Imidazo[1,5-*d*][1,2,4]triazines as Potential Antiasthma Agents

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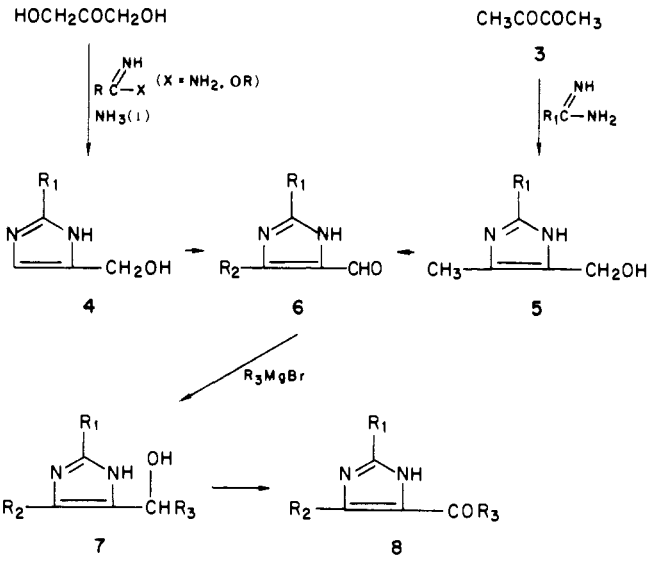
By using inhibition of histamine release from antigen-challenged, sensitized human basophils as a means of identifying a potentially prophylactic drug for the treatment of asthma, a series of substituted imidazo[1,5-*d*][1,2,4]triazines were found, which were active. These compounds were prepared by treating imidazolecarboxaldehydes with excess Grignard agent and then oxidizing the resulting alcohols to ketones with Jones reagent. Pyrolysis of a mixture of ketone and methyl carbazate at 200 °C in diphenyl ether produced the desired imidazo[1,5-*d*][1,2,4]triazines. Those compounds with the greatest basophil activity were tested for in vivo activity in the mouse passive cutaneous anaphylaxis (PCA) and the guinea pig passive anaphylaxis tests. The best compounds, 1-ethyl-8-methyl-6-propylimidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-one (**4–17**) and 1,8-dimethyl-6-propylimidazo[1,5-*d*][1,2,4]triazin-4-(3*H*)-one (**4–16**) were chosen for further study.

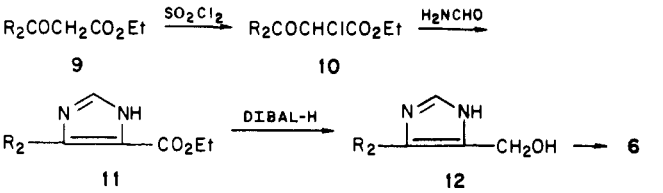
Mediators of immediate hypersensitivity such as histamine, leucotrienes, and others play an important role in the induction of an asthmatic attack.[1] Inhibition of the release of these mediators from activated mast cells or basophils is therefore an attractive approach to the development of a prophylactic drug for the treatment of asthmatics. During the last few years several compounds have been described as being capable of inhibiting the release of mediators from various tissues, but the question has been raised whether any drug currently being used for the treatment of asthma is achieving its clinical effect by this mechanism.[1c] The development of a drug with a well-defined action as a mediator release inhibitor would provide a novel means for the treatment of asthma. To this end we have synthesized, screened, and evaluated a large number of imidazo[1,5-*d*][1,2,4]triazines whose structure and activity we report.

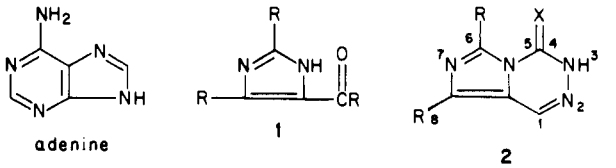
At the time this investigation was undertaken, other investigators were seeking a variety of biological activities such as phosphodiesterase inhibitors, purine analogues, antitumor compounds, and antibronchoconstrictors by exploring a number of bicyclic heterocycles resembling natural substances.[2] We chose to study the imidazotriazine system for two reasons: First, the imidazo[1,5-*d*]-[1,2,4]triazine was unknown and therefore had the desirable quality of novelty. Second, its structure resembles that of the adenine portion of cyclic adenosine 3′,5′-monophosphate (cAMP), which was known to be involved in the regulatory process of the mast cell. It could be speculated then that analogues of cAMP might possess antiasthmatic properties.

Scheme I



Scheme II





The most appropriate in vitro model to study inhibition of mediator release would be the human mast cell. However, such cells are not available in sufficient quantity to be useful in a screening format. Alternatives are the rat mast cell, which comes from an inappropriate species, or the human basophil, which although not fully appropriate does come from the proper species and shares several relevant properties with the mast cell.

In the present work we chose to follow, as the principle activity, the mediator release inhibitory properties of our

(1) Inter alia: (a) Kaliner, M.; Austen, K. F. "Bronchial Asthma Mechanisms and Therapeutics"; Weiss, E. B., Ed.; Little, Brown and Co.: Boston, 1976; p 163. (b) Lichtenstein, L. M. "Asthma-Physiology, Immunopharmacology and Treatment, Second International Symposium"; Lichtenstein, L. M., Austen, K. F., Eds.; Academic Press: New York, 1979; p 91. (c) Bach, M. K.; Johnson, H. G.; White, G. J. "Advances in Immunopharmacology"; Hadden, J., Chadid, L., Mullen, P., Eds.; Pergammon Press: Elmsford, NY, 1981; p 411. (d) Lichtenstein, L. M.; Osler, A. G. *J. Exp. Med.* **1964**, *120*, 507.

(2) Novinson, T.; Hanson, R.; Dimmitt, M. K.; Simon, L. N.; Robins, R. K.; O'Brien, D. E. *J. Med. Chem.* **1974**, 645. Novinson, T.; Senga, K.; Kobe, J.; Robins, R. K.; O'Brien, D. E.; Albert, A. A. *J. Heterocycl. Chem.* **1974**, *11*, 691. Senga, K.; Kobe, J.; Robins, R. K.; O'Brien, D. E. *J. Heterocycl. Chem.* **1975**, *12*, 893. Abushanab, E.; Bindra, A. P.; Goodman, L. *J. Org. Chem.* **1975**, *40*, 3379. White, D. F.; Burns, J. *J. Labeled Compd.* **1975**, *11*, 171. Clarke, R. W.; Garside, S. C.; Lunts, L. H. C.; Hartley, D.; Hornby, R.; Oxford, A. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1120. Elnagdi, M. H.; Kandeel, E. M.; Sadek, K. U. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1979**, *348*, 275. Senga, K. Novinson, T.; Wilson, H. R. *J. Med. Chem.* **1981**, *24*, 610.

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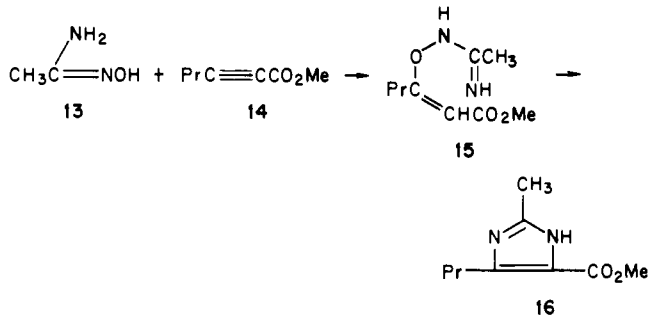
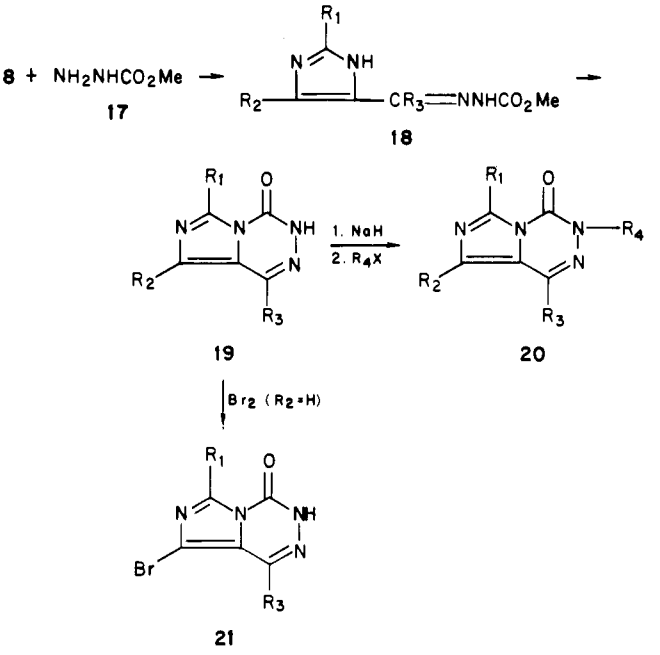
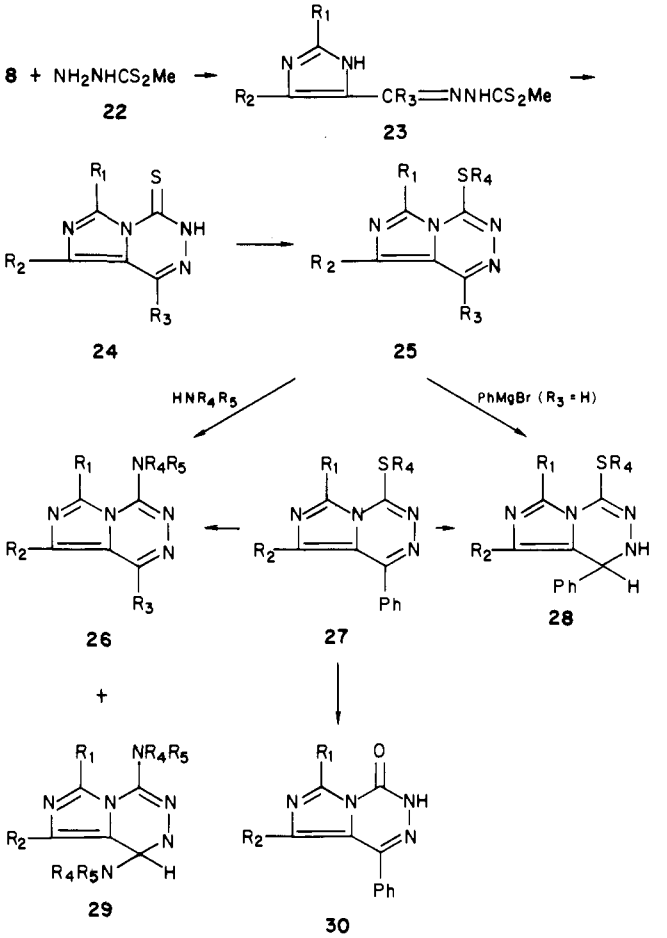
Scheme III



