a) Present address: American Cyanamid Company, Bound Brook, N. J.

(1b) C. Schöpf, *Ann.*, **465**, 132 (1928).

(2) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936).

(3) A. P. Orechoff, M. I. Kabatchnik, and T. J. Kefely, *Compt. rend. USSR*, **31**, 335 (1941).