Picrylamino-substituted Heterocycles. VI. Pyrimidines (1,2)

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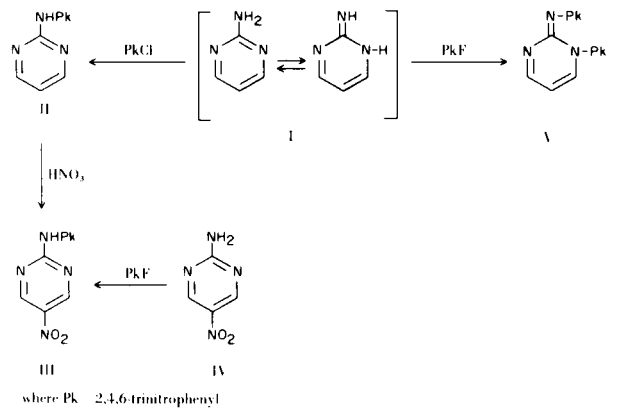
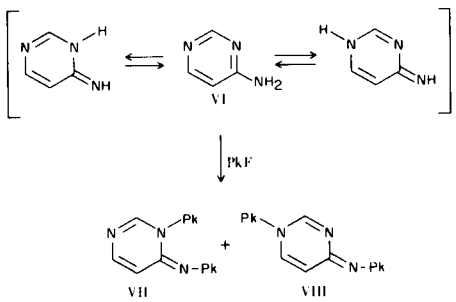
The condensation of various aminopyrimidines with picryl chloride and picryl fluoride has been investigated as part of our continuing effort in the field of picrylamino-substituted heterocycles. Most of the aminopyrimidines that can tautomerize reacted with picryl fluoride to form picryl derivatives of their imino forms, but they gave picrylamino derivatives when they condensed with picryl chloride.

2-Aminopyrimidine (I) reacted with picryl chloride in ethanol to give 2-picrylaminopyrimidine (II), which was nitrated to 5-nitro-2-picrylaminopyrimidine (III). Compound III was also obtained from the reaction of 2-amino-5-nitropyrimidine (IV) with picryl fluoride in DMF. Treatment of I with two molar equivalents of picryl fluoride in DMF gave 1-picryl-2-picrylimino-1,2-dihydropyrimidine (V) along with a trace of II, while the reaction of two molar equivalents of I with one equivalent of picryl fluoride produced a mixture of II (20%) and V (80%). Picryl fluoride failed to react with II to give V under the same conditions. The mechanism of the reaction of I with picryl halides may be similar to that suggested previously for the reaction of picryl halides with 2-aminopyridine (2). A more detailed study of these reactions is in progress. Although it has been reported (4) that I reacts with picryl chloride in benzene to give 7,9-dinitropyrimido[1,2-*a*]benzimidazole, we were unable to detect any of this material in our crude product.



Treatment of 4-aminopyrimidine (VI) with picryl chloride in ethanol gave the picrate of VI rather than the desired picrylamino derivative; however, VI reacted with picryl fluoride in DMF to provide a mixture of 1-picryl-6-picrylimino-1,6-dihydropyrimidine (VII) and 1-picryl-4-picrylimino-1,4-dihydropyrimidine (VIII). One of the isomers (VIII) was obtained in pure form by column chromatography. Unfortunately, VII was decomposed on the column and we were unable to isolate it by any other technique; however, the nmr chemical shifts of its protons were determined by subtracting those of VIII from the spectrum of the crude mixture. The similarity of the chemical shift of the 1-picryl protons of VII with that of V is the basis of the structural assignments of VII and VIII, and we believe that the significant difference between the chemical shifts of the 1-picryl protons of VII and VIII provides a criterion for distinguishing between various derivatives of VII and VIII (see Table I). We have utilized this concept in the assignment of structures to some of the compounds that will be subsequently discussed.



5-Aminopyrimidine (IX), which cannot tautomerize to an imino form, reacted with picryl fluoride in DMF to form 5-picrylaminopyrimidine (X).

