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The Chemistry of Pyrazine and its Derivatives. IX

The Pyrazylethylation of Amines

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A series of pyrazylethylated derivatives of the type $C_4H_3N_2CH_2CH_2N=$ has been prepared in high yields by the reactions of vinylpyrazine with amines using methanolic acetic acid or metallic sodium as the catalyst.

The pyridylethylation of ammonia (2) and a series of amines (3,4,5) by the conjugate addition of ammonia and amines to 2- and 4-vinylpyridine have been reported. More recently we described (6) the synthesis of vinylpyrazine by a Hofmann exhaustive methylation of the Mannich base obtained from methylpyrazine, aqueous formaldehyde and dimethylamine hydrochloride.

The present paper is concerned with the condensation of vinylpyrazine with a series of aliphatic, aromatic, heterocyclic amines and ammonia. By analogy this process is called pyrazylethylation.

The overall reactions are shown in the chart. If the amine to be pyrazylethylated has appreciably basic properties, the reaction is effected by an acidic catalyst (methanolic acetic acid) at atmospheric pressure or in a pressure bottle or steel bomb depending on the boiling point of the amine. If the amine is weakly basic, *e.g.*, 2-aminopyridine, or a pseudo-acid, *e.g.*, pyrrole, the reactions are effected using sodium metal as the catalyst.

The results appear in Table I. It should be pointed out that only two of the fourteen compounds listed were prepared previously. Thus, 2-aminoethylpyrazine (compound 2) has been prepared (7) by the following multi-stage sequence: $C_4H_3N_2CH_3 \longrightarrow C_4H_3N_2CH_2CHOHCCl_3$ (48%) $\longrightarrow C_4H_3N_2CH{=}CHCO_2H \longrightarrow C_4H_3N_2(CH_2)_2NH_2$ (80%). In addition 2-diethylaminoethylpyrazine was previously prepared (8) in 15% yield by a Mannich reaction between methylpyrazine, aqueous formaldehyde and diethylamine hydrochloride as compared with the 82.8% yield which was obtained in the present study.

Derivatives were prepared readily from all of the products except the pyrrole adduct. In this case the pyrazylethylated derivative (I) was reduced by sodium in alcohol to N-(2-piperazinylethyl)pyrrole (II) which was converted to its bis-styphnate. To prove the structures of the products, one of them (Compound 5, Table I) was prepared in 62.2% yield by the Mannich reaction route (6) and was identical with the material which was obtained in 90.9% yield by the pyrazylethylation route. The structure of all other compounds in Table I were assigned by analogy based upon the analytical data.

CHART

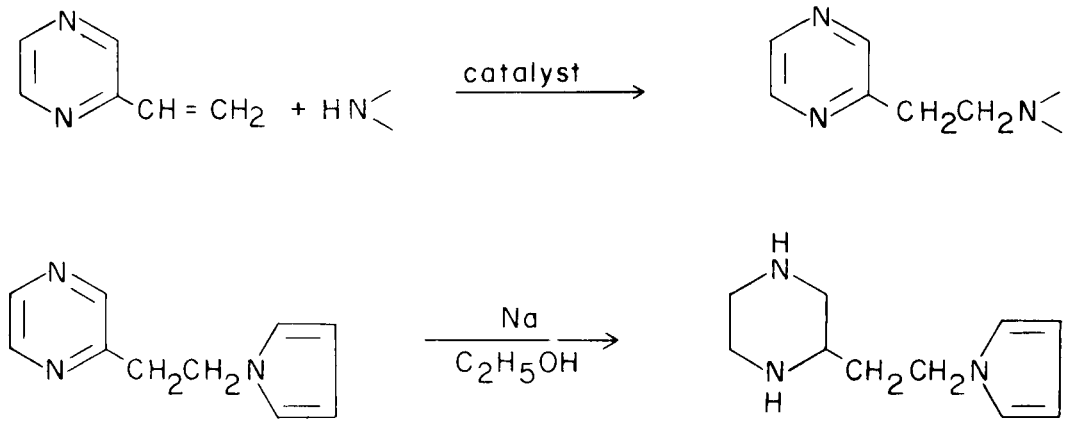
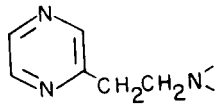


