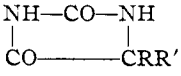
TABLE I

5-CYCLOALKYL-5-SUBSTITUTED-HYDANTOINS



R–	R'–	M.p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Cyclopropyl	Phenyl	211.5	56	66.65	66.44	5.60	5.62	12.93	12.75
Cyclopropyl	Isoamyl	176–177	15	62.80	62.40	8.56	8.45		
Cyclobutyl	Phenyl	234.5–235.5	85	67.90	67.61	6.13	6.00	12.17	12.01
Cyclobutyl	Cyclohexyl	254–255	70	66.07	66.00	8.53	8.65	11.86	11.42
cis-2-Methylcyclopentyl	Methyl	176–177	34	61.20	60.90	8.23	8.18		
trans-2-Methylcyclopentyl	Methyl	228–230	17	61.20	61.01	8.23	8.10		
2,3-Dimethylcyclopentyl	Methyl	145–150[a]		62.80	62.41	8.58	8.75	13.65	13.52
2,3-Dimethylcyclopentyl	Methyl	220–225[b]		62.80	62.51	8.58	8.70	13.65	13.50

[a] Fraction of lowest m.p. [b] Fraction of highest m.p.

sium cyanide and 58 g. (0.60 mole) of ammonium carbonate was dissolved in 500 ml. of 50% alcohol and warmed at 60° for 21 hours. After concentration to one-half volume and acidification, there were obtained white crystals melting at 163–175°. Considerable difficulty was experienced in recrystallizing this material, since there was a marked tendency for it to separate as an oil which finally would solidify to a non-crystalline mass. Recrystallization from a relatively large volume of diluted alcohol, with very slow cooling, gave 26 g. (62% yield) of material melting at 160–175°. The product was recrystallized in turn from diluted alcohol, acetone–water, chloroform, methanol, ether, benzene, petroleum ether and dioxane without appreciable sharpening of the melting point.[20] So the mixture was dissolved in acetone and fractionally precipitated by addition of water; from this procedure there were obtained fractions as follows:

Sample no.	M.p., °C. (cor.)	Weight, g.
1	220–225	0.5
2	210–220	1.0
3	210–215	1.2
4	175–195	6.5
5	140–180	1.5
6	145–157	1.2
7	145–150	3.0

Fractions 1 and 7 were crystallized and analyzed. The analytical data for these products, and of the other cycloalkylhydantoins prepared in this study, are listed in Table I.

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(20) This hydantoin possesses four asymmetric carbon atoms; the substituted carbon atoms at the 1'-, 2'- and 3'-positions of the cyclopentyl nucleus are capable of giving rise to *cis–cis*, *trans–trans*, *cis–trans* and *trans–cis* forms which would be expected to exhibit differences in melting point.

[CONTRIBUTION FROM THE LEDERLE LABORATORIES, AMERICAN CYANAMID COMPANY]

Experimental Chemotherapy of Tuberculosis. II. The Synthesis of Pyrazinamides and Related Compounds[1]

BY S. KUSHNER, H. DALALIAN, J. L. SANJURJO, F. L. BACH, JR., S. R. SAFIR, V. K. SMITH, JR., AND J. H. WILLIAMS

RECEIVED JANUARY 3, 1952

The preparation of a large number of pyrazinamides and related compounds for antituberculous activity is described. The majority of these compounds were alkyl, aryl, acyl and heterocyclic derivatives of pyrazinamides. Thiosemicarbazones of several related pyrazines were prepared for *in vivo* testing. Of the compounds prepared, pyrazinamide was found to be more active than *p*-aminosalicylic acid in the mouse test, and was found to be clinically active in humans.

The *in vivo* antituberculous activity of nicotinamide and N-thiazolylnicotinamide, which has been reported[2] by some of us, led to further synthesis in the field of heterocyclics closely related to them. Although in the field of pyrazine chemistry several compounds have been reported to be active as analeptics,[3] antipellagric agents[4] or local anesthetics,[5] to our knowledge no study of pyrazines has been made in the chemotherapy of tuberculosis. Since the pyrazine derivatives resemble, in structure, nicotinamide with an additional nitrogen atom substituted in the ring, it was of interest to determine whether or not this similarity in structure would enable us to develop new tuberculostatic compounds. We wish to report that in Aldinamide[6] pyrazinamide, a new, comparatively non-toxic, tuberculostatic agent, with a chemotherapeutic index of 500 in the mouse, has been found. This compound has an activity several times as great as P.A.S. and seven times that of nicotinamide in the mouse.[7] Corroborative activity was obtained in the guinea pig,[8] and subsequent evaluation in the human showed it to be clinically active.[9] It should be noted that pyrazinamide is similar to nicotinamide in that it does not lend itself to chemical variation with full retention of activity. A full

(1) Presented before the Medicinal Chemistry Section, American Chemical Society, Milwaukee, Wisconsin, April, 1952.