TABLE I

NMR Spectra (a)

Pyrimidine	Picryl Protons 1-Picryl	Picrylamino	Picrylimino	δ C-H (ppm) C-2	Pyrimidine Protons C-4	C-5	C-6
2-Picrylamino-		9.03			8.53 (d)	7.08 (t)	8.53 (d)
5-Picrylamino-		9.07		9.00 (s)	8.73 (s)		8.73 (s)
5-Nitro-2-picrylamino-		9.10			9.25 (s)		9.25 (s)
2-Amino-5-picrylamino-		8.95			8.17 (s)		8.17 (s)
2,5-bis(Picrylamino)-		9.00, 9.03			8.42 (s)		8.42 (s)
2,4,6-tris(Picrylamino)-		8.87, 9.04				6.46 (s)	
5-Nitro-2,4,6-tris(picrylamino)-		8.88, 9.07					
1-Picryl-2-picrylimino-1,2-dihydro-	9.44		8.87		8.55 (q)	6.95 (q)	8.72 (q)
1-Picryl-4-picrylimino-1,4-dihydro-	9.13		9.03	9.03 (s)		5.90 (d)	7.20 (d)
1-Picryl-6-picrylimino-1,6-dihydro-	9.42		9.00	8.47 (s)	7.98 (d)	6.70 (d)	
2-Amino-1-picryl-6-picrylimino-1,6-dihydro-	9.36		8.74		7.91 (d)	6.18 (d)	
4-Amino-1-picryl-6-picrylimino-1,6-dihydro-	9.40		8.85	8.58 (s)		5.17 (s)	
1-Picryl-4-picrylamino-6-picrylimino-1,6-dihydro-	9.42	9.15	9.02	8.67 (s)		6.08 (s)	
1-Picryl-5-picrylamino-2-picrylimino-1,2-dihydro-	9.43	9.03	8.86		8.53 (d)		8.70 (d)
1-Picryl-5-picrylamino-6-picrylimino-1,6-dihydro-	9.42	9.05	8.99	8.50 (d)	8.06 (d)		

(a) Determined with a Varian A-60A spectrometer as DMSO-d_6 solutions using tetramethylsilane as an internal standard.

TABLE II

Condensation of the Aminopyrimidines with Picryl Halides

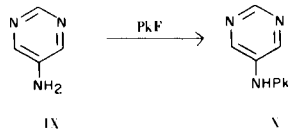
Reactants (moles)	Reaction Solvent (ml.)	Reaction Temp. (°C)	Reaction Time (hours)	Recrystallization Solvent	Product (% Yield)	M.p., °C
I (0.01), PkCl (0.005)	Ethanol (25)	Reflux	18	Ethanol-water	II (75)	127
I (0.01), PkF (0.02)	DMF (20)	25	16	Acetone-ethanol	V (88)	247 dec.
IV (0.01), PkF (0.02)	DMF (20)	80	6	Ethanol-water	III (20)	189
VI (0.01), PkF (0.02)	DMF (20)	25	17	Acetone-ethanol	VIII (a)	211
IX (0.01), PkF (0.01)	DMF (20)	25	17	Acetone-ethanol	X (75)	146
XI (0.01), PkF (0.03)	DMF (20)	25	17	Acetone-ethanol	XII (70)	264 dec.
XIII (0.01), PkCl (0.01), NaOAc (0.01)	Ethanol (25)	Reflux	5	Acetone-ethanol	XIV (91)	239 dec.
XIII (0.01), PkF (0.02)	DMF (20)	25	17	Acetone-ethanol	XV (96)	253 dec.
XV (0.01), PkF (0.03)	DMF (20)	25	96	Acetone-ethanol	XVI (73)	266 dec.
XVII (0.01), PkF (0.03)	DMF (20)	25	17	Acetone-ethanol	XVIII (85)	237 dec.
XIX (0.01), PkF (0.02)	DMF (10)	25	16	Acetone-ethanol	XX (78)	242 dec.
XX (0.01), PkF (0.02)	DMF (10)	25	168	Acetone-ethanol	XXI (97)	258 dec.
XXII (0.01), PkF (0.03)	DMF (50)	25	16	Acetone	XXIII (78)	301 dec.

(a) A mixture of VII and VIII was obtained in quantitative yield. An analytically pure sample of VIII, free of VII, was obtained by chromatographing the product over a silica gel column with a solvent mixture of 115 ml. of *n*-hexane, 80 ml. of 2-butanone, and 5 ml. of a 10% solution of propionic acid in *n*-hexane, followed by recrystallization from acetone-ethano. No VII could be eluted from the column.