Scheme IV



Scheme V



compounds, as measured in vitro, in the human basophil test described by Lichtenstein et al.[1d] Compounds that were active in the basophil screen were further evaluated for in vivo activity in the mouse passive cutaneous anaphylaxis test (PCA) and in the more demanding animal model of systemic passive anaphylaxis in the guinea pig.

Chemistry. The approach to the imidazo[1,5-*d*]-[1,2,4]triazines[3] may be broken down into three steps: (1) the preparation of a 3-carbonylimidazole **1**; (2) the cyclization to an imidazotriazine **2**; (3) further elaboration of the bicyclic structure. Scheme I shows the formation of (hydroxymethyl)imidazole **4** from 1,3-dihydroxyacetone by the method of Schunak[4] and the formation of 5-(hydroxymethyl)-4-methylimidazole **5** by the method of Jacquier.[5] Each product was oxidized to **6** by 2.2 equiv of hot HNO_3[6] or, if R_1 contained a phenyl group, 20 equiv of cold HNO_3.[7] Details up to this point have been published.[3] To obtain 1-substitution in the imidazotriazine, **6** was reacted with a Grignard agent and the resulting alcohol **7** converted via Jones oxidation to **8**.

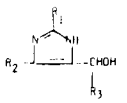
Thus far the synthetic methods described above have permitted only H or Me substitution in what will become the 8-position of the bicyclic system. Using the method of Durant et al.[8] (Scheme II), **9** was chlorinated with sulfuryl chloride and the resulting partially purified **10** refluxed with formamide to give **11**. Reduction of **11** with diisobutylaluminum hydride (DIBAL-H) gave **12**, which was oxidized with nitric acid to **6** (R_1 = H). Attempts to proceed directly from ester **11** to aldehyde **6** failed since at the low temperatures needed for partial reduction with diisobutylaluminum hydride, **11** was insoluble. Unfortunately, Scheme II could not be extended to disubstituted (hydroxymethyl)imidazoles. It was possible to make one disubstituted hydroxymethyl derivative by the method of Heindel.[9] This method (Scheme III) could certainly have been generalized but was not since the structure–activity relationships pointed in a different direction.

In Scheme III, acetamidoxime[10] (**13**) was reacted with methyl 2-hexynoate (**14**) to give **15**. Thermolysis in diphenyl ether induced a Cope rearrangement followed by an internal condensation to yield **16**. Reduction and oxidation as in Scheme II provided **6** (R_1 = Me, R_2 = Pr).

Imidazolecarboxaldehydes (**8**, R_3 = H) reacted with methyl carbazate (**17**) to furnish **18** (Scheme IV), which on thermolysis in diphenyl ether gave **19**.[3] However, when imidazole ketones (**8**, $R_3 \neq$ H) were employed under the same conditions, **18** could not be isolated and thin-layer chromatography (TLC) indicated the reaction was incomplete. After the solvent was removed, thermolysis of the crude residual mixture in diphenyl ether provided **19**. Bromination of **19** (R_1 = Pr; R_2, R_3 = H) probably reacted first in the 8-position (**21a**; R_1 = Pr, R_3 = H) and then in

(3) Paul, R.; Menschik, J. *J. Heterocycl. Chem.* **1979**, *16*, 277.
(4) Dziuron, P.; Schunack, W. *Arch. Pharmacol.* **1973**, *306*, 347.
(5) Imbach, J. L.; Jacquier, R.; Lacombe, J.-M. *Bull. Soc. Chim. Fr.* **1971**, 1052.
(6) Pyman, F. L. *J. Chem. Soc.* **1916**, 186.
(7) Diehls, O.; Schleich, K. *Chem. Ber.* **1916**, *49*, 1716.
(8) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Roe, A. R. GB 1 341 375, Dec 19, 1973.
(9) Heindel, N. A.; Chun, M. C. *Tetrahedron Lett.* **1971**, 1439.
(10) Nordmann, E. *Chem. Ber.* **1884**, *17*, 2746.

Table I. Preparation of Imidazole Alcohols



Compound	Substitution R_1	R_2	R_3	Yield %	MP °C	Recryst. Solvent	Method of Synth.	Starting Material	Formula[a]
1-1	2-C_6H_4OPr	H	H	40	90-92	EtOAc-PE	A	2-PrOC$_6H_4$ClOCH$_3$I=NH·HSO$_3$F[b]	$C_{13}H_{16}N_2O_2$
1-2	4-$C_6H_4OCH_3$	H	H	55	168-169	MeOH	A	4-MeOC$_6H_4$C(OMe)I=NH·HCl[c]	$C_{11}H_{12}N_2O_2$
1-3	CH_2Ph	Me	H	d	139.5-141.5	EtOAc	B	$PhCH_2ClNH_2$INH·HCl[e]	$C_{14}H_{12}N_2O\cdot I/8H_2O$
1-4	t-Bu	Me	H		195.5-196.5	2-PrOH	B	tBuClNH$_2$INH·HCl[f]	$C_9H_{16}N_2O$
1-5	Et	Me	H		oil		B	EtC(NH$_2$)=NH·HCl	$C_7H_{12}N_2O$[g]
1-6	H	Pr	H	28	95-100[h]	Me_2CO	C	2-34	$C_7H_{12}N_2O$
1-7	H	Et	H	58	84-85	Me_2CO-PE	C	2-35	$C_6H_{10}N_2O$
1-8	2-Pr	Me	H	36	157-161	2-PrOH	B	PrC(NH$_2$)=NH·HCl	$C_8H_{14}N_2O\cdot\frac{1}{2}H_2O$
1-9	H	2-Pr	H[h]						$C_7H_{12}N_2O$
1-10	Me	Pr	H	76	oil		C	2-33	$C_8H_{14}N_2O$[g]
1-11	$(CH_2)_{16}CH_3$	H	H	57	105-107	MeOH wash	A	$CH_3(CH_2)_{16}C(NH_2)$=NH·HCl[i]	$C_{21}H_{40}N_2O$
1-12	3-C_6H_4Cl	H	H	42	178-180	EtOH	A	3-ClC$_6H_4$ClOEt)=NH·HCl[j]	$C_{10}H_9ClN_2O$
1-13	CH_2OCH_3	Me	H	49		oil	B	$CH_3OCH_2ClNH_2$)=NH·HCl[k]	$C_7H_{12}N_2O_2$[g]
1-14	Pr	Me	Me	57	173-174	EtOH-H_2O	H	2-38	$C_9H_{16}N_2O$
1-15	Pr	Me	Et	54	193-196 d.	2-PrOH	H	2-38	$C_{10}H_{18}N_2O$[l]
1-16	Pr	Me	Pr	73	169-171 d.	EtOH-H_2O	H	2-38	$C_{11}H_{20}N_2O$
1-17	Pr	Me	Bu	10	177-179	EtOH	H	2-38	$C_{12}H_{22}N_2O$[m]
1-18	Pr	Me	2-Pr	57	196-197 d.	2-PrOH-Me_2CO	H	2-38	$C_{11}H_{20}N_2O\cdot\frac{1}{2}H_2O$
1-19	Pr	Me	cyclo-Pr	21	143-145 d.	EtOH-EtOAc	H	2-38	$C_{11}H_{18}N_2O\cdot\frac{1}{2}H_2O$
1-20	Me	Me	Me	46	141-143	CH_3CN	H	2-4	$C_7H_{12}N_2O$
1-21	CH_2OCH_3	Me	Me	24	gum		H	2-16	$C_8H_{14}N_2O_2$[g]
1-22	Me	Me	Et	34	150-152	EtOH-EtOAc	H	2-4	$C_8H_{14}N_2O$
1-23	Et	Me	Et	41	oil		H	2-8	$C_9H_{16}N_2O$[g]
1-24	sec-Bu	Me	Et	61	183-186	n-BuOH-CH_3CN	H	2-36	$C_{11}H_{20}N_2O$
1-25	t-Bu	Me	Et	53	131-134 d.	EtOAc	H	2-7	$C_{11}H_{20}N_2O$
1-26	Me	H	Pr		oil		H	2-37	$C_9H_{14}N_2O$[g]
1-27	Me	Me	Pr	40	157-160	CH_3CN	H	2-4	$C_9H_{16}N_2O$
1-28	CH_2-t-Bu	Me	H	98	189-191	2-PrOH	B	t-BuCH_2C(NH)NH$_2$·HCl[n,o]	$C_{10}H_{18}N_2O$
1-29	Pr	H	Me	42	84-86	CH_3CN	H	2-39	$C_8H_{14}N_2O$
1-30	sec-Bu	Me	H		oil		B	EtCHICH_3)C(NH)NH$_2$·HCl[n,p]	$C_9H_{16}N_2O$[g]
1-31	CH_2Ph	H	H[q]				A		
1-32	Ph	H	H[q]				A		
1-33	Me	Me	H[r]				B		
1-34	Pr	H	H[s]				A		
1-35	Pr	Me	H[s]				B		

