Formycin Analogs. 1. Model Studies in the Preparation of an Isomer of Formycin and Related Derivatives (*s*-Triazolo[4,3-*a*]pyrazines)

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The synthesis of a number of 8-substituted- and 3-methyl-8-substituted-*s*-triazolo[4,3-*a*]-pyrazines as model molecules for an isomer of formycin (*i.e.*, 8-amino-3-(β-D-ribofuranosyl)-*s*-triazolo[4,3-*a*]pyrazine (**2**)) and some of its derivatives (including aglycone) is reported. The C-8 substituents include amino (**3a** and **4a**), chloro (**3b** and **4b**), hydroxy (as the 8-ones **8a** and **9a**), mercapto (as the 8-thiones **8c** and **9c**), hydroxylamino (**3e** and **4e**), selenoxy (as the 8-selenones **8d** and **9d**), methoxy (**3g** and **4g**), and thiomethoxy (**3h** and **4h**). Also described are 7-methyl-*s*-triazolo[4,3-*a*]pyrazin-8(7*H*)one (**8b**) and its 3-methyl derivative (**9b**) together with imidazo[1,2-*g*]-*s*-triazolo[4,3-*a*]pyrazine (**10a**) and its 3-methyl derivative (**10b**). Complete spectral data for all of these molecules is presented.

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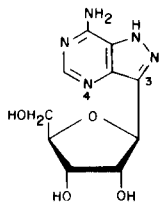
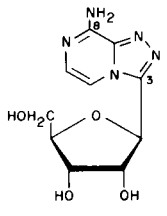
In recent years a number of biologically effective *C*-ribofuranosyl nucleosides have been isolated from natural sources (1) and have been of considerable value in biomechanistic and chemotherapeutic studies. One such molecule is formycin (**1**) which is isomeric to adenosine and owes its biological usefulness to its capability of substituting for adenosine in a variety of the processes which utilize this latter nucleoside (2). Stimulated by this formycin/adenosine relationship we have undertaken a program to seek more therapeutically beneficial C-nucleosides related to **1** (3) while, simultaneously, developing molecules which would add to the understanding of the active site demands of adenosine specific enzymes, which could be exploited in the design of agents to be employed for enzymatic inhibitory purposes.

One aspect of this program is focusing on an isomer of **1** (*i.e.*, **2**) in which the N_4 and C_{3a} atoms of **1** have been exchanged. However, prior to a synthesis of **2**, it was necessary to perform a variety of exploratory reactions which would be crucial to the realization of **2** and related molecules. Such investigations are described herein commencing with the preparation of **3a**, as the aglycone analog of **2**, and **4a**, as a model compound for **2**. Furthermore, other derivatives of **3** and **4** possessing C-8 substituents, which are known to render formycin related compounds and purine derivatives biologically functional (4), are also reported.



1



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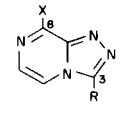
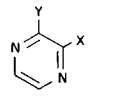
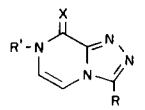


3 series R = H
4 series R = CH_3
a. X = NH_2
b. X = Cl
c. X = OH
d. X = SH
e. X = NHOH
f. X = SeH
g. X = OCH_3
h. X = SCH_3

Central intermediates to this study were 8-chloro- (**3b**) and 8-chloro-3-methyl-*s*-triazolo[4,3-*a*]pyrazine (**4b**). These molecules were obtained by chlorinating 2,3-dihydroxypyrazine (**5**) (5) to 2,3-dichloropyrazine (**6**) (6) and reacting this latter species with hydrazine to yield **7**. Treatment of **7** with triethyl orthoformate or triethyl orthoacetate then availed **3b** and **4b**. Subsequently, ammonolysis of **3b** and **4b** formed **3a** and **4a**, respectively, while subjecting **3b** and **4b** to sodium hydroxide, thiourea, hydroxylamine, and selenourea produced **3c** and **4c**, **3d** and **4d**, **3e** and **4e**, and **3f** and **4f**, respectively.