(2) S. Kushner, H. Dalalian, R. T. Cassell, J. L. Sanjurjo, D. McKenzie and Y. SubbaRow, *J. Org. Chem.*, **13**, 834 (1948).

(3) O. Dalmer and E. Walter, German Patent 632,257 (1936).

(4) W. B. Bean and T. D. Spies, *Am. Heart J.*, **20**, 62 (1940).

(5) E. Epstein, Thesis, Polytechnic Institute of Brooklyn, 1939.

(6) Trade-mark American Cyanamid Co.

(7) L. Malone, A. Schurr, H. Lindh, D. McKenzie, J. S. Kiser and J. H. Williams, *Am. Rev. Tuber.*, **65**, 511 (1952).

(8) F. I. Dessau, R. L. Yeager, F. J. Burger and J. H. Williams, *ibid.*, **65**, 519 (1952).

(9) R. L. Yeager, W. G. C. Munroe, and F. I. Dessau, *ibid.*, **65**, 523 (1952).

TABLE I

PYRAZINE ACID AND AMIDE DERIVATIVES

Substituent	Meth. of prep.	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	T. B.[h,i] activity
—COOH[a]			225-226	$C_5H_4N_2O_2$							–
—CN[b]			B. 87 (6–7 mm.)	$C_5H_3N_3$							–
—C(=NH.2HCl)OCH$_3$[b]			180	$C_7H_{10}ClN_3O$							–
—COOCH$_3$[c]·HCl			46	$C_6H_7ClN_2O_2$	41.4	4.0	16.1	41.7	4.4	16.2	–
—CONH$_2$[c]			189–191	$C_5H_5N_3O$							++++
—C(=NH.HCl)NH$_2$		18	215-218 dec.	$C_5H_7ClN_4$	43.2	3.6	30.2	43.5	3.5	30.2	–
—CNH$_2$‖S		90	195–196	$C_6H_6N_2S$	43.2	3.6	30.2	43.6	3.9	30.5	–
							S, 23.0			S, 23.5	
—2-COOH-6-CH$_3$[d]		70	138-140	$C_6H_6N_2O_2$							–
—2-CONH$_2$-6-CH$_3$[e]	B	83	204–205	$C_6H_7N_3O$	52.6	5.1	30.7	52.7	5.3	30.6	–
—2-CONH$_2$-3-NH$_2$[f]	B	50	237–239	$C_5H_6N_4O$							–
—2-CONH$_2$-3-NH$_2$[p] 6-Br	B	80	215–217	$C_5H_4BrN_4O$	27.5	2.3	Br 36.7[j]	27.9	2.7	Br 37.2	– (Toxic)
—2-CONH$_2$-3-OH[g]	B		265 dec.	$C_5H_4N_2O_2$							–
—2-COOH-3-COOH[j]			179-182	$C_6H_4N_2O_4$							– (Toxic)
—2-CONH$_2$-3-CONH$_2$[k]	B		240 dec.	$C_6H_6N_4O_2$							– (Toxic)
—2,3-CONHCO-[k]			245	$C_6H_3N_3O_2$							–
—2-COOCH$_3$-3-COOCH$_3$-6-CH$_3$[l]		60	32–34	$C_9H_{10}N_2O_4$	51.4	4.8	13.3	51.6	5.1	12.9	–
—2-CONH$_2$-6-CONH$_2$	B	90	300 dec.	$C_6H_6N_4O_2$	43.4	3.6	33.7	43.8			–
—2-CONH$_2$-3-CONH$_2$-6-CH$_3$[e]	B	80	215–217	$C_7H_8N_4O_2$	46.7	4.4	31.1	46.8	4.5	30.9	–
—CONHCH$_3$[m]	A		105	$C_6H_7N_3O$							–
—CON(CH$_3$)$_2$[m]	A		70–72	$C_7H_9N_3O$							–
—CONH-C$_4$H$_9$[n]	B		63–64	$C_9H_{13}N_3O$	60.3	7.3	23.5	60.0	7.6	23.4	–
—CON(C$_4$H$_9$)$_2$[m]	A	20	B. 167–170 (3 mm.)	$C_{13}H_{22}N_3O$							–