TABLE I

Pyrazylethylated Amines of the Type 

Compound	Amine	Method	Yield, %	n_D^{25}	B.p. (mm.) or m.p.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found
1	ammonia	A (a)	24.3 (b)	1.5337	102-103 (9)	$C_8H_9N_3$	58.51	58.85	7.36	7.23
2	ethylamine	A	74.7 (c)	1.5104	65-68 (0.55)	$C_8H_{13}N_3$	63.54	63.18	8.67	8.85
3	*iso*propylamine	A	89.2	1.5007	86-88 (3.0)	$C_9H_{15}N_3$	65.41	65.26	9.15	9.30
4	benzylamine	B (d)	95.5	1.5724	161-162 (1.55)	$C_{13}H_{15}N_3$	73.20	73.01	7.09	7.18
5	dimethylamine	A	90.9	1.5041	93-94 (10)	$C_8H_{13}N_3$	63.54	63.54	8.67	8.77
6	diethylamine	B	82.8	1.4969	83-84 (1.55) (e)	$C_{10}H_{17}N_3$	66.99	66.98	9.55	9.38
7	aniline	B	88.4		149-152 (0.3)					
					56.0-56.5 (m.p.)	$C_{12}H_{13}N_3$	72.33	72.52	6.58	7.02
8	methylaniline	B	34.6	1.5977	148-149 (0.55)	$C_{13}H_{15}N_3$	73.21	73.44	7.09	7.28
9	2-aminopyridine	C (f)	74.2	1.6105	162-163 (0.55)	$C_{11}H_{12}N_4$	65.97	65.69	6.04	6.30
10	morpholine	B	89.1	1.5272	101-102 (0.5)	$C_{10}H_{15}N_3O$	62.14	61.77	7.82	7.58
11	pyrrolidine	B	85.6	1.5248	127-128 (9.4)	$C_{10}H_{15}N_3$	67.76	67.85	8.53	8.41
12	piperidine	B	89.4	1.5234	110-110.5 (1.6)	$C_{11}H_{17}N_3$	69.07	69.06	8.96	9.36
13	pyrrole	C	83.1		115-117 (0.4)	$C_{10}H_{11}N_3$	69.34	69.39	6.40	6.28
					62 (m.p.)					
14	cyclohexylamine	B	84.8	1.5244	129-130 (1.05)	$C_{12}H_{19}N_3$	70.20	69.97	9.35	9.52
					Picrates					
1a					82-82.5	$C_{13}H_{14}N_4S$ (g)	60.44	60.54	5.46	5.37
2a					90-91	$C_{14}H_{16}N_6O_7$	44.21	44.27	4.24	4.15
3a					127.5-128	$C_{15}H_{18}N_6O_7$	45.68	45.52	4.60	4.64
4a					158-159	$C_{19}H_{18}N_6O_7$	51.58	51.28	4.10	4.19
5a					114.5-115	$C_{14}H_{16}N_6O_7$	44.21	44.18	4.24	4.35
6a					105-106 (h)	$C_{16}H_{20}N_6O_7$	47.06	47.11	4.94	5.00
7a					117.5-118	$C_{24}H_{19}N_9O_{14}$ (i)	43.84	44.18	2.91	3.26
8a					113-114	$C_{19}H_{18}N_6O_7$	51.58	51.33	4.10	4.25
9a					169-169.5	$C_{17}H_{15}N_7O_7$	47.55	47.47	3.52	3.68
10a					148.5-149	$C_{16}H_{18}N_6O_8$	45.49	45.29	4.30	4.31
11a					120-121	$C_{16}H_{18}N_6O_7$	47.28	47.27	4.47	4.49
12a					147-148	$C_{17}H_{20}N_6O_7$	48.59	48.81	4.80	5.46
13a					203-204	$C_{22}H_{21}N_9O_{16}$ (j)	39.58	39.57	3.17	3.44
14a					152-153	$C_{18}H_{22}N_6O_7$ (g)	49.76	49.73	5.10	5.26

