Imidazo[1,5-*a*]pyrazines. II. 3-Substituted Derivatives (1,2)

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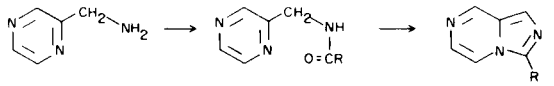
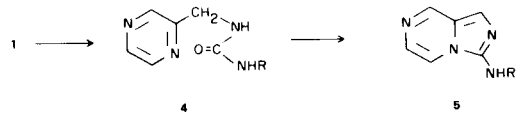
In a continuation of our study of imidazo[1,5-*a*]pyrazines as potential anticancer agents (2) we have prepared a number of 3-aryl derivatives as well as a number of derivatives that contain functional groups at C-3.

The key compound in preparing all these compounds was 2-(aminomethyl)pyrazine (**1**) (2). It smoothly formed amides (**2**) when treated with the appropriate benzoyl chlorides and with furoyl chloride, respectively. Ring closure to the derivatives (**3**) was best accomplished with polyphosphoric acid.



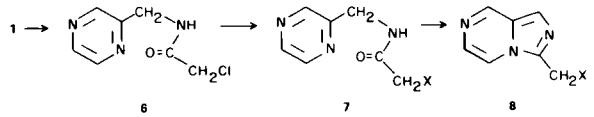
a: R = C_6H_5
b: R = 2-ClC_6H_4
c: R = 3,4-diClC_6H_3
d: R = 4-$NO_2C_6H_4$
e: R = 2-Furyl

Treatment of **1** with isocyanates led to derivatives of 3-aminoimidazo[1,5-*a*]pyrazine. The ureas (**4a** and **4b**) were obtained in high yields and were cyclized to the bicyclic heterocycles (**5a** and **5b**) with phosphoryl chloride.



a: R = C_6H_5
b: R = CH_3

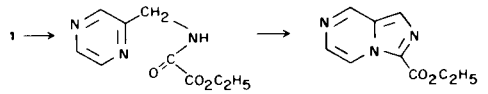
The chloroacetyl derivative (**6**) of **1** provided a versatile entry into 3-functionalized imidazo[1,5-*a*]pyrazines. Nucleophilic displacement of the reactive chlorine in **6** afforded the amides (**7**). Cyclodehydration of these amides proceeded to give the corresponding imidazo[1,5-*a*]pyrazines in yields which appeared to be affected greatly by the nature of the substituent to the cyclization conditions. While the 3-methoxymethyl compound (**8b**) was obtained in good yields, the 3-hydroxymethyl (**8a**) and 3-azidomethyl (**8c**) analogs were not. Conversion of **8a** back to **6**,



a: X = OH
b: X = OCH_3
c: X = N_3

which is unstable to phosphoryl chloride reaction conditions, could explain the difficulty observed in obtaining **8a**. Similarly, decomposition of the azido group could provide a rationale for obtaining **8c** in poor yields.

A final compound of interest was the 3-carboethoxy derivative (**10**) which was prepared by phosphoryl chloride cyclization of the oxalamide (**9**).



EXPERIMENTAL

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. Nmr spectra were determined on a Varian A-60 apparatus in deuteriochloroform using TMS as an internal standard. All evaporations were conducted *in vacuo* using a water aspirator or a vacuum pump. Extracts were dried over anhydrous potassium carbonate unless otherwise noted. Micro-Analysis, Inc., Marshallton, Delaware performed the microanalyses. Spectral data of representative compounds are found in Tables III and IV.

Representative examples of procedures for different types of compounds are given below. Where not specfically described, the procedures for preparing related compounds are essentially identical.

N-(2-Pyrazinylmethyl)benzamide (**2a**).