—CONHC$_{16}$H$_{34}$[n]	A	50	85–87	$C_{21}H_{37}N_3O$	72.6	10.7	12.1	73.1	11.1	11.9	–
—CONHCH$_2$C$_4$H$_3$[m]	A		116–118	$C_{12}H_{11}N_3O$							–
—CONHCH$_2$C$_6$H$_4$-*p*-OCH$_3$	B	50	134–136	$C_{13}H_{13}N_3O_2$	64.2	5.4	17.3		5.6	17.8	–
—CONHC$_6$H$_5$[m]	A	55–60	127–130	$C_{11}H_9N_3O$							–
—CONHC$_6$H$_4$-*p*-Cl	A	60	184–185	$C_{11}H_8ClN_3O$	56.5	3.4	18.0	56.8	3.7	18.2	–
—CONHC$_6$H$_4$-*o*-Cl	A	60	135–136	$C_{11}H_8ClN_3O$	56.5	3.4	18.0	56.6	3.8	18.3	–
—CONHC$_6$H$_4$-*m*-Cl	A	60	145–147	$C_{11}H_8ClN_3O$	56.5	3.4	18.0	56.7	3.7	17.9	–
—CONHOH		72	163–165	$C_5H_5N_3O_2$	43.2	4.3	30.2	43.5	4.0		–
—2-CONH$_2$-4-oxide		45	292–293 dec.	$C_5N_4N_3O_2$	43.2	3.6	30.2	43.5	3.5	30.2	–
—2-CONH$_2$-4-CH$_2$I		38	192–202	$C_5H_5IN_3O$			15.9			15.8	– (Toxic)
—CONHCCH$_3$‖O		55	92-97	$C_7H_7N_3O_2$	50.8	4.2	25.5	50.8	4.4	25.8	+
—CONHCH$_2$OH		80	129–136.5	$C_6H_7N_3O_2$	47.1	4.6	27.5	47.2	5.0	27.1	–
—CONH(CH$_2$)$_2$NHC$_2$H$_4$OH	B	84	107–108	$C_9H_{14}N_6O_2$	51.4	6.7	26.7	51.1	6.3	26.2	–
—CONHNH$_2$[p]			169	$C_5H_6N_4O$							– (Toxic)
—CONHNHSO$_2$C$_6$H$_5$		86	169–170	$C_{11}H_{10}N_4O_3S$	47.5	3.6	20.1 S, 11.5	47.8	4.1	20.2 S, 11.9	– (Toxic)
—CONHN=CHC$_6$H$_4$-*p*-NHCOCH$_3$		92	> 250	$C_{14}H_{13}N_5O_2$	59.4	4.6	24.7	59.3	4.9	24.9	–
—CONHC$_4$H$_3$NS[q]	A	60	187–189	$C_8H_6N_4OS$	46.6	2.9	27.2	46.8	3.4	26.9	–
—CONHC$_5$H$_4$N[r]	A	65	138–140	$C_{10}H_8N_4O$	60.0	4.0	28.0	60.1	4.5	27.8	
—CONHC$_5$H$_4$N[s]	A	62	185–186	$C_{10}H_8N_4O$	60.0	4.0	28.0	60.2	4.3	28.4	–
—COC$_5$H$_{10}$N[o,t]	A	80	68–69	$C_{10}H_{18}N_2O$	62.8	6.8	22.0	63.0	6.7	22.4	
—CONHC$_9$H$_6$N[u]	A	76	205–206	$C_{14}H_{10}N_4O$	67.2	4.0	22.4	67.7	4.4	22.4	–
—CONHC$_4$H$_3$N$_2$[v]	A	40	190–192	$C_8H_7N_5O$	53.7	3.5	34.8	54.2	4.5	35.4	–
—CH$_2$CC$_4$H$_8$NO[w]‖S		80	92-93	$C_{10}H_{13}N_3OS$	53.8	5.8	18.8 S, 14.4	53.8	5.9	18.7 S, 14.3	–
—CONH(CH$_2$)$_2$COOC$_2$H$_5$	C	50	87–89	$C_{10}H_{13}N_3O_3$	53.8	5.8	18.8	54.8	6.2	18.4	–
—CONH(CH$_2$)$_2$CONH$_2$	B	55	206–208	$C_8H_{10}N_4O_2$	49.5	5.2	28.9	49.5	5.4	28.5	–
—CONHCHCH$_2$COOC$_2$H$_5$COOC$_2$H$_5$	C	70	64-65	$C_{13}H_{17}N_3O_5$	52.9	5.8	14.2	53.0	5.8	14.4	–
—CONH(CH$_2$)$_2$CH=CHCOOH	C	70	200–201	$C_{10}H_{11}N_3O_3$	54.3	5.0	19.0	54.4	5.4	19.4	–