5. X = Y = OH
6. X = Y = Cl
7. X = $NHNH_2$, Y = Cl



8 series R = H
9 series R = CH_3
a. X = O, R' = H
b. X = O, R' = CH_3
c. X = S, R' = H
d. X = Se, R' = H

Inspection of the infrared spectral data for **3c** and **4c** suggests (see Table I) they exist predominantly in the keto tautomers (**8a** and **9a**) and, upon methylation, **3c**/**8a** and **4c**/**9a** formed the 7-methylated derivatives (**8b** and **9b**) exclusively. For correlation to **8b** and **9b** the isomeric methylated systems (**3g** and **4g**) were prepared from **3b** and **4b** and sodium methoxide. On the other hand, methylation of **3d** and **4d** yielded the 8-thiomethoxy derivatives (**3h** and **4h**) as evidenced by the disappearance of the thione absorbance in the infrared spectra for **3h** and **4h** which had prevailed in the spectra for **8c** (1335 cm^{-1}) and **9c** (1315 cm^{-1}). This latter observation, therefore, points to **8c** and **9c** as the principal tautomers for **3d** and **4d**. The isolation of **8b** and **9b** from **8a** and **9a**, yet **3h** and **4h** from **8c** and **9c** is merely a reflection of the difference in nucleophilicities of the order S > N > O. Extending these results to compounds **3f** and **4f** and considering the results of Townsend and Milne (7) with 7-selenoxo-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine

Table I

8-Substituted- and 3,8-Disubstituted-*s*-triazolo[4,3-*a*]pyrazines

Compound	Yield %	M.p. °C (a) (b)	Formula	Analyses % Calculated (Found) C	H	N	Ir (cm^{-1}) (c) ν	Pmr Data Chemical Shifts in δ (d) (e) C-3 Group	H-5, H-6	C-8 Group
3a	67	235-237 (d.p.) (M)	$C_5H_5N_5$	44.44 (44.31)	3.73 (3.84)	51.83 (51.71)	3300 (NH_2) 3140 (NH_2)	9.75	7.52 8.05	9.55
4a	90	294-296 (d.) (M)	$C_6H_7N_5$	48.32 (48.23)	4.73 (4.65)	46.95 (46.86)	3050 (NH_2)	3.16	7.67 7.92	9.44
3b	94	205-207 (d.p.) (M)	$C_5H_3ClN_4$	38.86 (38.76)	1.96 (1.94)	36.25 (36.30)	1610 (C=C)	9.55	7.78 8.64	
4b	92	206-207 (d.p.) (M)	$C_6H_5ClN_4$	42.75 (42.72)	2.99 (3.03)	33.23 (33.10)	1610 (C=C)	2.76	7.75 8.50	
3c (8a)	87	> 300 (M)	$C_4H_4N_4O$	44.12 (43.96)	2.96 (2.98)	41.16 (41.32)	3090 (NH) 1680 (C=O)	9.82	7.41 7.86	
4c (9a)	81	> 300 (E)	$C_6H_6N_4O$	48.00 (47.90)	4.03 (3.99)	37.32 (37.14)	3100 (NH) 1680 (C=O)	3.10	7.38 7.58	
3d (8c)	75	296-299 (d.p.) (M)	$C_5H_4N_4S$	39.46 (39.33)	2.64 (2.64)	36.82 (36.92)	3120 (NH) 1335 (C=S)	9.27	7.34 7.85	
4d (9c)	94	296-298 (M)	$C_6H_6N_4S$ (f)	39.12 (39.32)	4.38 (4.45)	30.41 (30.67)	3130 (NH) 1315 (C=S)	2.99	7.37 7.64	
3e	58	251-253 (d.) (W)	$C_5H_5N_5O$	39.74 (39.65)	3.33 (3.25)	46.34 (46.17)	3100 (NH) 1630 (C=C)	9.71	7.39 7.80	
4e	45	275-277 (d.) (W)	$C_6H_7N_5O$	43.64 (43.47)	4.27 (4.40)	42.40 (42.24)	3210 (NH) 1640 (C=C)	3.10	7.40 7.57	
3f (8d)	72	237-240 (d.p.) (W)	$C_5H_4N_4Se$	30.17 (30.16)	2.02 (2.00)	28.14 (28.13)	3070 (NH)	9.31	7.39 8.09	
4f (9d)	79	229-231 (d.p.) (W)	$C_6H_6N_4Se$ (h)	32.45 (32.65)	3.18 (3.17)	25.22 (25.70)	3110 (NH)	2.99	7.37 7.85	
3g	54 (g)	183-184 (M)	$C_6H_6N_4O$ (h)	45.28 (45.40)	4.43 (4.53)	35.20 (35.11)	1550 (C=C)	9.47	8.08 8.31	4.42
4g	64	207-210 (d.p.) (M)	$C_7H_8N_4O$	51.21 (51.35)	4.91 (4.96)	34.13 (34.20)	1620 (C=C)	3.05	8.09 (i)	4.41
3h	63	203-205 (I)	$C_6H_6N_4S$	43.36 (43.38)	3.64 (3.78)	33.71 (33.73)	1600 (C=C)	9.71	8.18 8.48	3.09