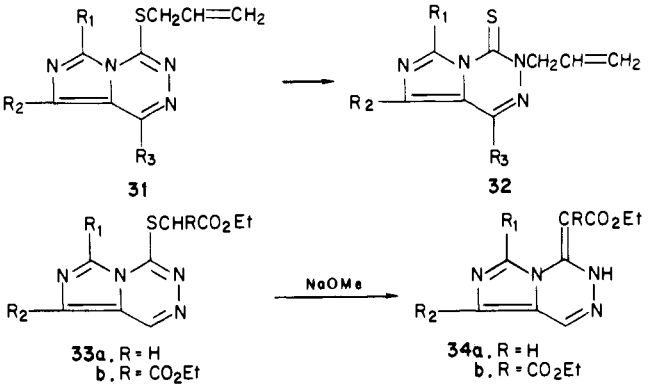
[a] Analyzed for C, H. N. [b] See Experimental Section. [c] Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* 1961, *26*, 412. [d] The product was an oil, a small sample of which was chromatographed for analysis. [e] Luckenbach, G. *Chem. Ber.* 1884, *17*, 1423. [f] Brown, D. J.; Evans, R. F. *J. Chem. Soc.* 1962, 4039. [g] Not analyzed. [h] A sample was recrystallized again for analysis, mp 103-104.5 °C. [i] Eitner, P.; Wetz, H. *Chem. Ber.* 1893, *26*, 2843. [j] DeWolfe, R. H.; Augustine, F. B. *J. Org. Chem.* 1965, *30*, 699. [k] Rule, H. G. *J. Chem. Soc.* 1918, *113*, 9. [l] C: calcd, 65.89; found, 66.40. [m] C: calcd, 68.53; found, 67.58. [n] The nitrile was converted to the crude amidine of the method of: Pinner, A.; Klein, F. *Chem. Ber.* 1877, *10*, 1889. [o] Homeyer, A. H.; Whitmore, F. C.; Wallingford, V. H. *J. Am. Chem. Soc.* 1933, *55*, 4209. [p] Neustadter, V. *Monatsch. Chem.* 1906, *27*, 929. [q] Reference 4. [r] Reference 5. [s] Reference 6.

the 1-position (**21b**; R_1 = Pr, R_3 = Br), since both **21a** and **21b** were isolated (HPLC), but no **19** (R_1 = Pr, R_2 = H, R_3 = Br) was found. Totally unsubstituted **19** (R_1, R_2, R_3 = H) with excess bromine gave tribromide **21** (R_1, R_3 = Br). Alkylation of **19** with sodium hydride and active alkyl halides produced **20**.

Scheme V shows the reaction of **8** with methyl thiocarbazate (**22**).[11] As in Scheme IV, **23** was crystalline if R_3 = H but not when R_3 = alkyl. In the latter case, thermolysis of the residue, left after removing the solvent from an attempted **23** preparation, gave **24**. Alkylation of **24** then produced **25**. If R_4 = Me (**25**), the SMe groups could be displaced by a variety of primary and secondary amines either neat or in refluxing toluene. When we had originally reported the latter reaction, we had hoped it would be general. More experience with this reaction showed some unexplained peculiarities. For instance, the reaction of **25** (R_1, R_2, R_3 = H; R_4 = Me) with 2-furfurylamine gave an 83% yield of product (**26**; R_1, R_2, R_3, R_4 = H; R_5 = furfuryl) after 7-h reflux in toluene, whereas benzylamine took 10 days of reflux in the same solvent to give a 56% yield of **26** (R_1, R_2, R_3, R_4 = H; R_5 = $PhCH_2$).

When a lengthy reflux period was necessary, the by-product **29** would appear. 3-Aminopyrazole gave very low

Scheme VI

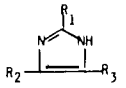


yields of **26** with refluxing toluene. Changing the solvent to refluxing water greatly improved the yield. In water it also was possible to effect the reaction of **25** with methylamine and dimethylamine. Unfortunately, ammonium hydroxide would not react with **25**.

When **25** (R_3 = H, R_4 = Me) was heated with phenylmagnesium bromide, **28** (R_4 = Me) was obtained. This reaction went well only with the phenyl Grignard. In one case, prolonged heating with an aliphatic Grignard was attempted, but only traces of the product were isolated. Dehydrogenation of **28** was effected by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, producing **27**, which was further reacted with an amine to yield **26**. Treatment of **27** with

(11) Audrieth, L. F.; Scott, E. S.; Kipper, P. S. *J. Org. Chem.* **1954**, *19*, 733.

Table II. Preparation of Imidazole Aldehydes, Ketones, and Esters



Compound	Substitution R_1	R_2	R_3	Yield %	MP °C	Recryst. Solvent	Starting Material	Method of Preparation	Formula[a]
2-1	2-C_6H_4OPr	H	CHO	79	104-105	EtOAc	1-1	C	$C_{13}H_{14}N_2O_2$
2-2	CH_2Ph	H	CHO	52	130-136	EtOAc	1-31	I	$C_{11}H_{10}N_2O\cdot\frac{1}{4}H_2O$
2-3	Ph	H	CHO	41	169-171.5	EtOH-H_2O	1-32	I	$C_{10}H_8N_2O$
2-4	Me	Me	CHO	62	164.5-166[b]	2-PrOH-EtOAc[c]	1-33	C	$C_8H_8N_2O\cdot1/8H_2O$
2-5	4-$C_6H_4OCH_3$	H	CHO	52	167-169	PhH-EtOH	1-2	I	$C_{11}H_{10}N_2O_2$
2-6	CH_2Ph	Me	CHO	24	169-172[d]	EtOH	1-3	I	$C_{12}H_{12}N_2O\cdot\frac{1}{4}H_2O$
2-7	t-Bu	Me	CHO	54	196-198	$CHCl_3$-PE[c]	1-4	C	$C_9H_{14}N_2O\cdot1/8H_2O$
2-8	Et	Me	CHO	32	103-104		1-5	C	$C_7H_{10}N_2O$[e]
2-9	H	Pr	CHO	22	138.5-141	Me_2CO	1-6	C	$C_7H_{10}N_2O$
2-10	H	Et	CHO	66	136-137	Me_2CO-PE	1-7	C	$C_6H_8N_2O$
2-11	2-Pr	Me	CHO	44	oil		1-8	C	$C_8H_{12}N_2O$[f]
2-12	H	2-Pr	CHO	75	158-160	H_2O	1-9	C	$C_7H_{10}N_2O$
2-13	Me	Pr	CHO	50	oil		1-10	C	$C_8H_{12}N_2O$[f]
2-14	$CH_3(CH_2)_{16}$	H	CHO	67	94-96	EtOH	1-11	C	$C_{21}H_{38}N_2O\cdot\frac{1}{4}H_2O$
2-15	3-C_6H_4Cl	H	CHO	53	166-172	EtOH-PE	1-12	I	$C_{10}H_7ClN_2O\cdot\frac{1}{4}H_2O$
2-16	CH_2OCH_3	Me	CHO	31	106.5-108	EtOAc	1-13	C	$C_7H_{10}N_2O_2$
2-17	Pr	Me	COMe	94	oil		1-14	J	$C_9H_{14}N_2O$
2-18	Pr	Me	COEt	78	63-67	$PhCH_3$	1-15	J	$C_{10}H_{16}N_2O$
2-19	Pr	Me	COPr	67	94-95	Hex	1-16	J	$C_{11}H_{18}N_2O$
2-20	Pr	Me	COBu	88	73-76[g]		1-17	J	$C_{12}H_{20}N_2O\cdot1/8H_2O$
2-21	Pr	Me	CO-2-Pr	80	103-105	$PhCH_3$	1-18	J	$C_{11}H_{18}N_2O$
2-22	Pr	Me	CO-cyclo-Pr	64	112-115	EtOAc-Cyhex	1-19	J	$C_{11}H_{16}N_2O\cdot1/8H_2O$
2-23	Me	Me	COMe	50	60-63[h]		1-20	J	$C_7H_{10}N_2O$[i]
2-24	CH_2OCH_3	Me	COMe	50	64-68[j]		1-21	J	$C_8H_{12}N_2O_3\cdot1/8H_2O$
2-25	Me	Me	COEt	66	89-91	Cyhex	1-22	J	$C_8H_{12}N_2O$
2-26	Et	Me	COEt	45	oil		1-23	J	$C_9H_{14}N_2O$[f]
2-27	sec-Bu	Me	COEt	92	bp 140-143/0.3 mm		1-24	J	$C_{11}H_{18}N_2O$
2-28	t-Bu	Me	COEt	66	97-100	Cyhex	1-25	J	$C_{11}H_{18}N_2O\cdot\frac{1}{4}H_2O$
2-29	Me	Me	COPr	64	106.5-116	EtOAc-PE	1-26	J	$C_8H_{12}N_2O$[k]
2-30	Me	Me	COPr	60	79-82	Et_2O	1-27	J	$C_9H_{14}N_2O$
2-31	CH_2-t-Bu	Me	CHO	39	144-145	EtOAC-Hex	1-28	C	$C_{10}H_{16}N_2O$
2-32	Pr	H	COMe	65	110-113	CH_3CN-Et_2O	1-29	J	$C_8H_{12}N_2O$
2-33	Me	Pr	CO_2Me	26	97-98.5	EtOAc[c]			$C_9H_{14}N_2O_2$
2-34	H	Pr	CO_2Et	24	171-174	2-PrOH	$PrCOCHClCO_2Et$	F	$C_9H_{14}N_2O_2$
2-35	H	Et	CO_2Et	27	160-170	Me_2CO-PE	$EtCOCHClCO_2Et$	F	$C_8H_{12}N_2O_2$
2-36	sec-Bu	Me	CHO	14	92-94	EtOAc	1-30	C	$C_9H_{14}N_2O$
2-37	Me	H	CHO[l]						$C_5H_6N_2O$
2-38	Pr	Me	CHO[m]				1-35		$C_8H_{12}N_2O$
2-39	Pr	H	CHO[m]				1-34		$C_7H_{10}N_2O$
2-40	Ph	Me	CHO[n]						$C_{11}H_{10}N_2O$
2-41	H	Me	CHO[o]						$C_5H_6N_2O$

