Russell Kwok (1)

Cutter Laboratories, Inc., Berkeley, California 94710

Received December 20, 1977

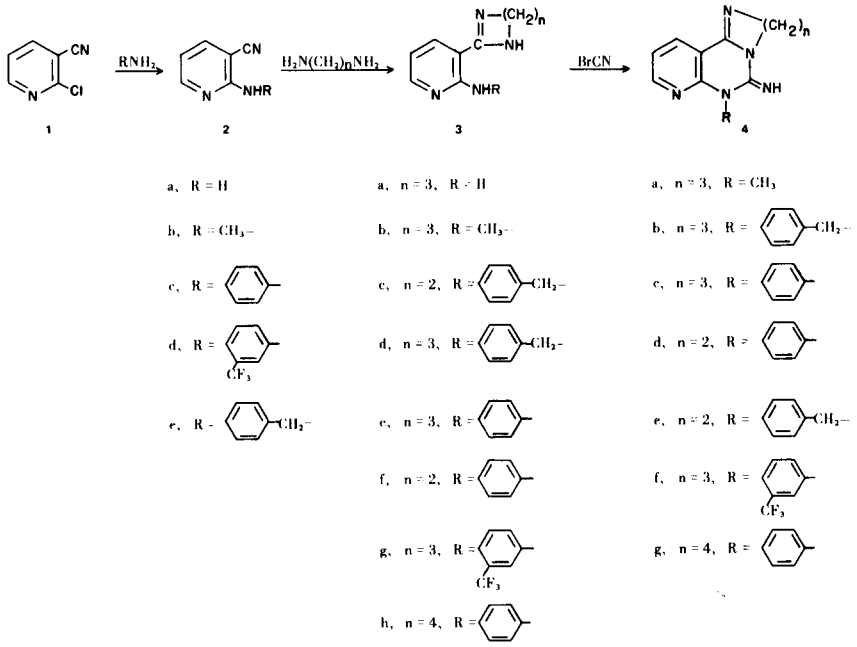
The preparation of a number of tricyclic fused ring iminopyrido[3,2-*e*]pyrimidines is described. Treatment of 2-chloronicotinonitrile with primary amines afforded the corresponding 2-amino derivative which was condensed with ethylenediamine or higher congeners to give substituted cyclic amidines. The latter on treatment with cyanogen bromide gave the desired iminopyrido[3,2-*e*]pyrimidines. The preparation of diaminopyrido[2,3-*d*]pyrimidines and tricyclic quinazolines by related procedures is discussed.

J. Heterocyclic Chem., 15, 877 (1978)

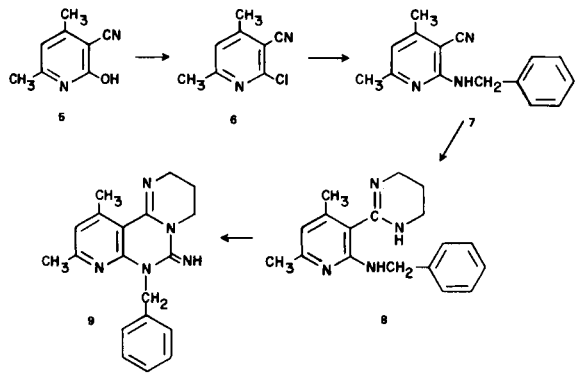
As a continuation of our studies of heterocyclic compounds with potential biological activity, we have prepared some tricyclic fused ring iminopyrido[3,2-*e*]pyrimidines.

Reaction of 2-chloronicotinonitrile (**1**) (2) with primary amines gave 2-aminonicotinonitrile (**2**) smoothly. Treatment of **2** with diamines according to the method of Oxly and Short (3) gave the substituted cyclic amidines **3** which when reacted with cyanogen bromide gave the desired iminopyrido[3,2-*e*]pyrimidines (**4**). However, the amidine **3** when R = H and n = 3, gave only tar when reacted with cyanogen bromide.

Scheme I



Scheme II

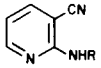


When the 2-amino nicotinonitrile was substituted in the 4 position as in **7**, formation of the cyclic amidine **8** was very slow due to steric hindrance.

4,6-Dimethyl-2-hydroxynicotinonitrile (**5**) (4) was converted to the chloro derivative **6** with phosphorus oxychloride in *N,N*-dimethyl aniline. Treatment of **6** with benzylamine gave **7** which reacted very slowly with 1,3-propanediamine to give **8**. Cyclization with cyanogen bromide gave **9**.