To a solution of aminomethylpyrazine (**1**) [generated from **1**, hydrochloride (4.4 g., 30 mmoles) with excess methanolic potassium hydroxide] and triethylamine (4 g., 40 mmoles) in 50 ml. of

Table I

Amides and Ureas Derived from Aminomethylpyrazine

Compound	M.P. (°C)	Yield (%)	Crystallization Solvent	Microanalytical Data Found C	Found H	Found N	Calculated C	Calculated H	Calculated N
2a	86	60	Hexane	67.80	5.27	19.75	67.59	5.20	19.71
2b (a)	49-50	55	Hexane	58.29	4.04	16.80	58.19	4.07	16.97
2c (b)	146	71	Ethanol	50.96	3.17	14.90	51.09	3.22	14.89
2d	143-145	65	Ethanol	55.96	3.94	21.45	55.81	3.90	21.70
2e	71-73	36	Ether-hexane	59.33	4.57	20.67	59.11	4.43	20.69
4a	127-128	92	Acetone-hexane	63.45	5.11	24.37	63.15	5.30	24.55
4b	134	90	Acetone	50.61	5.86	33.90	50.59	6.07	33.72
6 (c)	66	67	Hexane	45.57	4.28	22.42	45.30	4.34	22.64
7a	97-98	67	Acetone	50.57	5.63	25.01	50.30	5.63	25.14
7b	oil	55		52.21	6.40	22.48	53.03	6.12	23.19
7c	oil	71		43.84	4.16	43.43	43.75	4.20	43.73
9	34-35	81	Solidified distilled oil	51.67	5.26	20.19	51.61	5.31	20.01

(a) Cl, Calcd: 14.31. Found: 14.58. (b) Cl, Calcd: 25.13. Found: 25.10. (c) Cl, Calcd: 19.10. Found: 19.38.

Table II

3-Substituted Imidazo[1,5-*a*]pyrazines

Compound	M.P. (°C)	Yield (%)	Crystallization Solvent	Microanalytical Data Found C	Found H	Found N	Calculated C	Calculated H	Calculated N
3a	75-76	61	Hexane	73.62	4.93	21.40	73.83	4.65	21.52
3b (a)	84-85	71	Hexane	63.02	3.68	18.14	62.76	3.51	18.30
3c (b)	141	78	Ethanol	54.87	2.56	15.78	54.57	2.67	15.91
3d	252	30	Ethanol	59.87	3.46	23.51	60.00	3.36	23.32
3e	79-81	33	Ether-hexane	65.00	3.65	22.73	64.86	3.78	22.70
5a	155-156	67	Chloroform-hexane	68.78	4.75	26.49	68.56	4.79	26.65
5b	115	60	Acetone-hexane	56.55	5.42	37.53	56.75	5.41	37.83
8a	101	20	Acetone-hexane	56.09	4.94	27.99	56.37	4.73	28.17
8b	78-79	73	Hexane	58.96	5.38	25.64	58.89	5.55	25.75
8c	80-81	14	Hexane	48.41	3.61	48.15	48.27	3.47	48.25
10	105-106	30	Acetone-hexane	56.73	4.82	21.79	56.54	4.71	21.99

(a) Cl, Calcd: 15.44. Found: 15.43. (b) Cl, Calcd: 26.85. Found: 27.10.

ether was added, with stirring, a solution of benzoyl chloride (5.6 g., 40 mmoles) in 50 ml. of ether. The reaction was left at room temperature for one hour and the ether was evaporated. The residue was treated with 50 ml. of saturated aqueous sodium bicarbonate and the mixture was extracted with four 25 ml. portions of chloroform. The combined extracts were washed with water (100 ml.), *N* hydrochloric acid (100 ml.) and water (100 ml.), then dried. The residue after evaporation of the chloroform was crystallized from hexane to give 3.9 g. (60%) of product, m.p. 86°. Physical and analytical data for the amides of aminomethylpyrazine (**1**) are detailed in Table I.

3-Phenylimidazo[1,5-*a*]pyrazine (**3a**).