Table I (continued)

8-Substituted- and 3,8-Disubstituted-*s*-triazolo[4,3-*a*]pyrazines

Compound	Yield %	M.p. °C (a) (b)	Formula	Analyses % Calculated (Found) C	H	N	Ir (cm^{-1}) (c) ν	Pmr Data Chemical Shifts in δ (d) (e) C-3 Group	H-5,H-6	C-8 Group
4h	87	167-168 (I)	$C_7H_8N_4S$	46.65 (46.57)	4.47 (4.54)	31.09 (31.17)	1600 (C=C)	3.01	8.19	3.11
8b	53	> 300 (W)	$C_6H_6N_4O$	48.00 (48.03)	4.03 (4.09)	37.32 (37.19)	1680 (C=O)	9.69	7.41 7.87	3.81 (j)
9b	43	> 300 (W)	$C_7H_8N_4O$	51.21 (51.22)	4.91 (5.01)	34.13 (34.12)	1680 (C=O)	3.05	7.37 7.62	3.79 (j)

(a) Crystalline color--all white except **3d** (**8c**) and **4d** (**9c**) (both yellow), and **3f** (**8d**) and **4f** (**9d**) (both orange); the symbols following the temperature ranges are d. = melting with decomposition and d.p. = decomposition range. (b) Solvent system for purification: M, methanol; E, washed with diethyl ether; W, water: 1,2-propanol. (c) As compressed potassium bromide pellets. (d) In trifluoroacetic acid as solvent (except **3b** and **4b** which were performed in hexadeuteriodimethylsulfoxide) with tetramethylsilane as an internal standard. (e) The C-3 group absorptions were all singlets and the H-5 and H-6 absorptions were all doublets (J = *ca.* 5 Hz) except for **4g** and **4h** where they coalesced to a singlet in trifluoroacetic acid. The C-8 (or C-7 (j)) group absorptions were either broad singlets (**3a** and **4a**) or simple singlets (**3g**, **4g**, **3h**, **4h**, **8b**, and **9b**). (f) Possesses 1.0 mole of hydration. (g) Compound **3g** has been recently described (11) but was not fully characterized. (h) Possesses 0.5 mole of hydration. (i) In hexadeuteriodimethylsulfoxide as solvent this absorption became a pair of one proton doublets δ 7.41 and δ 8.06 (in this solvent H-3 appeared as a singlet at δ 4.06). (j) This represents the C-7 methyl group absorption.

Table II

Ultraviolet Absorption Spectra for the *s*-Triazolo[4,3-*a*]pyrazines (**3**, **4**, **8**, **9**, and **10**)