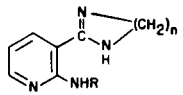
When **1** was heated with benzylamine at higher temperature, a fully substituted amidine **10** was obtained. Under similar conditions, **6** gave only **7**. There was no evidence of amidine formation. Facile addition of an amine to an unhindered nitrile followed by amine exchange with the imino nitrogen has been reported (5) to give substituted amidines. Treatment of **10** with cyanogen bromide gave

Table I



Compound	M.p. °C	Reaction Time/ Temperature	Solvent of Recrystallization	Yield %	Formula	Analyses % Calcd. C	H	N	Found C	H	N
2a	132-134[1]	1.5 hr./130°	Hexane	47	$C_6H_5N_3$						
2b	88-90	1 hr./90°	Water	87	$C_7H_7N_3$	63.14	5.28	31.56	63.38	5.42	31.32
2c	131-132[5]	5 hr./120°	2-Propanol	85	$C_{12}H_9N_3$						
2d	128-130	24 hr./150°	Hexane	45	$C_{13}H_8F_3N_3$	59.32	3.06	15.97	59.52	3.19	15.76
2e	96-98	20 min./90°	2-Propanol	75	$C_{13}H_{11}N_3$	74.62	5.30		74.48	5.41	
7	140-141	16 hr./90°	Hexane	75	$C_{15}H_{15}N_3$	75.92	6.37	17.71	75.78	6.17	17.84

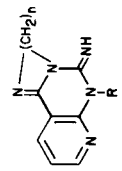
Table II



Compound	M.p. °C	Solvent of Recrystallization	Yield %	Formula	Analyses % Calcd. C	H	N	Found C	H	N
3a(a)	228-230	Ethanol	86	$C_9H_{12}N_4 \cdot C_7H_8O_3S$	55.15	5.79	16.08	55.26	5.63	15.91
3b	98-100	Hexane	58	$C_{10}H_{14}N_4$						
3c(a)	171-173	Water	60	$C_{15}H_{16}N_4 \cdot C_7H_8O_3S$	62.24	5.70	13.20	62.41	5.93	13.45
3c	74-76	Hexane		$C_{15}H_{16}N_4$	71.40	6.39	22.21	71.29	6.45	22.40
3d(a)	185-187	Water	79	$C_{16}H_{18}N_4 \cdot C_7H_8O_3S$	63.00	5.94	12.78	63.14	5.85	12.96
3d	58-60	Hexane		$C_{16}H_{18}N_4$	72.11	6.81		72.22	6.71	
3e	132-134	2-Propanol	52	$C_{15}H_{16}N_4$	71.40	6.39	22.21	71.19	6.45	22.38
3f	92-94	Hexane	50	$C_{14}H_{14}N_4$	70.59	5.92		70.71	6.09	
3g	90-92	Hexane	60	$C_{16}H_{15}F_3N_4$	59.63	4.72	17.49	59.88	4.64	17.22

(a) *p*-Toluenesulfonate salt.