[a] Analyzed for C, H, and N if the compound was new. [b] Recrystallized again for analysis; mp 166-168.5 °C. [c] Chromatographed on silica gel first. [d] Recrystallized from 2-PrOH for analysis; mp 171-174 °C. [e] C: calcd, 60.85; found, 60.36. [f] No analysis. [g] Distilled bp 140-145 °C (0.2 mm). [h] Distilled bp 128-133 °C (0.25 mm). [i] N: calcd, 20.28; found, 19.80. [j] Distilled bp 140-149 °C (0.1 mm). [k] N: calcd, 18.41; found, 17.27. [l] Streith, J.; Leibovici, C.; Martz, P. *Bull. Chim. Soc. Fr.* 1971, 4159. Abushanab, E.; Lee, D.-Y.; Goodman, L. *J. Org. Chem.* 1975, *40*, 3376. [m] Reference 3. [n] Diehls, O.; Schleich, K. *Chem. Ber.* 1916, *49*, 1711. [o] Hubball, W.; Pyman, F. L. *J. Chem. Soc.* 1928 21.

hydrogen peroxide in acetic acid produced **30**.

Since alkylation of the thiones went predominently on sulfur, the Claisen rearrangement could be used to convert **31** to **32** (Scheme VI). Eschenmoser sulfur extrusion[12] produced **34** from **33**.

The first step of this reaction is postulated to be the abstraction of a proton α to the carbonyl group. If this were the case, making the α-hydrogens more acidic should help the reaction. Indeed, when we tried to alkylate the sodium salt of **24** (R_1, R_2, R_3 = H) with diethyl bromomalonate instead of getting **33b** (R_1, R_2 = H), we obtained **34b** (R_1, R_2 = H) directly.

Results and Discussion

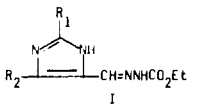
The biological activity of these imidazo[1,5-*d*][1,2,4]-triazines was assessed by measuring their ability to inhibit the release of histamine from antigen-challenged basophils, from allergic human donors. A concentration of 48 μM was chosen as an arbitrary cutoff for identifying potentially interesting compounds. If a compound reduced histamine release more than 50% at this concentration, it was further tested in a concentration–response format so that an IC_{50} could be estimated. Initially, higher values were accepted; hence, some compounds in the tables were tested at values above 48 μM. The synthetic effort was guided in a large part by the results of this assay. Active compounds were further evaluated in the mouse PCA and in the guinea pig anaphylaxis tests for in vivo activity.

Structure–Activity Relationships

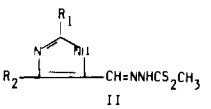
In examining the results in Table IV, it is apparant that when the 3- and 4-substituents of the imidazo[1,5-*d*]tri-

(12) Singh, H.; Narula, S. S.; Ghandi, C. S. *Tetrahedron Lett.* **1977**, 3747.

Table III. Preparation of Imidazole Hydrazones



I



II

Compound	Structure	Substitution R_1	Substitution R_2	Yield %	MP[a] °C	Recryst.[b] Solvent	Starting Material	Formula[c]
3-1	I	2-C_6H_4OPr	H	80	129-132	EtOAc	2-1	$C_{16}H_{20}N_4O_3$
3-2	I	CH_2Ph	H	87	184-185	EtOH	2-2	$C_{14}H_{16}N_4O_2$
3-3	I	Ph	H	95	196-200 d.	EtOAc	2-3	$C_{13}H_{14}N_4O_2$
3-4	I	Ph	Me	98	209-211 d.	MeOH	2-40	$C_{14}H_{16}N_4O_2 \cdot \frac{1}{4}H_2O$
3-5	I	Me	Me	90	207.5-210	EtOH	2-4	$C_9H_{14}N_2O_4 \cdot \frac{1}{4}H_2O$
3-6	I	4-$C_6H_4OCH_3$	H	85	192-193	EtOH-PE	2-5	$C_{14}H_{16}N_4O_3$
3-7	I	Me	H	83	210.5-211.5	EtOH	2-37	$C_8H_{12}N_4O_2$
3-8	I	H	Me	95	195-203 d.	EtOH	2-41	$C_8H_{12}N_4O_2$
3-9	I	CH_2Ph	Me	93	185-189	EtOAc-EtOH	2-6	$C_{15}H_{18}N_4O_2$
3-10	I	t-Bu	Me	82	226-228.5	EtOH	2-7	$C_{12}H_{20}N_4O_2$
3-11	I	Et	Me	82	208-212 d.		2-8	$C_9H_{14}N_4O_2 \cdot 1/8H_2O$
3-12	I	H	Pr	90	122-124	EtOH	2-9	$C_{10}H_{16}N_4O_2$
3-13	I	H	Et	38	189-191	EtOH	2-10	$C_9H_{14}N_4O_2$
3-14	I	2-Pr	Me[d]	30	187-192		2-11	$C_{10}H_{16}N_4O_2$
3-15	I	H	2-Pr	30	157-158	Chromat.	2-12	$C_{10}H_{16}N_4O_2$
3-16	I	Me	Pr	61	176-179.5	EtOH	2-13	$C_{11}H_{18}N_4O_2$
3-17	II	H	Me	94	180d.	EtOH	2-41	$C_7H_{10}N_4S_2 \cdot 1/8C_2H_5OH$
3-18	II	Ph	H	88	166-170 d.	MeOH	2-3	$C_{12}H_{12}N_4S_2 \cdot CH_3OH$
3-19	II	Ph	Me	96	180-185d.	EtOH	2-40	$C_{13}H_{14}N_4S_2 \cdot \frac{1}{4}C_2H_5OH$
3-20	II	$(CH_2)_{16}CH_3$	H	70	65-74	MeOH	2-14	$C_{23}H_{42}N_4S_2 \cdot \frac{1}{2}H_2O$
3-21	II	3-C_6H_4Cl	H	15	157-159	MeOH-boil	2-15	$C_{12}H_{11}ClN_4S_2 \cdot CH_3OH$
3-22	II	Me	Me	94	198d.	MeOH	2-4	$C_8H_{12}N_2S_2$
3-23	II	Me	H	94	175d.	EtOH	2-37	$C_7H_{10}N_4S_2$
3-24	II	Et	Me	83	164-166	2-PrOH	2-8	$C_9H_{14}N_4S_2$
3-25	II	H	Pr	93	163-164	Me_2CO-PE	2-9	$C_9H_{14}N_4S_2$
3-26	II	H	Et	80	175d.	EtOH	2-10	$C_8H_{12}N_4S_2$
3-29	II	2-Pr	Me	78	162-163	EtOH-H_2O	2-11	$C_{10}H_{14}N_4S_2$[e]
3-30	II	H	2-Pr	81	153-154d.	Me_2CO-PE	2-12	$C_9H_{14}N_4S_2$
3-31	II	CH_2OCH_3	Me	50	150-152	2-PrOH	2-16	$C_9H_{14}N_4OS_2$

[a] Melting points of these compounds are of limited significance since the products were mixtures of syn and anti isomers. On recrystallization, a separation of isomers was often observed as determined by NMR. In addition, almost all of the compounds cyclized on melting, exhibiting a second melting point. Detailed experimental description is given in ref 3. [b] Recrystallized for analysis only. [c] Anal. C, H, N, S. [d] Methyl ester. [e] Used crude—no analysis.

azine are H and carbonyl, respectively, the 8-substituent must be methyl or bromo for the compound to be active (**4-13**, **4-16**, **4-17**, **4-18**, **4-26**, **4-27**, **4-28**, **4-35**, **4-38**, **4-41**) (with the single anomaly of **4-45**). The 6-position may be substituted by aliphatic groups from C_2 to C_4 and also bromine, while the 1-position may vary from hydrogen to *n*-propyl or bromine for activity (again with **4-45** as an anomaly).

In Table V, variations at the 3-position are described. To retain activity, the 6- and 8-positions must be substituted by propyl and methyl groups, respectively (**5-3**, **5-7**, **5-29**, **5-30**). The 3-substituents, allyl and methyl, make the activity slightly better if there was no 1-substitution (compare **5-3** and **5-7** to **4-15**). With a 1-substituent in place, the addition of a 3-methyl or 3-allyl group did not improve the activity (compare **4-18** to **5-29** or **5-30** and compare **4-16** to **5-28**). Substitution of a variety of groups at position 3, of the more active members of Table IV, resulted in a total loss of activity (**5-31** to **5-40**). Two of the thiones on Table VI (**6-9**, **6-22**) and two of the thioethers in Table VII (**7-9**, **7-10**) had basophil activity, but all four lacked in vivo activity. Of the 4-amine substitutions in Table VIII, only amino heterocycles (**8-12**, **8-13**) showed any activity, with 3-aminopyrazoles (Table IX) being active with a variety of 1-, 6-, and 8-substituents (**9-3**, **9-6**, **9-7**, **9-14**, **9-15**). Unfortunately, none of the amines had in vivo activity.