[a] S. Gabriel and A. Sonn, *Ber.*, **40**, 4885 (1907). [b] H. Van Del Vecchio, Thesis, Polytechnic Institute of Brooklyn, 1944. [c] S. A. Hall and P. E. Spoerri, THIS JOURNAL, **62**, 664 (1940). The hydrochloride was formed from direct esterification and isolated. [d] F. Leonard and P. E. Spoerri, *ibid.*, **68**, 526 (1946). [e] Compounds were recrystallized from ethanol. [f] R. C. Ellingson, *et al.*, THIS JOURNAL, **67**, 1712 (1945). [g] F. G. McDonald and R. C. Ellingson, *ibid.*, **69**, 1035 (1947). [h] A standardized mouse test using survival as a criterion was used to evaluate activity. These compounds were tested at the arbitrary level of 0.2% of diet, fed *ad libitum*. (8 mg./day). When the level was toxic as shown by the body weight of the mice the drug concentration was altered. [i] The technical details of the test and the results will be published elsewhere.[6] [j] R. G. Jones and K. C. McLaughlin, *Org. Syntheses*, **30**, 86 (1950). [k] S. Gabriel and A. Sonn, *Ber.*, **40**, 4856 (1907).[7] [l] R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, THIS JOURNAL, **72**, 3540 (1950). The acid was prepared according to the procedure described in this report. [m] O. Dalmer and E. Walter, U. S. Patent 2,149,279 (March 7, 1939). [n] Compound recrystallized from benzene–alcohol solution. [o] Compound recrystallized from hot acetone. [p] O. Dalmer, C. Diehl and E. Walter, U. S. Patent 2,176,063 (October 17, 1940). [q] N-2-Thiazolyl. [r] N-2-Pyridyl. [s] N-3-Pyridyl. [t] 1-Piperidyl. [u] N-3-Quinoxalyl. [v] N-2-Pyrazinyl. [w] 1-Morpholinyl.

and complete study of the activity of pyrazinamide and its derivatives in the mouse will be reported by Malone and co-workers elsewhere.[7]

Table I outlines the acid and amide derivatives of pyrazine which were prepared, in the main following usual procedures as described under Experimen-

TABLE II

RELATED PYRAZINE COMPOUNDS AND THIOSEMICARBAZONES

Substituent	Meth. of prep.	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	T. B.[a] activity
—C(H)=NNHC(=S)NH$_2$		9	237–239 dec.	$C_6H_7N_5S$	39.8	3.9	38.6 S, 17.7	40.2	4.2	38.0 S, 17.7	± (Toxic)
—C(=O)—CH$_3$		77	76–78	$C_6H_6N_2O$	59.0	4.9	23.0	58.8	5.1	22.6	–
—C(=NOH)—CH$_3$		50	113–115[b]	$C_6H_7N_3O$	52.6	5.1	30.7	52.3	5.4	30.9	–
—C(CH$_3$)=NNHC(=S)NH$_2$		67	226–227 dec.	$C_7H_9N_5S$	43.1	4.7	35.9 S, 16.4	43.6	5.0	35.9 S, 16.7	– (Toxic)
—C(=O)—CH$_2$Cl		30	85–86	$C_6H_5ClN_2O$							–
N(H)—N=C(—NH$_2$)—C(=S)		30	222–224	$C_7H_8ClN_5S$			15.2[c] S, 13.9			15.5[c] S, 14.4	–
—C(=O)—CH$_2$—OC(=O)CH$_3$		10	67–68	$C_8H_8N_2O_3$	53.3	4.4	15.5	53.1	4.6	15.6	–
CH$_3$C$_8$H$_4$N$_2$CH=NNHC(=S)NH$_2$[d]		30	251–252 dec.	$C_{11}H_{11}N_5S$	53.8	4.5	28.6 S, 13.1	53.3	4.8	28.0 S, 13.6	–
C$_8$H$_4$N$_2$ClCONH$_2$[e]	C		207–209	$C_9H_6ClN_3O$							–
C$_8$H$_4$N$_2$ClCONHCH$_2$C$_6$H$_5$[f]		60	145–147	$C_{16}H_{12}ClN_3O$	64.5	4.0	14.2 11.9	64.8	4.3	14.0 11.9[c]	–
—CHN$_4$[g]		30	182–184	$C_5H_4N_6$	40.5	2.7	56.8	40.8	2.9		–
—NHCSNH$_2$		80	128	$C_5H_6N_4S$	39.0	3.9	36.4 S, 20.8	39.0	3.9	36.3 S, 21.1	–
—OH			187–189	$C_4H_4N_2O$							–
—OC$_6$H$_5$		72	50–52	$C_{10}H_8N_2O$	69.8	4.7	16.3	69.5	5.2		–