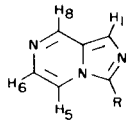
N-(2-Pyrazinylmethyl)benzamide (**2a**, 0.2 g., 1.0 mmole) was added to polyphosphoric acid (2.8 g.) and the mixture stirred overnight at 100°. Water (10 ml.) was added and the solution made alkaline by the addition of 10% aqueous sodium hydroxide, then extracted with three 10 ml. portions of chloroform. The combined extracts were washed with water (25 ml.), dried, and evaporated. The residue was chromatographed over alumina (Woelm dry-column, 20 g.) to give the product as an oil, 0.12 g. (61%), which was crystallized from hexane as a yellow solid, m.p. 75-76°. Physical and analytical data for the 3-substituted imidazo[1,5-*a*]pyrazines are found in Table II.

N-Methyl-*N'*-2-pyrazinylmethyl Urea (**4b**).

A solution of aminomethylpyrazine (**1**) [prepared from 1.16 g. (8.0 mmoles) of **1**, hydrochloride], methylisocyanate (0.49 g., 8.5 mmoles), triethylamine (0.86 g., 8.5 mmoles) and 30 ml. of absolute ethanol was heated at reflux for 2 hours, then evaporated. The residue, after two recrystallizations from acetone, yielded 1.2 g. (90%) of needles, m.p. 134°. Analytical data are reported in Table I.

Table III

Nmr of 3-Substituted Imidazo[1,5-*a*]pyrazines (a,b,c)

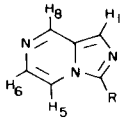


Compound	R	H_1	H_5 or H_6	H_8	R
3a	C_6H_5–	7.9, s (1)	8.0, m (1)	8.9, d (1)	7.3-7.8, m (6) (d)
5b	CH_3NH–	7.6, s (1)	7.3, d (1) and 7.6, m (1)	8.8, d (1)	3.2, s (3) and 5.3-5.8, broad (1)
8b	CH_3OCH_2–	7.8, s (1)	7.6, d (1) and 8.0, m (1)	9.0, d (1)	3.4, s (3) and 4.9, s (2)
10	$CH_3CH_2O_2C$–	8.0, s (1)	7.9, d (1) and 8.1-8.5, m (2) (e)		1.5, t (3) and 4.5, q (2)

(a) Expressed as δ units relative to TMS at 0. (b) Integration number in parentheses. (c) $J_{H_8-H_5}$ or H_6 = 2 Hz and $J_{H_5-H_6}$ = 5 Hz were always noted. (d) This signal included either H-5 or H-6. (e) Signals for two of the three protons, H_5, H_6 and H_8 could not be resolved.

Table IV

Uv Spectra of 3-Substituted Imidazo[1,5-*a*]pyrazines (a)



Compound	R	λ max (log ε)
3a	C_6H_5–	300 (4.04), 353 (sh.)
5b	CH_3NH–	282 (4.08), 295 (sh.), 398 (3.74)
8b	CH_3OCH_2–	265 (3.65), 275 (3.77), 286 (3.76), 333 (3.54)
10	$CH_3CH_2O_2C$–	308 (3.84), 318 (sh.)

(a) Spectra obtained in ethanol on Cary-15 spectrophotometer.

3-Methylaminoimidazo[1,5-*a*]pyrazine (**5b**).

Phosphoryl chloride (5 ml.) and the urea (**4b**, 0.33 g., 2.0 mmoles) were combined and the mixture heated, with stirring, at 100° for 2 hours. The excess phosphoryl chloride was evaporated and the residue, dissolved in 20 ml. of water, was made alkaline with 20% aqueous sodium hydroxide. The solution was extracted with three 100 ml. portions of 9:1 chloroform/methanol and the combined extracts dried, then evaporated. The residue was recrystallized from acetone-hexane to give 0.18 g. (60%) of yellow needles, m.p. 115°. Analytical data are found in Table II.

N-(2-Pyrazinylmethyl)chloroacetamide (**6**).