Compound	*p*H 1 λ max nm	*p*H 1 log ε	Water λ max nm	Water log ε	*p*H 11 λ max nm	*p*H 11 log ε
3a	224.8	4.40	225.4	4.19	225.5	4.17
	230 sh	4.31	267 sh	3.79	267 sh	3.74
	252 sh	3.65	276 sh	3.85	277 sh	3.82
	261 sh	3.68	295	3.95	296	3.93
	293	3.94				
4a	228.4	4.30	230	4.12	203.5	3.95
	257 sh	3.58	236 sh	4.04	230	4.14
	265	3.62	259 sh	3.58	259 sh	3.65
	274 sh	3.65	268 sh	3.65	268 sh	3.70
	296.5	3.75	277 sh	3.70	277 sh	3.74
	322 sh	3.42	297	3.80	297	3.84
3b	216	4.42	216	4.42	216	4.39
	255	3.38	253	3.37	255	3.40
	261	3.40	262	3.41	264	3.44
	270 sh	3.44	270 sh	3.45	297	3.74
	299	3.73	297	3.74		
4b	203 sh	3.92	219	4.40	220	4.39
	211 sh	4.15	249	3.29	249	3.29
	220	4.39	256	3.34	256	3.34
	249	3.28	266	3.34	265	3.36
	256	3.33	274 sh	3.34	276 sh	3.37
	266	3.34	304	3.64	304	3.68
	276 sh	3.36				
	303	3.63				
3c (**8a**)	216	4.26	216	4.30	216	4.12
	248 sh	3.57	250 sh	3.60	276	3.81
	257 sh	3.60	256 sh	3.62	289 sh	3.80
	265 sh	3.64	266 sh	3.66		
	284	3.73	283	3.76		
4c (**9a**)	217	4.15	219	4.27	220 sh	4.05
	257	3.65	248	3.54	223	4.05
	285	3.62	255	3.54	268 sh	3.65
			265 sh	3.55	275	3.67
			284	3.65	292	3.63
3d (**8c**)	208.4	4.22	207.5	4.23	210.3	4.20
	268	3.84	268	3.84	270	3.76
	343 sh	4.08	342 sh	4.08	336.5	4.05
	353	4.13	353	4.13		
	365 sh	4.03	365 sh	4.02		
4d (**9c**)	210.2	4.25	212	4.26	209.8	4.31
	271	3.86	268	3.86	272	3.70
	355	4.08	309 sh	3.66	337	4.02
			342 sh	4.08		
			354	4.14		
3e	202 sh	3.90	226	4.14	228	4.13
	231	4.18	273	3.90	240 sh	4.09
	293	3.86	306 sh	3.68	283	3.89
	306 sh	3.82			303 sh	3.80
4e	200	3.83	234	4.13	201	3.87
	229	4.21	273	3.92	224	4.18
	249 sh	3.84	303 sh	3.70	240 sh	4.13
	295	3.86			280	3.92
					307 sh	3.76

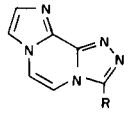
Table II (continued)

Ultraviolet Absorption Spectra for the *s*-Triazolo[4,3-*a*]pyrazines (**3**, **4**, **8**, **9**, and **10**)

Compound	*p*H 1 λ max nm	log ε	Water λ max nm	log ε	*p*H 11 λ max nm	log ε
3f (**8d**)	213	4.33	213	4.35	212.2	4.32
	291	3.72	262 sh	3.58	255 sh	3.74
	386	3.84	312	3.77	292 sh	3.70
			332 sh	3.69	317 sh	3.72
			382 sh	3.52	344	3.82
4f (**9d**)	217	4.27	217	4.31	215.7	4.29
	286	3.66	305	3.65	220 sh	4.24
	387	3.84	385	3.80	231 sh	3.98
					265 sh	3.79
					275	3.80
					287 sh	3.76
					353	3.54
3g	212.8	4.26	212	4.29	213	4.26
	239 sh	3.41	240 sh	3.39	239 sh	3.36
	248 sh	3.50	246 sh	3.46	249 sh	3.48
	256 sh	3.55	255 sh	3.55	255 sh	3.54
	267 sh	3.62	266 sh	3.64	266 sh	3.63
	278	3.70	278	3.71	278	3.70
	287 sh	3.53	286 sh	3.69	286 sh	3.68
	299 sh	3.48	301 sh	3.39	302 sh	3.36
4g	217	4.31	217	4.41	217	4.38
	242 sh	3.56	247 sh	3.52	247 sh	3.51
	249 sh	3.61	261 sh	3.62	258 sh	3.61
	258 sh	3.65	271 sh	3.69	269 sh	3.68
	269 sh	3.68	282	3.76	281	3.75
	283	3.76	287 sh	3.74	289 sh	3.73
	291 sh	3.75	304 sh	3.47	304 sh	3.46
	301 sh	3.59				
3h	207	4.42	208	4.44	210	4.35
	257	3.96	250 sh	3.90	258.5	4.15
	305 sh	4.09	257	3.97	270 sh	4.06
	314	4.13	262 sh	3.93	291 sh	4.04
	326 sh	4.00	305 sh	4.11	304 sh	4.12
			313	4.14	312	4.15
			325 sh	4.00	320 sh	4.06
4h	210	4.42	210	4.49	212	4.42
	259	3.97	259	4.01	258	4.01
	305 sh	4.02	291 sh	3.92	291 sh	3.92
	318	4.08	307 sh	4.06	306 sh	4.06
	332 sh	3.93	317	4.08	316	4.09
			331 sh	3.87	331 sh	3.87
8b	215.5	4.39	216	4.08	216.5	4.35
	250 sh	3.76	249 sh	3.43	251 sh	3.73
	257 sh	3.81	257 sh	3.48	257 sh	3.77
	266 sh	3.84	267 sh	3.51	267 sh	3.83
	282	3.90	283	3.57	283	3.86
9b	219	4.25	220.4	4.24	220	4.24
	251 sh	3.70	250 sh	3.57	249 sh	3.57
	258 sh	3.75	258	3.61	258	3.62
	267	3.76	267	3.62	267	3.63
	282 sh	3.75	285	3.67	285.5	3.68
10a	204 sh	4.16	209 sh	4.39	212 sh	4.17
	214 sh	4.32	225	4.50	219 sh	4.37
	220	4.38	231	3.47	225	4.49
	226	4.37	246	3.90	231	4.46
	231 sh	4.21	268 sh	3.87	246	3.89
	241 sh	3.93	277	3.92	269 sh	3.86
	262 sh	3.85	290	3.76	279	3.91
	277	3.95			290	3.76
	290 sh	3.74				
10b	221	4.37	220 sh	4.38	220 sh	4.38
	226 sh	4.36	227	4.51	226	4.51
	235 sh	4.20	233	4.49	233	4.48
	244 sh	4.03	247	3.93	246	3.91
	277	3.91	269 sh	3.84	269 sh	3.83
	287 sh	3.88	281	3.89	280	3.88
	299 sh	3.69	293	3.74	292	3.73