[a] See Table I. [b] Sublimed for analysis at 100° at 0.05 mm. [c] Chlorine analysis. [d] 2-Methyl-3-quinoxalinaldehyde thiosemicarbazone. [e] A. H. Gowenlock, *et al.*, *J. Chem. Soc.*, 624 (1945). 2-Chloroquinoxaline-3-carboxamide. [f] N-Benzyl-2-chloroquinoxaline-3-carboxamide recrystallized from an alcohol–water solution. [g] 5-Tetrazole.

tal. Pyrazinoic acid was prepared by the classical method wherein quinoxaline is first oxidized and subsequently decarboxylated. Pyrazinoyl chloride was purified by vacuum distillation and used promptly. Pyrazinamide, itself, was prepared by ammonolysis of methyl pyrazinoate according to the procedure of Dalmer and Walter.[3]

Since the unsubstituted amide was highly active, cyanopyrazine was tested on the assumption that it might hydrolyze in the body fluids to yield an active compound. Since cyanopyrazine was not active it was decided to convert it to methyl pyrazinimidate, the assumption being that this compound might be more easily hydrolyzed at body *p*H. However, tests at this *p*H showed a slow reconversion to the cyanopyrazine derivative. This approach is under further investigation. Of all the compounds in Table I the N-acetyl derivative prepared by the action of acetic anhydride on pyrazinamide was the only other derivative to show activity.

Table II outlines related pyrazine compounds and thiosemicarbazones. The latter have become increasingly important since they were first reported by Domagk, Behnisch, Mietzsch and Schmidt.[10]

The work of Gardner, Smith, Wenis and Lee[11] has recently been reported confirming our nicotinamide work and extending it to pyridine thiosemicarbazones with successful results. The comparable preparation of pyrazinaldehyde thiosemicarbazone had questionable activity. It was prepared in 9% yield from the benzenesulfonpyrazinohydrazide utilizing the McFadyen–Stevens reaction with modifications. A dry mixture of the substituted hydrazide and sodium carbonate was heated under vacuum, and the vapors were passed into a 3% thiosemicarbazide solution from which the desired product precipitated.

The preparation of acetylpyrazine from cyanopyrazine *via* a Grignard reaction was straightforward. Its conversion through the Willgerodt reaction to pyrazinylacetamide could be effected only in poor yield. Conversion to the thioacetomorpholide was effected in the usual good yield, with freshly-distilled morpholine. This compound was unusually stable when subjected to the usual acid or alkali hydrolysis conditions.

We have designated pyrazinamide as having an arbitrary rating of 4+ in the tables.

(10) G. Domagk, R. Behnisch, F. Mietzsch and H. Schmidt, *Naturwissenschaften*, **33**, 315 (1946).

(11) T. S. Gardner, F. A. Smith, E. Wenis and J. Lee, *J. Org. Chem.*, **16**, 1121 (1951).

Acknowledgment.—We wish to thank L. Brancone and staff for the analyses contained within.

Experimental

N-Substituted Pyrazinamides.—These products were prepared by treating pyrazinoyl chloride suspended in ethyl acetate with a suitable amine as described in method A, by the ammonolysis or aminolysis of an appropriate ester as in method B, or by a modified Schotten–Baumann reaction in method C. The compounds prepared by method A were recrystallized from ethyl acetate, and those prepared by method B were recrystallized from ethanol, unless a different method is specified in the footnotes to the tables.

Method A. N-(2-Thiazolyl)-pyrazinamide.—To 5.0 g. (0.05 mole) of 2-aminothiazole was added slowly a suspension of 3.5 g. (0.02 mole) of freshly prepared pyrazinoyl chloride in 15 cc. of ethyl acetate. The suspension was heated on a steam-cone for 10 minutes, and the clear, hot supernatant ethyl acetate was decanted into an evaporating dish. The residue from the reaction mixture was again suspended in 15 cc. of ethyl acetate, and the procedure repeated. The combined layers of ethyl acetate were evaporated to dryness on a steam-cone, leaving a solid, yellow residue. This material was washed with cold water, filtered, dried and recrystallized from hot ethyl acetate. The recrystallized product weighed 3.0 g.

N-Hexadecylpyrazinamide.—The emulsion formed between the crude product and the solvent was separated into two layers by the addition of a saturated aqueous solution of sodium chloride, and worked up in the usual manner.

Method B (Ammonolysis). β-(N-Pyrazinoylamido)-propionamide.—One gram of ethyl N-pyrazinoyl-β-alanate was dissolved in 25 cc. of methanol, and saturated with anhydrous ammonia gas at 0°. An oil deposited during the ammonia addition, and crystallized on standing in the cold.

Method B (Aminolysis). N-β-Hydroxyethyl-N'-pyrazinoylethylenediamine.—A suspension of 5.0 g. (0.04 mole) of methyl pyrazinoate, 7.5 g. (0.07 mole) of hydroxyethylethylenediamine and 30 cc. of absolute alcohol was refluxed on a steam-cone for 60 hours. After this time the alcohol was distilled off, and the residual liquid solidified on cooling. The crude product after recrystallization from acetone weighed 4.2 g.