At this point it was concluded that 6-propyl and 8-methyl substitution gave the best basophil activity. A comparison of 1-substitution, **4-15** through **4-22**, demonstrated that the activity peaked when R_1 was methyl, ethyl, or propyl. The guinea pig anaphylaxis and mouse PCA tests for a further comparison of these three (Table XI) indicated the 1-propyl (**4-18**) had only borderline activity in the guinea pig assay. Thus, **4-16** and **4-17** were chosen for further evaluation.

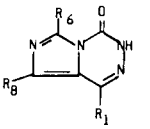
Experimental Section

Melting points were taken on a Mel-Temp block and are uncorrected. The instruments used for spectra were as follows: ^1H and ^{13}C nuclear magnetic resonance, Varian FT 80; ultraviolet, Hewlett-Packard 4050A; infrared, Nicolet 7199; mass, Finnigan-MAT CH7. All compounds had IR and ^1H NMR spectra that were compatible with published data.[3] Compounds without references were commercially available. In vitro human basophil histamine release was measured as described by Siraganian.[13]

Column chromatography was carried out by evaporating a MeOH solution of impure material onto a small amount of silica gel. The dried gel was placed on top of a wet silica gel column (CCl_4). The column was eluted with $CHCl_3$ and then 1% increments of MeOH to 10% MeOH/$CHCl_3$. TLC was carried out

(13) Siraganian, R. P. *J. Allergy Clin. Immunol.* **1976**, *57*, 525. Siraganian, R. P.; Hook, W. A. *J. Immunol.* **1977**, *119*, 2078.

Table IV. Synthesis and Activities of Imidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-ones



Compound	R_1	R_6	R_8	Yield %	MP °C	Recryst. Solvent	Starting Material	Method of Synthesis	Bas[a] IC_{50}	Formula[b]
4-1	H	H	H		Ref 3				1	$C_5H_4N_4O$
4-2	H	2-C_6H_4OPr	H	81	199-200	MeOH	3-1	O	1	$C_{14}H_{14}N_4O_2$
4-3	H	CH_2Ph	H	94	215-217	MeOH-PhH	3-2	O	1	$C_{12}H_{10}N_4O$
4-4	H	Ph	H	74	245-248	MeOH	3-3	O	1	$C_{11}H_8N_4O$
4-5	H	Ph	Me	78	182-184.5	PhH	3-4	O	1	$C_{12}H_{10}N_4O$
4-6	H	Pr	H		Ref 3				1	$C_8H_{10}N_4O$
4-7	H	Me	Me	70	263-263.5	MeOH	3-5	O	1	$C_7H_8N_4O$
4-8	H	4-$C_6H_4OCH_3$	H	69	241-242.5	MeOH-PhH	3-6	O	1	$C_{12}H_{10}N_4O_2$
4-9	H	t-Bu	H		Ref 3				1	$C_9H_{12}N_4O$
4-10	H	Me	H	94	303-305.5	MeOH wash	3-7	O	1	$C_6H_6N_4O$
4-11	H	H	Me	87	276-282	MeOH	3-8	O	1	$C_6H_6N_4O$
4-12	H	CH_2Ph	Me	87	244-247	MeOH	3-9	O	1	$C_{13}H_{12}N_4O$
4-13	H	t-Bu	Me	81	198-200	2-PrOH	3-10	O	31 (1)	$C_{10}H_{14}N_4O$
4-14	H	CH_2OCH_3	H		Ref 3				1	$C_7H_8N_4O_2$
4-15	H	Pr	Me		Ref 3				56.8±5.5 (66)	$C_9H_{12}N_4O$
4-16	Me	Pr	Me	87	152-153	CCl_4-Hex[c]	2-17	K	14±1.0 (291)	$C_{10}H_{14}N_4O$
4-17	Et	Pr	Me	59	147-150	CH_3CN	2-18	K	15.6±3.5 (22)	$C_{11}H_{16}N_4O$
4-18	Pr	Pr	Me	69	145-146	CCl_4-Hex	2-19	K	16±7.0 (8)	$C_{12}H_{18}N_4O$
4-19	Bu	Pr	Me	33	139-142	$CHCl_3$-Hex	2-20	K	1	$C_{13}H_{20}N_4O \cdot 1/8H_2O$
4-20	2-Pr	Pr	Me	20	188-190	CH_3CN	2-21	K	1	$C_{21}H_{18}N_4O$
4-21	Cyclo-Pr	Pr	Me	25	170-172	EtOAc	2-22	K	1	$C_{12}H_{16}N_4O$
4-22	Ph	Pr	Me	58	210-211	Me_2CO-PE	7-31	O	1	$C_{15}H_{16}N_4O$
4-23	Me	Me	Me	53	302-305	DMF	2-23	K	Fl	$C_8H_{10}N_4O$
4-24	Me	CH_2OCH_3	Me	23	160-163	EtOAc	2-24	K	1	$C_9H_{12}N_4O_2$
4-25	Et	Me	Me	65	247-249	EtOH	2-25	K	1	$C_9H_{12}N_4O$
4-26	Et	Et	Me	58	206-208	EtOH	2-26	K	24±13.0 (3)	$C_{10}H_{14}N_4O$
4-27	Et	sec-Bu	Me	54	133-135	Et_2O-PE	2-27	K	45±13.2 (9)	$C_{12}H_{18}N_4O$
4-28	Et	t-Bu	Me	54	142-145	EtOAc-Cyhex	2-28	K	26±8.4 (4)	$C_{12}H_{18}N_4O$
4-29	H	Et	Me	84	170-172	2-PrOH	3-11	O	1	$C_8H_{10}N_4O$
4-30	H	CH_2Ph	Br	57	185-187	CH_3CN	4-3	L	1	$C_{12}H_9BrN_4O$
4-31	H	H	Pr	81	128-129	H_2O	3-12	O	1	$C_8H_{10}N_4O$
4-32	H	H	Et	91	207-209	H_2O	3-13	O	1	$C_7H_8N_4O$
4-33	Br	CH_2OCH_3	Br	21	201-202	EtOH[d]	4-14	L	1	$C_7H_6Br_2N_4O_2$
4-34	H	2-Pr	Me	74	175-178	2-PrOH	3-14	O	1	$C_9H_{12}N_4O$
4-35	H	t-Bu	Br	50	151	DME-Heptane	4-9	L	19 (1)	$C_9H_{11}BrN_4O$
4-36	H	CH_2OCH_3	Br	2	177	CH_3CN[d]	4-14	L	1	$C_7H_7BrN_4O_2 \cdot \frac{1}{4}H_2O$
4-37	H	H	2-Pr	83	207-208	Hex wash	3-15	O	1	$C_8H_{10}N_4O$
4-38	Br	Pr	Br	22	200	CH_3CN[d]	4-6	L	48±22 (4)	$C_8H_8Br_2N_4O$
4-39	H	Pr	Br	39	162-163	CH_3CN[d]	4-6	L	1	$C_8H_9BrN_4O$
4-40	H	CH_2-t-Bu	Me	62	127-130	CCl_4	2-31	K	1	$C_{11}H_{16}N_4O$
4-41	Br	Br	Br	2	276-277	EtOH[d]	4-1	L	27±4.9 (6)	$C_5HBr_3N_4O$[e]
4-42	Me	Pr	H	97	197-199	EtOH	2-32	K	1	$C_9H_{12}N_4O$
4-43	Ph	2-Pr	Me	29	185-186	Me_2CO-PE	7-37	O	1	$C_{15}H_{16}N_4O$
4-44	Ph	Et	Me	60	239-241	EtOAc	7-36	O	1	$C_{14}H_{14}N_4O$[f]
4-45	Ph	H	H	83	289-293	DMF-Me_2CO	7-28	O	19±8 (3)	$C_{11}H_9N_4O$
4-46	Pr	Me	H	36	217.5-218.5	EtOH	2-29	K	1	$C_9H_{12}N_4O$
4-47	H	Me	Pr	74	133-134.5d.	EtOAc	3-16	O	1	$C_9H_{12}N_4O$
4-48	Pr	Me	Me	51	198-201	EtOH	2-30	K	1	$C_{10}H_{14}N_4O$

[a] Dose in μM at which 50% inhibition of histamine release from basophils was seen. Inactive was defined as $IC_{50} > 48$ μM. Initially we screened at a higher dose, and some higher values are listed. The standard error and number of experiments are shown. FL means fluoroescent compound, obscuring the histamine assay. See Table XI for comparison to theophylline. [b] Anal. C, H, N, and Br for new compounds. [c] Hex = hexane; Cyhex = cyclohexane; DME = dimethoxyethane. [d] Purified by high-pressure liquid chromatography first. [e] Br: calcd, 63.08; found, 64.30. [f] No analysis. Mass spectrum, M^+: theory, 254.1168; found, 254.1170.

on silica gel plates, using MeOH/$CHCl_3$ (1:3 or 1:19).