it can be assumed that **8d** and **9d** are the preferred tautomers for these derivatives.

A particularly valuable feature of formycin is its intrinsic fluorescence properties (2). As might be anticipated with the model studies described here, **3a** and **4a**, as well as the tricyclic molecules **10a** and **10b** which are aglycone systems structurally related to the fluorescent 3,N^4-ethenocytidine (8) and 1,N^6-ethenoadenosine (9), did not display any fluorescence spectral properties.



10a, R = H
b, R = CH_3

EXPERIMENTAL

All melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Ir spectra were recorded as compressed potassium bromide pellets on a Beckman AccuLab 3 spectrophotometer. The uv spectra were performed on a Perkin Elmer 200 spectrophotometer and the fluorescence spectra on a Perkin Elmer 512 spectrophotometer. The pmr spectra were obtained on a Varian EM-360 spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard. The pmr spin multiplicities are indicated by the symbols s (singlet), d (doublet), and m (multiplet). Elemental analyses were conducted by Galbraith Laboratories, Knoxville, Tennessee.

2,3-Dichloropyrazine (**6**).

Via a modification of two reported procedures (6) a solution of 1 g. (8.9 mmoles) of **5** (5) in 3.9 ml. (27 mmoles) of phenylphosphonic dichloride was heated at 150-170° for 2 hours. The solution was cooled to room temperature and then poured over 80 ml. of ice water, neutralized with 30 ml. of 1 *N* sodium hydroxide, and extracted with ether (4 x 100 ml.). The combined ether extracts were dried over anhydrous magnesium sulfate and then evaporated on a rotary evaporator to a red oil which was distilled *in vacuo* (6a) to yield **6** (1.36 g., 100%) as a clear liquid; pmr (neat): δ 8.5 (s, 2 H, aromatic H).

3-Chloro-2-hydrazinopyrazine (**7**).

2,3-Dichloropyrazine (**6**) (1 g., 6.7 mmoles) was dissolved in

2 ml. of 95% ethanol and to this was added, dropwise and with stirring, 1 ml. of 95% hydrazine. During the addition of the hydrazine the solution became quite warm and yellowish crystals began to precipitate. Following cooling of this mixture in an ice bath, the resultant material was isolated by filtration, washed with cold aqueous ethanol to yield **7** (0.62 g., 66%) which was recrystallized from ethanol as colorless crystals, m.p. 152-153°; pmr (hexadeuteriodimethylsulfoxide): δ 4.31 (s, 2 H, NH_2), 7.5 (d, J = 1 Hz, 1H, H-5 or H-6), 8.01 (d, J = 1 Hz, 1 H, H-5 or H-6), 8.2 (s, 1 H, NH); ir 3270 (NH) cm^{-1}.

Anal. Calcd. for $C_4H_5ClN_4$: C, 33.23; H, 3.49; N, 38.76. Found: C, 33.38; H, 3.78; N, 38.94.

8-Chloro-*s*-triazolo[4,3-*a*]pyrazine (**3b**) and 8-Chloro-3-methyl-*s*-triazolo[4,3-*a*]pyrazine (**4b**).