N-Isobutylpyrazinamide.—A suspension of 5.0 g. (0.04 mole) of methyl pyrazinoate, 5.2 g. (0.07 mole) of isobutylamine and 30 cc. of absolute alcohol was treated in a similar manner. The residual liquid was taken up in pet. ether, treated with Norit, filtered and allowed to cool to room temperature. The solid material which separated was collected, and weighed 4.0 g.

N-(*p*-Methoxybenzyl)-pyrazinamide.—A mixture of 13.7 g. (0.1 mole) of *p*-methoxybenzylamine, 13.8 g. (0.1 mole) of methyl pyrazinoate and 100 cc. of absolute alcohol was refluxed for 12 hours. After cooling, yellow crystals deposited which were collected and recrystallized from ethanol. The yield was 21.0 g.

Method C. 5-Pyrazinoylamido-2-pentenoic Acid.—To a stirred ice-cold alkaline solution of 15 g. (0.13 mole) of 5-amino-2-pentenoic acid and 5.2 g. (0.13 mole) of sodium hydroxide in 100 cc. of water contained in a three-necked flask was added simultaneously over a 30-minute period 9 g. of sodium hydroxide in 50 cc. of water and 10 g. (0.07 mole) of pyrazinoyl chloride in 50 cc. of benzene. After stirring at 0° and at room temperature for 30 minutes, the benzene was removed under vacuum with minimal heating. The aqueous solution was then acidified with 6 *N* hydrochloric acid, and the precipitated brown solid filtered and washed with water. The product was taken up in alkali, treated with Norit and reprecipitated; yield 10 g.

Diethyl N-Pyrazinoylaspartate.—This compound was prepared in essentially the same manner as the pentenoic acid derivative, utilizing sodium bicarbonate. The benzene layer was evaporated to give yellow needles and was recrystallized from aqueous alcohol.

Ethyl N-Pyrazinoyl-β-alanate.—Prepared in the same manner as the aspartate.

Pyrazinylcarboxamidine Hydrochloride.—A mixture of 21.9 g. of cyanopyrazine, 125 cc. of dry ether and 8.4 cc. of dry methanol was saturated with dry hydrochloric acid gas at 0°. The mixture was then stored at room temperature for about 15 hours, and the white solid was filtered, washed with ether and pumped dry; yield 25.6 g. This material is methyl pyrazinimidate dihydrochloride; m.p. above 150° with darkening and decomposition.

To 600 cc. of ice-cold 8% ethanolic ammonia was added 25.6 g. of the aforementioned imidic ester. The mixture was then shaken for one day at room temperature in a stoppered flask, then filtered from a white solid (2.7 g.) which consists of ammonium chloride and an unidentified substance. The alcoholic filtrate was evaporated to dryness *in vacuo*. The solid residue was boiled briefly with 125 cc. of acetone and filtered. It was then recrystallized from ethanol using Norit; yield 6 g., m.p. 211–214° (dec.).

For analysis, a sample was recrystallized once more from ethanol.

The picrate forms readily in aqueous solution; m.p. 221–224°.

Anal. Calcd. for $C_{11}H_9N_7O_7$: C, 37.6; H, 2.6; N, 27.9. Found: C, 37.6; H, 3.1; N, 28.0.

Thiocarbamylpyrazine.—To an ice-cold solution of 15 g. (0.14 mole) of cyanopyrazine in 200 cc. of saturated alcoholic ammonia was added hydrogen sulfide until saturation. After standing overnight at room temperature the solid was filtered and washed with cold alcohol. The crude product (14.0 g.) was recrystallized from alcohol after treatment of the hot solution with Norit.

Pyrazinohydroxamic Acid.—To a solution of 13.8 g. (0.1 mole) of methylpyrazinoate and 7.0 g. (0.1 mole) of hydroxylamine hydrochloride in 50 cc. of ice-water was added, with swirling, 16 cc. of 12.5 *N* sodium hydroxide over a two-minute period. After standing in an ice-bath for 15 minutes, the solution was neutralized with hydrochloric acid. The solid, after filtration and washing with water, weighed 10.0 g. and melted at 160°. After several recrystallizations from water, it melted at 163–165° and gave a characteristic wine color with alcoholic $FeCl_3$.

2-Carboxamidopyrazine-4-oxide.—A mixture of 21 g. of pyrazinamide, 84 cc. of acetic acid and 210 cc. of 30% hydrogen peroxide was heated at 56° for 34 hours. The mixture containing the separated product was cooled to 5°, filtered and washed with cold water; yield 10.7 g., m.p. 285–290° (dec.).