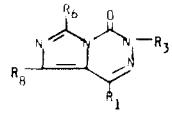
Methods A–E. These methods have been previously published in detail[3] for the compounds shown.

method	compd
A ($RC(NH)NH_2$ + $HOCH_2COCH_2OH$)	1-34
B ($RC(NH)NH_2$ + $CH_3COCOCH_3$)	1-35
C (HNO_3 oxidn)	2-38
D (thermolysis)	4-1
E ($RSMe + HNR_2$)	8-2

Ethyl 5-Propyl-4-imidazolecarboxylate (2-34). Method F. By the method of Falco et al.[14] 15.8 g (0.100 mol) of ethyl butyrylacetate in 20 mL of $CHCl_3$ was treated with 8.11 mL (13.5 g, 0.100 mol) of sulfuryl chloride at such a rate that the temperature did not rise above 35 °C. After the reaction was stirred for 30 min, while copious amounts of hydrogen chloride came off, the reaction was refluxed for 2 h. On cooling, the clear solution was washed with water, with aqueous $KHCO_3$, and again with water. The organic layer was dried (Na_2SO_4), concentrated under vacuum to an oil, and then distilled to give 17.02 g (88%) of light

(14) Falco, E. A.; Russell, P. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1951**, *73*, 3753.
(15) Emele, J. F. U.S. Patent 3 068 147, 1962; *Chem. Abstr.* **1963**, *58*, P10136*b*.

Table V. Preparation and Activities of 3-Substituted Imidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-ones



Compound	R_1	R_3	R_6	R_8	Yield %	MP or BP °C	Recryst. Solvent	Starting Material	Alkylating Agent[a]	8as[b] IC_{50}	Formula[c]
5-1	H	Me	CH_2Ph	H	54	74-75	Mecyhex[d]	4-3	C	1	$C_{13}H_{12}N_4O$
5-2	H	$CH_2CH=CH_2$	Me	Me	37	60-62	Et_2O-Hex	4-7	B	73±22 (14)	$C_{10}H_{12}N_4O$
5-3	H	$CH_2CH=CH_2$	Pr	Me	73	bp 125-130/.5 mm		4-15	B	40±15 (7)	$C_{12}H_{16}N_4O$
5-4	H	$CH_2CH=CH_2$	Et	Me	57	69-71	Cyhex[e]	4-29	B	I	$C_{11}H_{14}N_4O$
5-5	H	$CH_2CH=CH_2$	t8u	Me	75	bp 145-150/.03 mm		4-13	B	1	$C_{13}H_{18}N_4O$
5-6	H	$CH_2CH=CH_2$	Me	H	63	97-99	Cyhex	4-10	B	1	$C_9H_{10}N_4O$
5-7	H	Me	Pr	Me	61	74.5-77	EtOAc-cyhex	4-15	C	20±5 (6)	$C_{10}H_{14}N_4O$
5-8	H	$CH_2CH=CH_2$	CH_2OCH_3	H	50	103-106	EtOAc	4-14	B	1	$C_{10}H_{12}N_4O_2$
5-9	H	CH_2CO_2Et	CH_2OCH_3	H	39	87-89	Cyhex	4-14	D	I	$C_{11}H_{14}N_4O_4$
5-10	H	$CH_2CH=CH_2$	H	H	65	95-97	Cyhex	4-1	B	1	$C_8H_8N_4O$
5-11	H	CH_2CO_2Et	H	H	78	130-132	Et_2O	4-1	D	1	$C_9H_{10}N_4O_3$
5-12	H	$CH_2CH=CH_2$	4-$C_6H_4OCH_3$	H	49	82-84	Cyhex	4-8	B	1	$C_{15}H_{14}N_4O_2$
5-13	H	$CH_2CH=CH_2$	CH_2Ph	H	75	bp 145-150/.03 mm		4-3	B	I	$C_{13}H_{18}N_4O$
5-14	H	$CH_2CH=CH_2$	H	Me	62	53-55	Cyhex	4-11	D	1	$C_9H_{10}N_4O$
5-15	H	CH_2CO_2Et	H	Me	60	150-152	CH_3CN	4-11	D	1	$C_{10}H_{12}N_4O_3$
5-16	H	$CH_2CH=CH_2$	CH_2Ph	Br	23	oil	Chromat.	4-30	B	1	$C_{15}H_{13}BrN_4O$
5-17	H	CH_2cyclopropyl	Pr	Me	53	bp 118-121/.01 mm		4-15	E	1	$C_{13}H_{18}N_4O$
5-18	H	$CH_2CH=CHCO_2Et$	Pr	Me	20	bp 175-179/.03 mm		4-15	F	I	$C_{15}H_{20}N_4O_3$
5-19	H	$CH_2CH=CH_2$	H	Pr	75	bp 109-112/.005 mm		4-31	B	1	$C_{11}H_{14}N_4O$
5-20	H	$CH_2CH=CH_2$	H	Et	48	bp 112-115/.2 mm[f]		4-32	B	1	$C_{10}H_{12}N_4O$
5-21	H	$CH_2CH=CH_2$	2-Pr	Me	69	bp 106-110/.2 mm		4-34	B	1	$C_{12}H_{16}N_4O$
5-22	H	$CH_2CH=CH_2$	CH_2Ph	Me	53	bp 155-158/.1 mm		4-12	B	1	$C_{16}H_{16}N_4O$
5-23	H	CH_2CO_2Et	Pr	Me	50	70-73	Cyhex	4-15	D	1	$C_{13}H_{18}N_4O$
5-24	H	Et	Pr	Me	25	bp 100-105/.03 mm[g]		4-15	G	1	$C_{11}H_{16}N_4O$
5-25	H	Me	Me	Me	50	140-143	Cyhex	4-7	C	1	$C_8H_{10}N_4O$
5-26	Br	$CH_2CH=CH_2$	Pr	Br	50	84-86	Cyhex	4-38	B	1	$C_{11}H_{12}Br_2N_4O$
5-27	H	$CH_2CH=CH_2$	Pr	Br	74	bp 125-130/.1 mm		4-39	B	1	$C_{11}H_{13}BrN_4O$
5-28	Me	$CH_2CH=CH_2$	Pr	Me	77	83-84	PE	4-16	B	69 (1)	$C_{13}H_{18}N_4O$
5-29	Pr	$CH_2CH=CH_2$	Pr	Me	93	bp 170-180/.25 mm		4-18	B	29±29 (3)	$C_{15}H_{22}N_4O$[h]
5-30	Pr	Me	Pr	Me	82	bp 130-140/.15 mm		4-18	C	18±6.4 (7)	$C_{13}H_{20}N_4O$[i]
5-31	Me	CH_2CO_2Et	Pr	Me	49	65-68	Hex	4-16	D	I	$C_{14}H_{20}N_4O_3$
5-32	Me	$CH_2CH=CH_2$	Pr	Me	40	120-123	Me_2CO-Hex	4-16	H	1	$C_{13}H_{16}N_4O$
5-33	Me	$CH=C=CH_2$	Pr	Me	19	85-92	Me_2CO-Hex	4-16[j]	H	I	$C_{13}H_{16}N_4O$
5-34	Me	Me	Pr	Me	50	82-83	Me_2CO-Hex	4-16	C	1	$C_{11}H_{16}N_4O$
5-35	Me	Et	Pr	Me	86	98.5-101.5	Me_2CO-Hex	4-16	G	I	$C_{12}H_{18}N_4O$
5-36	Me	Pr	Pr	Me	92	101-104	Me_2CO-Hex	4-16	I	I	$C_{13}H_{20}N_4O$
5-37	Me	CH_2Ph	Pr	Me	76	90-93	Me_2CO-Hex	4-16	A	1	$C_{17}H_{20}N_4O$
5-38	Me	CH_2CO_2H	Pr	Me	79	217-221	Me_2CO-CH_2Cl_2	4-16	J	1	$C_{12}H_{16}N_4O_3$
5-39	Me	$CH_2CHOHCH_2OH$	Pr	Me	85	178-180	MeOH-EtOAc	4-16	K	1	$C_{13}H_{20}N_4O_3$
5-40	Me	CH_2COPh	Pr	Me	69	118.5-122	CH_2Cl_2-Hex	4-16	L	1	$C_{18}H_{20}N_4O_2$
5-41	H	$CH_2CHOHCH_2OH$	Pr	Me	37	117-121	Me_2CO	4-15	K	1	$C_{12}H_{18}N_4O_3$
5-42	H	Et	2-Pr	Me	24	53-55	Cyhex	4-34	G	1	$C_{11}H_{16}N_4O$
5-43	H	Et	Et	Me	63	78-80.5	CH_2Cl_2-Hex	4-29	G	75.6±47 (3)	$C_{10}H_{14}N_4O$

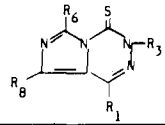
[a] Prepared by Method P. Alkylating agents: A = benzyl bromide, B = allyl bromide, C = iodomethane, D = ethyl bromoacetate, E = cyclopropanemethanol methanesulfonate,[k] F = ethyl 4-bromocrotonate, G = iodoethane, H = propargyl bromide, I = iodopropane, J = 2-bromoacetic acid, K = 3-chloro-1,2-propanediol, L = phenacyl bromide. [b] See Table IV, footnote *a*. [c] Anal. C, H, N, and Br if necessary. [d] Methylcyclohexane. [e] Cyclohexane. [f] Crystallized after distillation; mp 43-45 °C. [g] Crystallized to mp 41-44 °C. [h] M^+/e: calcd, 274; found, 274. No analysis. [i] M^+/e: calcd, 248; found, 248. No analysis. [j] Found as a byproduct in the formation of 5-23. Identified by NMR and IR. [k] Nikoletic, M.; Borcic, S.; Sunko, D. E. *Tetrahedron* **1967**, *23*, 649.

yellow liquid: bp 30–42 °C (0.1 mm); $n^{22.5} = 1.4444$. On analysis it proved to be impure, but the impurities, probably unreacted starting material or dichloro compound, dropped out in the next step. A mixture of 5.78 g (0.30 mol) of ethyl 2-chloro-3-oxohexanoate, 13.5 g (0.30 mol) of 98% formamide, and 1.08 g (0.060 mol) of water was heated. At 137 °C a mild exotherm took the temperature to 148 °C. Reflux was continued at 139 °C for 5 h. On standing at room temperature overnight, a precipitate formed that was collected and washed with water to give 2.18 g of yellow plates, mp 158–166 °C. Two recrystallizations from 2-PrOH gave 1.30 g (24%) of off-white crystalline 2-34, mp 171–174 °C. Anal. C, H, N.