To a solution of 24 ml. of triethyl orthoformate (for **3b**) or 27 ml. of triethyl orthoacetate (for **4b**) in 75 ml. of dry (calcium chloride) xylene was added either 7.93 g. (54.8 mmoles) of **7** for **3b** or 9 g. (62.2 mmoles) of **7** for **4b** and the resulting mixture refluxed for 3 hours. After the reflux period, the solution was evaporated to dryness on a rotary evaporator and the residue purified and characterized as **3b** or **4b** as described in Tables I and II.

8-Amino-*s*-triazolo[4,3-*a*]pyrazine (**3a**) and 8-Amino-3-methyl-*s*-triazolo[4,3-*a*]pyrazine (**4a**).

To a solution of 60 ml. of anhydrous methanol containing 35 ml. of anhydrous ammonia was added 2 g. of **3b** (12.9 mmoles) or 2 g. of **4b** (11.9 mmoles) and this mixture then heated in sealed reaction vessel at 125° for 24 hours. After cooling and opening the reaction vessel and allowing the excess ammonia to evaporate at room temperature, the remaining methanolic solution was filtered to isolate the precipitated material. This product and that obtained from evaporation of the filtrate were combined and purified and characterized as **3a** or **4a** in the manners described in Tables I and II.

s-Triazolo[4,3-*a*]pyrazin-8(7*H*)one (**8a**) and 3-Methyl-*s*-triazolo-[4,3-*a*]pyrazin-8(7*H*)one (**9a**).

To a solution composed of 5 ml. of 25% aqueous sodium hydroxide and 32 ml. of methanol was added 2 g. of **3b** (12.9 mmoles) or **4b** (11.9 mmoles). The mixture was then refluxed for 3 hours, cooled to room temperature, and neutralized with concentrated hydrochloric acid. The white precipitate which formed at this time was isolated by filtration and characterized as **8a** or **9a** (see Tables I and II).

s-Triazolo[4,3-*a*]pyrazin-8(7*H*)thione (**8c**) and 3-Methyl-*s*-triazolo-[4,3-*a*]pyrazin-8(7*H*)thione (**9c**).

To 57 ml. of methanol was added 2 g. of **3b** (12.9 mmoles) or **4b** (11.9 mmoles) followed by 2 g. (26.3 mmoles) of thiourea. This mixture was refluxed for 10 minutes, cooled in an ice bath and the resultant yellow powder isolated by filtration and washed with cold methanol. The purification and characterization of this material as **8c** or **9c** is summarized in Tables I and II.

8-Hydroxylamino-*s*-triazolo[4,3-*a*]pyrazine (**3e**) and 8-Hydroxylamino-3-methyl-*s*-triazolo[4,3-*a*]pyrazine (**4e**).

Hydroxylamine hydrochloride (0.81 g., 12 mmoles for **3e** and 1.72 g., 24.8 mmoles for **4e**) was added to methanol (25 ml. for **3e**) or ethanol (30 ml. for **4e**) followed by dry triethylamine (1.6 ml. for **3e** and 3.5 ml. for **4e**). In turn, **3b** (1 g., 6.5 mmoles) or **4b** (0.71 g., 4.2 mmoles) was added to this and the mixture refluxed (25 minutes for **3e** and 2 hours for **4e**) and, following this period, the solution was cooled and the resultant precipitate isolated by filtration and washed with cold methanol. This material and that obtained from evaporation of the alcoholic filtrate were combined and purified and characterized as **3e** or **4e** as described in Tables I and II.

s-Triazolo[4,3-*a*]pyrazin-8(7*H*)selenone (**8d**) and 3-Methyl-*s*-triazolo[4,3-*a*]pyrazin-8(7*H*)selenone (**9d**).

In a manner analogous to that for the synthesis of **8c** and **9c**, 0.85 g. (6.9 mmoles) of selenourea (10) with 1 g. of **3b** (6.47 mmoles) or **4b** (5.93 mmoles) in 30 ml. of methanol produced **8d** or **9d** (see Tables I and II) following a 30 minute reflux period.

7-Methyl-*s*-triazolo[4,3-*a*]pyrazin-8(7*H*)one (**8b**) and 3,7-Dimethyl-*s*-triazolo[4,3-*a*]pyrazin-8(7*H*)one (**9b**).