After one recrystallization from acetic acid white crystals were obtained.

The same substance is formed when pyrazinyl cyanide is oxidized in the manner described above.

2-Carbamyl-4-methylpyrazinium Iodide.—Ten grams (0.08 mole) of pyrazinamide in 100 cc. of methyl alcohol was refluxed with 17 g. of methyl iodide for 12 hours. The reddish-brown solution was concentrated and, upon cooling, a brown crystalline solid was obtained. The product was recrystallized from water and alcohol, yield 8.0 g.

N-Acetylpyrazinamide.—A mixture of 4 g. of pyrazinamide and 20 cc. of acetic anhydride was refluxed one and one-quarter hours, evaporated to dryness *in vacuo*, and the residue was evaporatively distilled at 110° (0.05 mm.). A white solid, melting indefinitely at 90°, was collected; weight 3.8 g. This material was purified by boiling with 35 cc. of benzene, cooling to room temperature and filtering the insoluble portion. The latter amounts to 0.6 g. and consists of pyrazinamide. The benzene filtrate on evaporation yielded 3 g. of the acetyl derivative as a colorless solid.

N-Methylolpyrazinamide.—A mixture of 15 g. (0.12 mole) of pyrazinamide, 18 cc. of formalin and 0.2 g. of potassium carbonate was heated on a steam-cone until a clear straw-colored solution was obtained. After standing overnight at 5°, alcohol was added and the solid filtered. After washing several times with alcohol, the air-dried solid weighed 14.5 g.

Benzenesulfopyrazinohydrazide.—This compound was prepared in the usual manner in pyridine with molar equivalents of benzenesulfonyl chloride and pyrazinohydrazide.

Pyrazinaldehyde Thiosemicarbazone.—A 250-ml. Claisen flask was charged with a dry mixture of 18 g. of finely-ground sodium carbonate and 10 g. of benzenesulfonpyrazinohydrazide. An aqueous solution of thiosemicarbazide (3%) was placed in a round-bottom flask equipped with an inlet and outlet tube. The side-arm of the Claisen flask was fitted to the inlet tube, allowing any vapor or distillate from the reaction to pass into the solution of thiosemicarbazide, and the outlet tube was connected to the vacuum pump. The dry mixture was heated to 150–170° (37 mm.), and as the vapors were bubbled through the thiosemicarbazide solution, a blue-green precipitate was formed. This com-

plex formation, on standing overnight, yielded a tan, granular substance which was collected and taken up in hot absolute ethanol. The alcoholic solution was treated with Norit, filtered, dried over anhydrous sodium sulfate and concentrated to one-third its original volume. On cooling the solution a light-yellow granular substance was obtained which melted at 237–239°. Recrystallization of the material from alcohol did not change the melting point.

p-**Acetamidobenzolpyrazinohydrazide.**—A mixture of 2.8 g. (0.02 mole) of pyrazinohydrazide, 3.3 g. (0.02 mole) of *p*-acetaminobenzaldehyde and 100 cc. of absolute alcohol was heated to reflux. After five minutes, solid started to precipitate from the clear solution. The chilled reaction mixture was filtered and washed with 70 cc. of alcohol; wt. 5.2 g.

Acetylpyrazine.—To a stirred ice-cold Grignard solution prepared from 9 g. (0.37 mole) of magnesium, 50 g. of methyl iodide and 300 cc. of dry ether was added, dropwise, over 20 minutes, 13 g. (0.12 mole) of cyanopyrazine in 150 cc. of dry ether. The reaction mixture was poured onto cracked ice and the ether layer decanted. The ice-cold aqueous fraction was cautiously acidified with dilute hydrochloric acid and then thoroughly extracted with ether. The combined ether extracts were treated with Norit, and dried over anhydrous magnesium sulfate. Upon evaporation of the ether, 10 g. of a brown solid was obtained. After several recrystallizations from ether, the acetylpyrazine was obtained as a white product.

Acetylpyrazine Thiosemicarbazone.—The above compound was refluxed overnight with two equivalents of thiosemicarbazide in alcohol. The solid obtained by filtering the cold solution was leached with boiling water leaving the desired compound analytically pure.

Acetylpyrazine Oxide.—The compound was prepared in the usual manner using hydroxylamine hydrochloride and sodium acetate in alcohol. The oxime was recrystallized from ether–pet. ether.