TABLE III

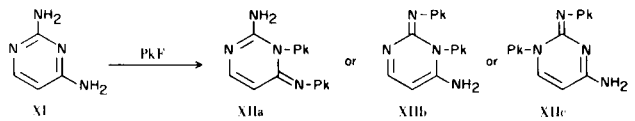
Elemental Analyses

Compound	Molecular Formula	Calculated, % C	H	N	Found, % C	H	N
II	$C_{10}H_6N_6O_6$	39.23	1.98	27.45	39.13	1.96	27.24
III	$C_{10}H_5N_7O_8$	34.20	1.44	27.92	34.25	1.56	27.88
V	$C_{16}H_7N_9O_{12}$	37.15	1.36	24.37	37.29	1.35	24.40
VIII	$C_{16}H_7N_9O_{12}$	37.15	1.36	24.37	36.75	1.65	23.94
X	$C_{10}H_6N_6O_6$	39.23	1.98	27.45	39.57	1.71	27.87
XII	$C_{16}H_8N_{10}O_{12}$	36.10	1.51	26.31	36.39	1.56	26.83
XIV	$C_{10}H_7N_7O_6$	37.39	2.20	30.52	37.81	2.25	30.43
XV	$C_{16}H_8N_{10}O_{12}$	36.10	1.51	26.31	36.47	1.71	26.02
XVI	$C_{22}H_9N_{13}O_{18}$	35.55	1.22	24.49	35.66	1.36	24.13
XVIII	$C_{22}H_9N_{13}O_{18}$	35.55	1.22	24.49	35.34	1.05	24.18
XX	$C_{16}H_8N_{10}O_{12}$	36.10	1.51	26.31	35.97	1.49	25.88
XXI	$C_{22}H_9N_{13}O_{18}$	35.55	1.22	24.49	35.91	1.22	24.22
XXIII	$C_{22}H_{10}N_{14}O_{18}$	34.84	1.33	25.86	34.81	1.37	25.70
XXIV	$C_{22}H_9N_{15}O_{20}$	32.89	1.13	26.15	33.04	1.35	26.19



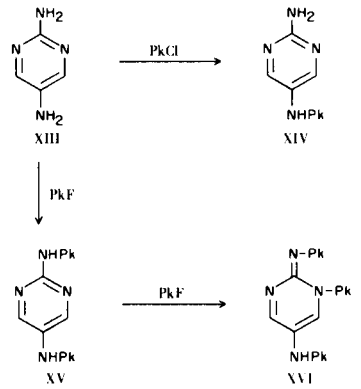
IX V

2,4-Diaminopyrimidine (XI) condensed with two molecules of picryl fluoride in DMF to yield a compound that has one of three possible structures (XIIa, XIIb, or XIIc; the observed chemical shift of the 1-picryl protons eliminates the other possible isomer). We tentatively propose that the product is 2-amino-1-picryl-6-picrylimino-1,6-dihydropyrimidine (XIIa) because the chemical shifts of its pyrimidine protons are similar to those of VII; however, structures XIIb and XIIc cannot be disregarded on this basis. Treatment of XI or XII with an excess of picryl fluoride failed to provide a tripicryl derivative of XI, while the picrate of XI was the only product obtained from the reaction of XI with picryl chloride in ethanol.



XI XIIa XIIb XIIc

When 2,5-diaminopyrimidine (XIII) was treated with picryl chloride in ethanol, 2-amino-5-picrylaminopyrimidine (XIV) was obtained. Compound XIII condensed with two molecules of picryl fluoride in DMF to give 2,5-bis(picrylamino)pyrimidine (XV), which was slowly converted into 1-picryl-5-picrylamino-2-picrylimino-1,2-dihydropyrimidine (XVI) in the presence of excess picryl fluoride.

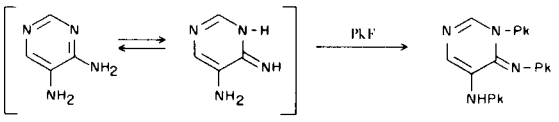


XIII XIV XV XVI

The assignment of structure XIV to the monopicryl derivative of XIII is based upon the deshielding of the pyrimidine protons by the picryl group. The chemical shift of the pyrimidine protons of XIII is 7.78 δ, while those of XIV and XV are 8.17 δ and 8.42 δ, respectively. Thus, the effect of the first picrylation of XIII to give the monopicryl derivative is to deshield the pyrimidine protons by 0.39 δ, while picrylating the second amino group to give XV deshields the pyrimidine protons by 0.25 δ. Since the chemical shifts of the 4,6 protons of I and II are 8.28 δ and 8.53 δ, respectively, and those of