Methyl 3-[(1-Aminoethylidene)aminoxy]-2-hexenoate (15). A solution of 19.98 g (0.2201 mol) of acetamidoxime,[10] 100 mL of MeOH, and 33.05 g (0.2623 mol) of methyl 2-hexenoate was heated under reflux overnight. After concentrating under vacuum, the residue was washed with CCl_4/petroleum ether, then taken up in $CHCl_3$, and passed through hydrous magnesium silicate. Evaporation to dryness and recrystallization from toluene gave 38.18 g (73%) of white crystals, mp 68–85 °C. A sample, recrystallized again from toluene for analysis, had a melting point of 92–94.5 °C. Anal. C, H, N.

Methyl 2-Methyl-5-propyl-4-imidazolecarboxylate (2-33). Heat was applied to a mixture of 83.2 g (0.416 mol) of methyl 3-[(1-aminoethylidene)aminoxy]-2-hexenoate and 400 mL of diphenyl ether to keep it at 200 °C for 22 min. After a vigorous evolution of gas had subsided, gentle bubbling was noted. The reaction was cooled to room temperature and diluted with 200

Table VI. Preparation and Activities of Imidazo[1,5-*d*][1,2,4]triazine-4(3*H*)-thiones



Compound	R_1	R_3	R_6	R_8	Yield %	MP °C	Recryst. Solvent	Starting Material	Method of Synthesis	Bas[a] IC_{50}	Formula[b]
6-1	H	H	H	H[c]							$C_5H_4N_4S$
6-2	H	H	H	Me	94	272.5-275	MeOH wash	3-17	O	I	$C_6H_6N_4S$
6-3	H	H	Ph	H	47	222 d.[d]	EtOH	3-18	O	I	$C_{11}H_8N_4S$
6-4	H	H	Pr	H[c]						I	$C_8H_{10}N_4S$
6-5	H	H	Ph	Me	13	273.5-239	EtOH-MeOH	3-19	O	1	$C_{12}H_{10}N_4S$
6-6	H	H	$(CH_2)_{16}CH_3$	H	68	137-139	MeOH wash	3-20	O	1	$C_{22}H_{38}N_4S$
6-7	H	H	3-C_6H_4Cl	H	20	208-209	MeOH	3-21	O	1	$C_{11}H_7ClN_4S$
6-8	H	H	Me	Me	95	287.5-290 d.	EtOH	3-22	O	1	$C_7H_8N_4S$
6-9	H	H	Pr	Me[c]						10±4.2 (3)	$C_9H_{12}N_4S$
6-10	H	H	Me	H	93	280.5-284 d.	EtOH wash	3-23	O	1	$C_6H_6N_4S$
6-11	H	H	CH_2OCH_3	H[c]						I	$C_7H_8N_4OS$
6-12	H	Et	H	H	1	143-144.5	Me_2CO[e]	6-1	R	1	$C_7H_8N_4S$
6-13	H	H	Et	Me	90	233-236		3-24	O	1	$C_8H_{10}N_4S$
6-14	H	H	H	Pr	94	178-180	Me_2CO-PE	3-25	O	1	$C_8H_{10}N_4S$
6-15	H	H	H	Et	85	233-234	EtOH	3-26	O	1	$C_7H_8N_4S$
6-16	H	H	2-Pr	Me	75	183-185	2-PrOH	3-29	O	1	$C_9H_{12}N_4S$
6-17	H	H	H	2-Pr	95	245-246 d.	Me_2CO-PE	3-30	O	1	$C_8H_{10}N_4S$
6-18	H	$CH_2CH{=}CH_2$	H	Et	30	74-77	Cyhex	7-26	Q	1	$C_{10}H_{12}N_4S$
6-19	H	$CH_2CH{=}CH_2$	Pr	Me	48	45-47.5	Cyhex	7-12	Q	1	$C_{12}H_{16}N_4S$
6-20	H	$CH_2CH{=}CH_2$	Me	H	17	92-95	EtOAc-Cyhex[f]	7-16	Q	1	$C_9H_{10}N_4S$
6-21	H	H	CH_2OCH_3	Me	70	229-231	EtOH	3-31	O	1	$C_8H_{10}N_4OS$
6-22	Me	H	Pr	Me	31	186-189	2-PrOH-Hex	2-17	O	45±16 (4)	$C_{10}H_{14}N_4S$
6-23	Pr	H	Pr	Me	50	199-200	2-PrOH-Hex	2-19	O	1	$C_{12}H_{18}N_4S$
6-24	Et	H	Pr	Me	49	215-218	2-PrOH	2-18	O	1	$C_{11}H_{16}N_4S$
6-25	2-Pr	H	Pr	Me	53	214-215	n-BuOH	2-21	O	1	$C_{12}H_{18}N_4S$
6-26	Me	H	Pr	H	46	220-222	n-BuOH	2-32	O	1	$C_9H_{12}N_4S$
6-27	Et	H	sec-Bu	Me	28	150-153	EtOAc-Et_2O	2-27	O	1	$C_{12}H_{18}N_4S$
6-28	Me	H	Me	Me	20	298-300	DMF	2-23	O	1	$C_8H_{10}N_4S$

[a] See Table IV, footnote *a*. [b] Anal. C, H, N, and S and if necessary Cl on new compounds. [c] Reference 3. [d] Recrystallized again (EtOH) for analysis; mp 230–231 °C dec. [e] After chromatography on silica gel. Distinguished from *S*-alkyl by UV and IR. [f] After silica gel column chromatography.

mL of EtOAc. Some black decomposition products were filtered off, and the filtrate was extracted with 2 × 250 mL of 2 N HCl and then 2 × 250 mL of 1 N HCl. After the aqueous extracts were combined, they were basified with K_2CO_3 and extracted with EtOAc. The organic extract was dried (Na_2SO_4) and concentrated under vacuum to leave 34.7 g of a black oil. Chromatography on silica gel gave 19.67 g (26%) of an orange oil, whose TLC indicated a fair degree of purity.

In an earlier experiment a small amount of product had crystallized. Two recrystallizations of that material from EtOAc gave an off-white solid, mp 97–98.5 °C, identified by IR and NMR as **2-33**: NMR ($CDCl_3$) (CH_3 ester, 3 H) δ 3.83 (s), (CH_3-2, 3 H), 2.36 (s), (Pr-4, 2 H), 2.89 (t), (2 H) 1.66 (q), (3 H), 0.90 (t); IR ester 1712 cm^{-1}.

4-(Hydroxymethyl)-2-methyl-5-propylimidazole (1-10). Method G. To a stirred solution, cooled to 0 °C and under N_2, of 19.67 g (0.108 mol) of oily **2-33** in 200 mL of toluene was added dropwise, over 1 h, 275 mL (232 g, 0.40 mol) of 24.8% of diisobutylaluminum hydride in toluene. The reaction was refluxed for 1 h and then recooled to 0 °C. Slow addition of 50 mL of MeOH decomposed any excess reagent. Next, 205 mL of 6 N HCl was slowly added, and the two layers thus formed were separated. The organic layer was extracted with another 50 mL of 6 N HCl. After the aqueous layer was concentrated under vacuum, the residue was extracted with 3 × 100 mL of boiling 2-PrOH, leaving a colorless salt. The 2-PrOH solution was concentrated under vacuum, the residue taken up in water, and solid K_2CO_3 added to saturate the solution. Some aluminum ions were still present, as indicated by gel formation. Ethyl acetate was added, and the mixture was readily filtered. More EtOAc was used to wash the filter cake until all the yellow color present went into the filtrate. The organic portion of the filtrate was dried (Na_2SO_4) and evaporated. Silica gel chromatography of the residue gave 12.6 g (76%) of oily alcohol **1-10**.

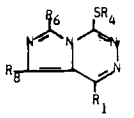
α,5-Dimethyl-2-propyl-4-imidazolemethanol (1-14). Method H. To a solution of 106.4 g (0.70 mol) of **2-38** in 1400 mL of THF, under argon and at 0 °C, was added 429 mL (1.48 mol) of 3 M MeMgBr in Et_2O, with vigorous mechanical stirring, in ca. 20 min. After the mixture was stirred for 3.5 h at ambient temperature, 900 mL (1.58 mol) of 1.75 M HCl was added to decompose the magnesium salts, giving the product as a white solid. The mixture was saturated with solid NH_4Cl and the product collected and then dried on the filter funnel by suction. Upon separation of the two layers of the filtrate, the organic layer was concentrated under vacuum. The residue was triturated with a little acetone and the solid thus obtained added to the above product. The product was dissolved in a minimal amount of EtOH and diluted with 1 volume of water to give 71.1 g (60%) of white, crystalline **1-14**, mp 200–202 °C dec.

Methyl *o*-Propoxybenzimidate Fluorosulfate (Table I). A solution of 109.0 g (0.61 mol) of *o*-propoxybenzamide, 500 mL of $CHCl_3$, and 49.4 mL (0.61 mol) of methyl fluorosulfonate was refluxed for 2 h. The reaction was then cooled and concentrated in vacuo to a milky oil. Upon addition of ether, the product crystallized exothermically, giving 200 g of hygroscopic solid, slightly damp with ether; mp 70–82 °C. A sample was dried under vacuum for analysis. Anal. C, H, N.