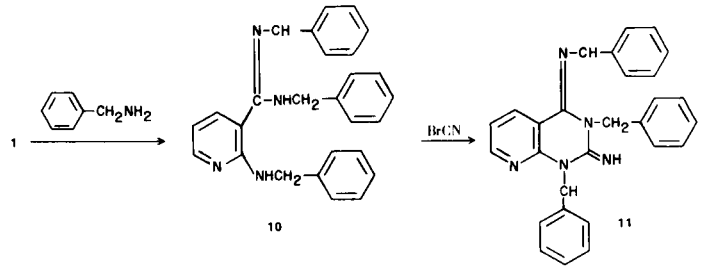
Table III



Compound	M.p. °C	Solvent of Recrystallization	Yield %	Formula	Analyses % Calcd. C	H	N	Found C	H	N
4a (a)	312	Methanol-ether	48	$C_{11}H_{13}N_5 \cdot HBr$	44.60	4.76	23.65	44.88	4.91	23.47
4a	119-121	Hexane		$C_{11}H_{13}N_5$	61.38	6.09		61.17	5.92	
4b (a)	273-274	Ethanol	50	$C_{17}H_{17}N_5 \cdot HBr$	54.83	4.88	18.79	54.69	5.03	18.92
4b	149-150	Acetonitrile		$C_{17}H_{17}N_5$	70.08	5.88	24.04	70.16	5.94	24.04
4c (a)	301-303	Ethanol	45	$C_{16}H_{15}N_5 \cdot HBr \cdot H_2O$	51.07	4.82	18.61	51.4	4.7	18.4
4d (a)	>340	Methanol-ether	60	$C_{15}H_{13}N_5 \cdot HBr$	52.34	4.10	20.35	52.15	4.35	20.19
4e (a)	260-261	Acetonitrile	52	$C_{16}H_{15}N_5 \cdot HBr$	53.64	4.50	19.55	53.86	4.63	19.71
4e	182-183	Acetonitrile		$C_{16}H_{15}N_5$	69.29	5.45	25.26	69.21	5.28	25.42
4f (a)	330	Methanol-ether	50	$C_{17}H_{14}F_3N_5 \cdot HBr$	47.96	3.55	16.43	47.94	3.39	16.62
4g	161-163	Hexane	35	$C_{17}H_{17}N_5$	70.08	5.88		69.92	5.66	
9 (a)	258-259	Ethanol	40	$C_{19}H_{21}N_5 \cdot HBr$	57.00	5.54	17.47	57.29	5.69	17.31

(a) Hydrobromide salt.

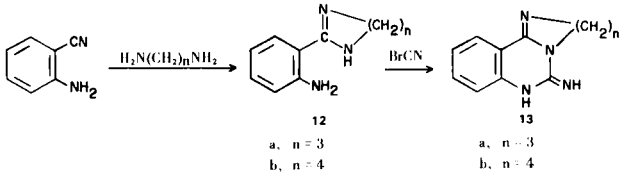
Scheme III



the diiminopyrido[2,3-*d*]pyrimidine (**11**).

Similarly, anthranilonitrile was converted to fused tricyclic quinazolines.

Scheme IV



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. Microanalyses were performed by Chemical Analytical Services, University of California, Berkeley, California.

General Procedure for the Preparation of 2-Aminonicotinonitrile (**2**).

A solution of **1** in five times its weight of amine was heated in an oil bath (see Table I for reaction time and temperature) and then kept at room temperature for four hours. The mixture was poured into ice cold water and the precipitated product was collected and recrystallized.

General Procedure for the Preparation of Cyclic Amidines (**3**).

A mixture of 0.1 mole of **2**, 0.055 mole of the diamine and 0.05 mole of the diamine ditosylate salt was heated at 200° for 1-3 hours. The progress of the reaction could be estimated by the rate of evolution of ammonia. The reaction mixture was either worked up as the salt or as the free base.

Preparation of pyridopyrimidines **4** is exemplified by the preparation of **4b**.

7-Benzyl-3,4,6,7-tetrahydro-6-imino-2*H*-pyrimido[1,2-*c*]pyrido-[3,2-*e*]pyrimidine Hydrobromide (**4b**).

A mixture of 22 g. (0.083 mole) of **3d** and 9.65 g. (0.91 mole) of cyanogen bromide in 300 ml. of 1-propanol was refluxed with stirring for 6 hours. After cooling, the precipitated product was filtered and washed with acetone and dried to give 14 g. of colorless material, m.p. 272-274°. Recrystallization from ethanol gave colorless crystals, m.p. 273-274°.

2-Chloro-4,6-dimethylnicotinonitrile (**6**).

To a suspension of 14.8 g. (0.1 mole) of **5** (4) in 46 g. (0.3 mole) of phosphorus oxychloride was added portionwise 12.6 g. (0.1 mole) of *N,N*-dimethylaniline. The mixture was heated on a steam bath for one hour. Excess phosphorus oxychloride was removed under reduced pressure. The residue was poured into ice

and the precipitate was filtered and washed with water. The product was recrystallized from hexane and 12 g. of product, m.p. 98-100°, was obtained.

Anal. Calcd. for $C_8H_7ClN_2$: C, 57.67; H, 4.24; Cl, 21.28. Found: C, 57.89; H, 4.15; Cl, 21.44.

N,N-Dibenzyl(2-benzylamino-3-pyridyl)amidine (**10**).

A mixture of 2 g. of **1** and 15 ml. of benzylamine was refluxed for 16 hours and was poured into ice water. The oily precipitate solidified after scratching with a glass rod. The product was filtered and washed with water. Recrystallization from acetonitrile gave 3 g. of colorless crystals, m.p. 137-139°. Further recrystallization from the same solvent gave the analytical sample, m.p. 137-139°.

Anal. Calcd. for $C_{27}H_{26}N_4$: C, 79.77; H, 6.45; N, 13.78. Found: C, 79.74; H, 6.22; N, 13.49.