α-**Pyrazinylacetamide.**—A mixture consisting of 1.5 g. (0.05 mole) of powdered sulfur dissolved in 15 cc. of a concentrated solution of ammonium hydroxide saturated with hydrogen sulfide, 3.0 g. (0.02 mole) of acetylpyrazine and 12 cc. of dioxane was heated 24 hours in a sealed tube at 170°. The reaction mixture was evaporated to dryness, and extracted with hot acetone until all soluble material had been taken up. The solution was concentrated and, on standing, a black mass deposited which was recrystallized from ethanol–pet. ether (20–40°) soln. The recrystallized product weighed 0.2 g., m.p. 108–110°.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.6; H, 5.1; N, 30.7. Found: C, 52.6; H, 5.3; N, 30.9.

Pyrazinylthioacetmorpholide.—A mixture of 12.2 g. (0.10 mole) of acetylpyrazine, 5.2 g. (0.16 mole) of powdered sulfur and 15 cc. of freshly distilled morpholine was refluxed for six hours. The cooled reaction mixture was poured onto 100 g. of cracked ice, stirred well, and left in a refrigerator overnight. The crystalline product was filtered, washed with a small amount of cold water, dried and recrystallized twice from hot alcohol; yield 9.7 g. This compound could not be hydrolyzed by refluxing in acid or alkali.

ω-**Chloroacetylpyrazine.**—The following preparation is a modification of the procedure reported by Glantz and Spoerri.[12] Anhydrous hydrogen chloride gas was passed through a solution of 29.6 g. (0.2 mole) of pyrazinoyldiazomethane in 600 cc. of dry ether until the evolution of nitrogen ceased. The light-tan, granular precipitate which separated from the ethereal solution was collected, washed with 100 cc. of ice-water and recrystallized from chloroform. The solvent was distilled off *in vacuo*, and the temperature of the water-bath was kept below 50°. The recrystallized product weighed 9.4 g.

ω-**Chloroacetylpyrazine Thiosemicarbazone.**—Four grams (0.03 mole) of ω-chloroacetylpyrazine and 2.7 g. (0.03 mole) of thiosemicarbazide in 25 cc. of ethanol were warmed on a steam-cone for five minutes and then concentrated to one-half the original volume. On cooling, 4.1 g. of a light-yellow, curdy precipitate formed. The crude thiosemicarbazone was recrystallized twice from hot ethanol.

ω-**Acetoxyacetylpyrazine.**—To 30 cc. of glacial acetic acid warmed to 50° was added portionwise 6.4 g. of pyrazinoyl diazomethane. (A boiling chip added to the reaction facilitated the evolution of nitrogen.) After all the nitrogen had been evolved, 0.5 g. of potassium acetate was added and the solution was warmed to 100° for 1.0 hour. The glacial acetic acid was then distilled off *in vacuo*, and the remaining thick, dark-brown residue was allowed to evaporate in air. The dark-brown needle-shaped crystals which formed were recrystallized from acetone. A sample which sublimed at steam-cone temperature and under atmospheric conditions, was analyzed.

3-Methyl-quinoxalinaldehyde Thiosemicarbazone.[13]—The 3-methylquinoxalinaldehyde-2 (0.14 g.) was dissolved in 10 cc. of dry ethanol and refluxed with (0.07 g.) of thiosemicarbazide for 2 hours. The alcoholic solution, on cooling, yielded a yellow crystalline mass. This material was recrystallized from alcohol.

5-Pyrazinyltetrazole.—A mixture of 5.1 g. (0.05 mole) of cyanopyrazine, 3.3 g. (0.05 mole) of sodium azide, 10 cc. of glacial acetic acid and 15 cc. of isopropyl alcohol was autoclaved for five days at 150° according to the method of Herbst.[14] The crystalline mass was removed from the bomb by dissolving in hot isopropyl alcohol. After removing the alcohol under vacuum, the solid residue was taken up in hot water. The aqueous solution was acidified with dilute hydrochloric acid, filtered and washed with water. Several recrystallizations were made from ethyl acetate; yield 2.5 g.

N-Pyrazinylthiourea.—Equimolar concentrated aqueous solution of 2-aminopyrazine and of potassium thiocyanate were mixed and acidified during one hour with one molar equivalent of dilute hydrochloric acid. After being stored at room temperature overnight, the solution was concentrated to a small volume and cooled. The crystalline mass was filtered. This crude product was recrystallized from ethyl acetate. The total recovered was 6.6 g. About 6 g. more was recovered from the filtrates.

Phenyl Pyrazinyl Ether.—A suspension of 36 g. (0.31 mole) of sodium phenoxide and 36 g. (0.32 mole) of chloropyrazine was refluxed for 13 hours. The cold mixture was extracted three times with ether, and the combined ether extracts were washed with ice-cold dilute sodium hydroxide, treated with Norit and dried over anhydrous magnesium sulfate. In evaporation of the ether 26 g. of the desired product was obtained analytically pure.

PEARL RIVER, N. Y.

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