Methyl iodide (2 g., 14 mmoles) in 15 ml. of 1 *N* potassium hydroxide solution was stirred at room temperature for 5 minutes and to this 1 g. of **8a** (7.35 mmoles) or **9a** (6.66 mmoles) was added. The resultant mixture was stirred at room temperature for 10 hours, cooled in an ice bath, and the precipitated material isolated by filtration and found to be **8b** or **9b** as presented in Tables I and II.

8-Methoxy-*s*-triazolo[4,3-*a*]pyrazine (**3g**) and 8-Methoxy-3-methyl-*s*-triazolo[4,3-*a*]pyrazine (**4g**).

Compound **3b** (2 g., 12.9 mmoles) or **4b** (1 g., 5.9 mmoles) was added to a freshly prepared sodium methoxide solution (0.9 g., 0.039 g.-atom of sodium in 40 ml. of absolute methanol for **3b**; 0.4 g., 0.017 g.-atom of sodium in 20 ml. of absolute methanol for **4b**) and the mixture refluxed for 1 hour. Following this period, the solution was cooled in an ice bath and the precipitated material isolated by filtration and combined with an additional amount of product obtained from partial evaporation of the methanolic filtrate. This solid was purified and characterized as **3g** or **4g** in the manners presented in Tables I and II.

8-Methylthio-*s*-triazolo[4,3-*a*]pyrazine (**3h**) and 3-Methyl-8-methylthio-*s*-triazolo[4,3-*a*]pyrazine (**4h**).

In a manner analogous to that used in preparing **8b** and **9b**, **8c** (1 g., 6.6 mmoles) and **9c** (1 g., 6 mmoles), when placed in 15 ml. of 1 *N* potassium hydroxide solution containing 1 g. (7 mmoles) of methyl iodide, yielded **3h** and **4h**, respectively, as described in Tables I and II.

Imidazo[1,2-*g*]-*s*-triazolo[4,3-*a*]pyrazine (**10a**).

Bromoacetaldehyde diethyl acetal (2.62 g., 2 ml., 13.3 mmoles) and 1 g. (7.4 mmoles) of **3a** were placed in 30 ml. of water. This mixture was then heated under reflux for 4 hours, cooled to room temperature, neutralized with 25% sodium hydroxide solution, and evaporated to dryness on a rotary evaporator. The brown residue was dissolved in methanol and this solution treated with petroleum ether to produce a precipitate which was isolated by filtration, redissolved in methanol, treated with decolorizing charcoal, and reprecipitated with petroleum ether to give 1.17 g. of a yellow compound. This solid was subjected to column chromatography (silica gel using chloroform-methanol (4:1) as the eluent) to produce 0.51 g. (44%) of crude **10a**. Subsequent recrystallization first from methanol-2-propanol (1:4) followed by absolute ethanol gave **10a** as white crystals, m.p. 247-248°; pmr (trifluoroacetic acid): δ 8.45 (m, 4 H, H-5, H-6, H-8, and H-9), 9.86 (s, 1 H, H-3); ir (potassium bromide): 1523 (C=C) cm^{-1}.

Anal. Calcd. for $C_7H_5N_5$: C, 52.83; H, 3.17; N, 44.00. Found: C, 52.79; H, 3.24; N, 44.08.

3-Methylimidazo[1,2-*g*]-*s*-triazolo[4,3-*a*]pyrazine (**10b**).

Bromoacetaldehyde diethyl acetal (2.62 g., 2 ml., 13.3 mmoles) and 1 g. (6.7 mmoles) of **4a** were mixed together in 30 ml. of water and heated at 70-80° (oil bath) for 4.5 hours. At this point more bromoacetaldehyde diethyl acetal (1 ml.) was added and

the temperature of the reaction raised to 105° (oil bath) and held at this point for 1 hour. The solution was then cooled in an bath and the precipitated material isolated by filtration and washed with cold water. Recrystallization of this material from methanol yielded white crystals of **10b**, m.p. 337-338° dec., in 48% (0.56 g.) yield; pmr (trifluoroacetic acid): δ 3.2 (s, 3 H, CH_3), 8.3 (d, 4 H, H-5, H-6, H-7, and H-8); ir (potassium bromide): 1580 (C=C) cm^{-1}.

Anal. Calcd. for $C_8H_7N_5$: C, 55.49; H, 4.07; N, 40.44. Found: C, 55.35; H, 4.11; N, 40.59.

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