1,3-Dibenzyl-4-benzylamino-2-imino(1*H*,3*H*)pyrido[2,3-*d*]pyrimidine Hydrobromide (**11**).

A mixture of 10 g. (0.025 mole) of **10** and 2.55 g. (0.025 mole) of cyanogen bromide in 200 ml. of ethanol was refluxed for 10 hours. The mixture was concentrated under reduced pressure. The yellow oily residue was triturated with 300 ml. of ether to afford a solid. After filtering and washing with ether, the solid was recrystallized from methanol-ether to give 5 g. of product, m.p. 195-196°. From the mother liquor was isolated 2.5 g. hydrobromide salt of the starting material, m.p. 109-210° from acetonitrile.

Anal. Calcd. for $C_{28}H_{25}N_5 \cdot HBr$: C, 65.62; H, 5.11; N, 13.67. Found: C, 65.46; H, 4.98; N, 13.39.

1-(2-Aminophenyl)-1,4,5,6-tetrahydropyrimidine (**12a**).

A mixture of 11.8 g. (0.1 mole) of anthranonitrile, 4.4 g. (0.06 mole) of 1,3-diaminopropane and 21 g. (0.05 mole) of 1,3-diaminopropane ditosylate was heated at 200° for 3.5 hours. On cooling, the mixture solidified into a yellow glass. The crude product was dissolved in 100 ml. of hot water. After cooling in an ice bath, it was made alkaline with excess sodium hydroxide. The free base was extracted with chloroform and dried. Removal of solvent under reduced pressure gave an oily residue which crystallized slowly. The product was recrystallized from hexane to give 10 g. of needles, m.p. 78-82°.

Anal. Calcd. for $C_{10}H_{13}N_3$: C, 68.54; H, 7.47; N, 23.98. Found: C, 68.71; H, 7.88; N, 23.63.

2-(2-Aminophenyl)-1,4,5,6,7-pentahydro-1,3-diazopine (**12b**).

In a manner similar to the preparation of **12a**, 11.8 g. (0.1 mole) of anthranonitrile was reacted with 5.3 g. (0.06 mole) 1,4-diaminobutane and 0.05 mole of the diamine ditosylate to give 3 g. of the free base as faintly yellow crystals, m.p. 120-122°, from hexane.

Anal. Calcd. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99. Found: C, 69.97; H, 7.76.

3,4,6,7-Tetrahydro-6-imino-2*H*-pyrimido[1,2-*c*]quinazoline Hydrobromide Monohydrate (**13a**).

A mixture of 6 g. (0.034 mole) of **12a** and 3.64 g. (0.034 mole) of cyanogen bromide in 75 ml. of 1-propanol was refluxed with stirring for 6 hours. A yellow precipitate was obtained. After cooling, the precipitate was filtered and washed with acetone to give 6 g. of yellow material, m.p. 331° with decomposition. The product was recrystallized from methanol to give 4.5 g. of yellow crystals, m.p. 336°.

Anal. Calcd. for $C_{11}H_{12}N_4 \cdot HBr \cdot H_2O$: C, 44.16; H, 5.06; N, 18.73. Found: C, 44.15; H, 5.09; N, 18.14.

2,3,4,5,7,8-Hexahydro-7-imino[1,3]diazapino[1,2-*c*]quinazoline Hydrobromide (**13b**).

Similar to the preparation of **13a**, 6.8 g. (0.036 mole) of **13b** was reacted with 4 g. (0.038 mole) of cyanogen bromide to give 5 g. of yellow product, m.p. 253-255°. The product was recrystallized from methanol to give yellow crystals, m.p. 256-257°.

Anal. Calcd. for $C_{12}H_{14}N_4 \cdot HBr$: C, 48.82; H, 5.12; N, 18.98. Found: C, 48.69; H, 5.31; N, 18.82.

REFERENCES AND NOTES

(1) Present address: The Wing On Co., Ltd., P.O. Box 1508 Hong Kong.

(2) E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, 19, 1636 (1954)l

(3) P. Oxly and W. F. Short, *J. Chem. Soc.*, 497 (1947).

(4) J. L. Green, Jr., and J. A. Montgomery, *J. Med. Chem.*, 7, 18 (1964).

(5) Pawel Nantka-Namviski, *Acta Pol. Pharm.*, **24**, 111 (1967); *Chem. Abstr.*, **67**, 108538d (1967).