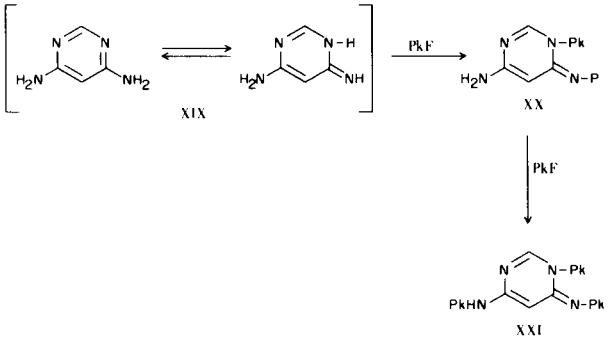
IX and X are 8.20 δ and 8.73 δ, respectively, we have concluded that picrylation of a 5-amino group in the pyrimidine series deshields the 4,6 protons approximately twice as much as picrylation of a 2-amino group.

The reaction of 4,5-diaminopyrimidine (XVII) with picryl fluoride in DMF produced 1-picryl-5-picrylamino-6-picrylimino-1,6-dihydropyrimidine (XVIII). Treatment of XVII with picryl chloride in ethanol gave only the picrate of XVII.



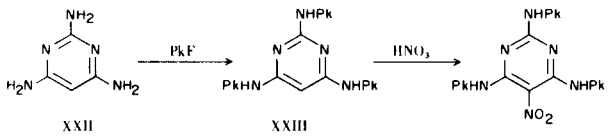
XVII XVIII

The picrate of 4,6-diaminopyrimidine (XIX) was the only product isolated from the reaction of XIX with picryl chloride in ethanol; however, 4-amino-1-picryl-6-picrylimino-1,6-dihydropyrimidine (XX) was obtained when XIX was treated with two molar equivalents of picryl fluoride in DMF. Subsequent treatment of XX with picryl fluoride in DMF provided 1-picryl-4-picrylamino-6-picrylimino-1,6-dihydropyrimidine (XXI).



XIX XX XXI

In contrast with the results thus far obtained from the condensation of picryl fluoride with various aminopyrimidines that can tautomerize to imino forms, 2,4,6-triaminopyrimidine (XXII) failed to give a picryl derivative of an imino form when it was treated with an excess of picryl fluoride in DMF. The only product isolated from this reaction was 2,4,6-tris(picrylamino)pyrimidine (XXIII). Nitration of XXIII gave 5-nitro-2,4,6-tris(picrylamino)pyrimidine (XXIV).



XXII XXIII XXIV

EXPERIMENTAL (5)

Most of the aminopyrimidines used in this study were purchased from commercial sources. 4-Aminopyrimidine (VI) and 5-aminopyrimidine (IX) were prepared by hydrogenating 4-amino-6-chloropyrimidine and 5-amino-4,6-dichloropyrimidine, respectively, according to a published procedure (6).

Condensation of the Aminopyrimidines with Picryl Halides.

The appropriate quantities of the reactants and solvent indicated in Table II were mixed and allowed to react under the conditions given in the table. The resulting mixtures were diluted with ten times their volume of water to precipitate the products, which were collected by filtration, washed with water, dried, and recrystallized from the appropriate solvents. In some instances, the precipitates were colloidal, but the addition of a saturated sodium chloride solution caused the precipitates to coagulate. The yields and melting points of the recrystallized products are given in Table II and the elemental analyses of these compounds are given in Table III. The nmr chemical shifts of the new compounds prepared in this study are tabulated in Table I.

Nitration of 2-Picrylaminopyrimidine (II).

2-Picrylaminopyrimidine (1.3 g., 0.004 mole) was added to 10 ml. of fuming nitric acid (90% nitric acid). The resulting solution was heated under reflux for 8 hours, then it was poured over ice. The solid was collected by filtration and recrystallized from ethanol-water to give 1.24 g. (89%) of 5-nitro-2-picrylaminopyrimidine (III), m.p. 189-190°, which was identical with that obtained from the reaction of 2-amino-5-nitropyrimidine (IV) with picryl fluoride.

5-Nitro-2,4,6-tris(picrylamino)pyrimidine (XXIV).

2,4,6-tris(Picrylamino)pyrimidine (XXIII) (1.0 g., 0.0013 mole) was added to 10 ml. of fuming nitric acid (90% nitric acid). The mixture was heated at 75° for 15 minutes, then cooled to 5° with an ice bath. The solid was collected by filtration, washed with concentrated nitric acid, then with water, and dried to give 1.06 g. (100%) of XXIV, m.p. 334° dec.

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