(a) In method A, 0.1 mole (10.6 g.) of vinylpyrazine, 0.2 of the amine, 0.05 mole (3.0 g.) of glacial acetic acid and 30 ml. of methanol were placed in a 200 ml., borosilicate pressure bottle (Fisher) or a small steel bomb and the mixture heated in an oil bath at 65-70° for 24 hrs. (b) In addition, 5.06 g. (44.1%) of bis-(pyrazylethyl) amine was obtained (b.p. 170-172° at 0.55 mm., n_D^{25} 1.5643; *Anal.* calcd. for $C_{12}H_{15}N_5$: C, 62.85; H, 6.59. Found: C, 62.65; H, 6.59. Picrate, m.p. 133-134° (from 95% ethanol). *Anal.* calcd. for $C_{18}H_{18}N_8O_7$: C, 47.16; H, 3.96. Found: C, 47.29; H, 4.13. (c) When the reaction was effected using 0.1 mole rather than 0.2 mole of amine, a mixture of compound 2 (59.9%) and of ethylbis-(pyrazylethyl) amine was obtained (21.1%, b.p. 154-156° at 0.5 mm.). *Anal.* calcd. for $C_{14}H_{19}N_2$: C, 65.33; H, 7.44. Found: C, 65.19; H, 7.49. Styphnate, m.p. 122-123° (from 95% ethanol); *Anal.* calcd. for $C_{20}H_{22}N_8O_8$: C, 47.80; H, 4.41. Found: C, 47.48; H, 4.30. (d) Method B is the same as method A except that the reactions are effected at atmospheric pressure at the reflux temperatures of the mixtures. (e) Lit. value, 70-72° (0.6 mm.), see ref. 8. (f) Effected by interactions of 0.1 mole of vinylpyrazine, 0.2 mole of the amine and 0.1 g. of sodium. (g) This is a phenylthiourea. (h) Lit. value, 103-105°, see ref. 8. (i) Dipicrate. (j) This is the bis-styphnate of the reduced (sodium in alcohol) product, N-(2-piperazinyl)pyrrole.

EXPERIMENTAL

Procedures for Effecting Reactions, Method A.

A mixture of vinylpyrazine (0.1 mole, 10.6 g.), the amine to be pyrazylethylated (0.2 mole), glacial acetic acid (0.05 mole, 3.0 g.) and 30 ml. of methanol is placed in a 200 ml. borosilicate glass pressure bottle (Fisher) or a 200 ml. steel bomb and heated at 65-70° in an oil bath for 24 hrs. The reactor is allowed to cool to room temperature and then its contents are distilled to remove the methanol. The cooled mixture is made basic with sodium hydroxide (0.1 mole, 4.0 g. in 40 ml. of water) and extracted with several portions of chloroform. The chloroform extracts were dried over sodium sulfate, the solvent removed and the residue distilled.

Method B.

The procedure is the same as Method A except that the reaction was effected in an open flask at the reflux temperature of the mixture.

Method C.

A mixture of vinylpyrazine (0.1 mole, 10.6 g.), the amine to be pyrazylethylated (0.2 mole, 13.4 g.) and sodium metal (0.1 g.) was heated to 90° when the reaction became exothermic. The heat was removed and the mixture allowed to seek its own temperature (140-165°). It was allowed to cool to 100° and then heated at 110-115° for 20-30 min. Then, ethanol (2.0 ml.) was added and the mixture poured onto ice and processed in the usual manner.

REFERENCES

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