To **1** (generated from 2.2 g., 15 mmoles of the hydrochloride) dissolved in 50 ml. of ether was added, with stirring, a solution of chloroacetic anhydride (3.0 g., 17 mmoles) dissolved in 50 ml. of ether. The mixture was left at room temperature for one hour, then evaporated. The residue was dissolved in 30 ml. of saturated aqueous sodium bicarbonate and extracted with four 100 ml. portions of chloroform. The dried extracts were evaporated to give an oil which was crystallized from benzene, 1.85 g. (67%), m.p. 66°. Analytical data appear in Table I.

N-(2-Pyrazinylmethyl)azidoacetamide (**7c**).

To the chloroacetamide (**6**, 2.04 g., 11 mmoles), dissolved in 35 ml. of acetonitrile was added a solution of sodium azide (1.0 g., 15 mmoles) in 5 ml. of water and the mixture was heated at reflux for four hours, then concentrated to about 5 ml. The residue was diluted with 50 ml. of water and extracted with four 100 ml. portions of chloroform. The extracts were washed with water (100 ml.) and dried. The residue was chromatographed over alumina (Woelm dry column, 100 g.) and the product eluted with chloroform to afford 1.5 g. (71%) of a pale yellow oil that discolored on standing. Analytical data appear in Table I.

3-Methoxymethylimidazo[1,5-*a*]pyrazine (**8b**).

N-(2-Pyrazinylmethyl)methoxyacetamide (**7b**) (2.8 g., 15 mmoles) dissolved in dichloromethane (20 ml.) was added to phosphoryl chloride (25 ml.) with stirring and left overnight. After evaporating most of the phosphoryl chloride the residue was dissolved in water, made alkaline by adding 10% sodium hydroxide solution and extracted repeatedly with chloroform (6 x 150 ml.). The combined chloroform extracts were dried, filtered and the chloroform evaporated. The residue was chromatographed on a

dry alumina (150 g.) column to give the product as a pale yellow solid that crystallized from hexane as cream-colored needles, (2.05 g., 73%), m.p. 78-79°. Sublimation (60°/0.05 mm) furnished the product as a colorless solid, m.p. 78-79°. Analytical data appear in Table II.

3-Azidomethylimidazo[1,5-*a*]pyrazine (**8c**).

The azidoacetamide (**7c**, 0.96 g., 5.0 mmoles), dissolved in 10 ml. of benzene, was added to 10 ml. of phosphoryl chloride and the mixture heated at reflux for 20 minutes. The mixture was evaporated, 50 ml. of water added to the residue and the solution made alkaline with 10% aqueous sodium hydroxide. The solution was extracted with six 75 ml. portions of chloroform, the combined extracts dried, then evaporated. The residue (0.3 g.) was chromatographed over alumina (Woelm dry column, 100 g.) to give 0.12 g. (14%) of a colorless solid that was crystallized from hexane as colorless needles, m.p. 80-81°. Analytical data appear in Table II.

3-Carboethoxyimidazo[1,5-*a*]pyrazine (**10**).

Phosphoryl chloride (10 ml.) was added to a solution of the oxalamide (9), prepared in 81% yield using ethyloxalyl chloride, (2.1 g., 10 mmoles) in 100 ml. of toluene and the reaction mixture was heated at reflux for 3 hours. Hexane (250 ml.) was added to the cooled solution and the solvent was decanted. The residue was dissolved in water (20 ml.), the solution adjusted to *p*H 8 with *N* aqueous sodium hydroxide and extracted with four 100 ml. portions of chloroform. The extracts were dried over sodium sulfate, evaporated and the residue chromatographed over alumina (15 g.) using chloroform (200 ml.) as the eluent. Evaporation of the chloroform left 0.55 g. (30%) of a residue that was recrystallized from acetone-hexane to give **10** as yellow crystals, m.p. 105-106°. Analytical data are detailed in Table II.

REFERENCES

(1) This work was supported by Contract No. NIH-71-2312 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

(2) Part I: E. Abushanab, A. P. Bindra, L. Goodman and H. Petersen, Jr., *J. Org. Chem.*, **38**, 2049 (1973).