2-Benzyl-5-methyl-4-imidazolecarboxaldehyde (2-6). Method I. With external cooling, 8.79 g (0.0435 mol) of gummy **1-31** was dissolved in 55.7 mL (0.87 mol) of concentrated HNO_3 and the resulting solution permitted to stand at room temperature overnight. Then, the solution was heated on a steam bath for 30 min. Upon cooling, the solution was poured into 2 volumes of water and adjusted to pH 7, first with concentrated aqueous NaOH, then with solid Na_2CO_3. A solid was collected and washed with 5 mL of water. Two recrystallizations from EtOH gave 1.72 g of **2-2**, mp 169–172 °C. Concentration of the mother liquors gave an additional 0.36 g of **2-2**, mp 171–174 °C.

Methyl 5-Methyl-2-propyl-4-imidazolyl Ketone (2-17). Method J. Jones' reagent was prepared by dissolving 120 g of CrO_3 in 257 mL of water, adding 106.7 mL of concentrated H_2SO_4, and diluting to 461.7 mL with water. To a round-bottomed flask, equipped with a mechanical stirrer whose paddle was at least 3 cm from the bottom of the flask, was added 86.2 g (0.513 mol)

Table VII. Preparation and Activities of 4-(Thioalkyl)imidazo[1,5-*d*][1,2,4]triazines



Compound	R_1	R_4	R_6	R_8	Yield %	MP °C	Recryst. Solvent	Starting Material	Alkylating agent[a]	8as IC_{50}[b]	Formula[c]
7-1	Me	H	H	H	Ref 3				A	I	$C_6H_6N_4S$
7-2	H	Me	Me	H	57	182.5-184	EtOH	6-10	A	1	$C_7H_8N_4S$
7-3	H	Me	Pr	H	69	135.5-137	EtOAc	6-4	A	1	$C_9H_{12}N_4S$
7-4	H	Me	H	Me	37	128-129	Me_2CO[d]	6-2	A	I	$C_7H_8N_4S$
7-5	H	Me	CH_2OCH_3	H	54	179-181	EtOH	6-11	A	1	$C_8H_{10}N_4OS$
7-6	H	Me	Me	Me	27	174-176.5	EtOH	6-8	A	I	$C_8H_{10}N_4S$
7-7	H	Me	Pr	Me	68	82-87	EtOAc	6-9	A	1	$C_{10}H_{14}N_4S \cdot \frac{1}{4}H_2O$
7-8	H	$CH_2CH{=}CH_2$	Pr	H	32	85-88	CH_3CN-Et_2O	6-4	B	I	$C_{11}H_{14}N_4S$
7-9	H	CH_2CO_2Et	H	H	17	114-117	$PhCH_3$-Cyhex	6-1	C	7	$C_9H_{10}N_4O_2S$
7-10	H	$CH_2CH_2CHMe_2$	H	H	23	55-57	Cyhex	6-1	D	9 (1)	$C_{10}H_{14}N_4S$
7-11	H	CH_2COPh	H	H	22	165-168	CH_3CN	6-1	E	I	$C_{13}H_{10}N_4OS$[e]
7-12	H	$CH_2CH{=}CH_2$	Pr	Me	35	68-70	Cyhex	6-9	B	-	$C_{12}H_{16}N_4S$
7-13	H	$CH_2CH{=}CH_2$	Ph	Me	35	gum[f]		6-5	B	1	$C_{15}H_{14}N_4S \cdot \frac{1}{4}H_2O$
7-14	H	$CH_2CH{=}CH_2$	Me	Me	14	64-67	Cyhex	6-8	B	59 (1)	$C_{10}H_{12}N_4S$
7-15	H	$CH_2CH{=}CH_2$	Ph	H	30	101-103	Cyhex	6-3	B	I	$C_{14}H_{12}N_4S$
7-16	H	$CH_2CH{=}CH_2$	Me	H	32	68-71	EtOAc-Cyhex	6-10	B	61±27(6)	$C_9H_{10}N_4S$
7-17	H	$CH_2CH{=}CH_2$	CH_2OCH_3	H	47	37-40	Cyhex	6-11	B	79 (1)	$C_{10}H_{12}N_4OS$
7-18	H	CH_2CO_2Et	Pr	Me	20	108-111	EtOAc	6-5	C	I	$C_{13}H_{18}N_4O_2S$
7-19	H	CH_2CO_2Et	Me	Me	52	134-137	CH_3CN	6-8	C	1	$C_{11}H_{14}N_4O_2S$
7-20	H	CH_2CO_2Et	Me	H	45	83-86	EtOAc-Cyhex	6-10	C	52 (1)	$C_{10}H_{12}N_4O_2S \cdot \frac{1}{4}H_2O$
7-21	H	CH_2CO_2Et	H	Me	46	122-125	CH_3CN	6-2	C	1	$C_{10}H_{12}N_4O_2S$
7-22	H	$CHMeCO_2Et$	H	H	10	oil		6-1	F	1	$C_{10}H_{12}N_4O_2S$
7-23	H	$CH_2CH{=}CHCO_2Et$	H	H	17	71-73	EtOAc-Cyhex	6-1	G	1	$C_{11}H_{12}N_4O_2S$
7-24	H	Me	H	Pr	59	71-72[f]		6-14	A	I	$C_9H_{12}N_4S$
7-25	H	$CH_2CH{=})_2$	H	H	21	218-221	DMF	6-1	H	1	$C_{14}H_{12}N_8S_2$
7-26	H	$CH_2CH{=}CH_2$	H	Et	23	53-55	Cyhex	6-15	B	1	$C_{10}H_{12}N_4S$
7-27	H	Me	H	2-Pr	57	74-76	f	6-17	A	1	$C_9H_{12}N_4S \cdot 1/8H_2O$
7-28	Ph	Me	H	H	90	136-137	2-PrOH	10-1	g	1	$C_{12}H_{10}N_4S$
7-29	Me	Me	Pr	Me	12	80-83	Cyhex	6-22	A	1	$C_{11}H_{16}N_4S$
7-30	2-Pr	Me	Pr	Me	83	73-75	Me_2CO-PE	6-25	A	1	$C_{13}H_{20}N_4S$
7-31	Ph	Me	Pr	Me	54	92-93	Cyhex	10-4	g	I	$C_{16}H_{18}N_4S \cdot 1/8H_2O$
7-32	Et	Me	Pr	Me	63	37-41	EtOAc	6-24	A	1	$C_{12}H_{18}N_4S$
7-33	Me	Me	Pr	H	75	79-80	Cyhex	6-26	A	1	$C_{10}H_{14}N_4S$
7-34	H	Me	2-Pr	Me	60	104-106	e	6-16	A	1	$C_{10}H_{14}N_4S$
7-35	H	Me	Et	Me	65	106-108	Et_2O-Cyhex	6-13	A	1	$C_9H_{12}N_4S \cdot \frac{1}{4}H_2O$
7-36	Ph	Me	Et	Me	78	108-111	Et_2O-Cyhex	10-6	g	I	$C_{15}H_{18}N_4S$
7-37	Ph	Me	2-Pr	Me	39	94-96	Cyhex	10-7	g	1	$C_{16}H_{18}N_4S$
7-38	Pr	Me	Pr	Me	92	48-51	h	6-23	A	I	$C_{13}H_{20}N_4S$
7-39	Me	Me	Me	Me	56	157-159	EtOH	6-28	A	1	$C_9H_{12}N_4S \cdot 3/4H_2O$
7-40	Pr	Me	Me	H	32	76.5-79	CH_3CN	10-5	g		$C_{10}H_{14}N_4S$

[a] By using method R with the following alkylating agents: A = iodomethane, B = allyl bromide, C = ethyl bromoacetate, D = 1-bromo-3-methylbutane, E = phenacetyl bromide, F = ethyl 2-bromopropionate, G = ethyl 4-bromocrotonate, H = 1,4-dibromo-2-butene. [b] See Table IV, footnote *a*. [c] Anal. C, H, N, S. [d] Chromatographed on silica gel first. A 1:1 complex of compound with NaI formed in this reaction, which may be recrystallized to analytical purity. [e] C: calcd, 57.77; found, 58.22. [f] Chromatographed on silica gel. [g] Method N. [h] Distilled bp 150-155 °C (0.02 mm). M^+/e: calcd, 264; found 264.

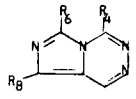
of 1-14 and 2.16 L of acetone. The suspension was stirred in an ice bath and 430.9 mL (1.12 mol) of Jones' reagent was dripped in at 20–30 °C internal temperature. After the addition was completed (~1 h), stirring was continued for 30 min at room temperature and then 256 mL of water was added. Next, the reaction was cooled in an ice bath followed by the slow addition of 256 mL of 2-PrOH at 20–30 °C (internal) to decompose excess reagent. Stirring was continued for 1 h, giving a suspension of solid and liquid. The liquid was decanted and concentrated to remove most of the acetone. After the aqueous residue and the solid were recombined, the mixture was basified with concentrated aqueous $KHCO_3$ and an additional amount of solid $KHCO_3$. The mixture was extracted with EtOAc (3 × 300 mL) and the combined extracts back-washed with 100 mL of saturated aqueous $KHCO_3$. After the extracts (Na_2SO_4 then $CaSO_4$) were dried, the solvent was removed by vacuum. The residual ketone (79.1 g, 93%) crystallized on standing, to a low-melting solid, **2-17**.

1,8-Dimethyl-6-propylimidazo[1,5-*d*][1,2,4]triazin-4-(3*H*)-one (4-16). Method K. A mixture of 59.7 g (0.360 mol) of methyl 5-methyl-2-propyl-4-imidazolyl ketone (**2-17**), 41.14 g (0.396 mol) of ethyl carbazate, 200 mL of *n*-BuOH, and 4 drops of glacial HOAc, which formed a solution on warming, was heated under reflux for 5 h. After the solution was concentrated under vacuum, 250 mL of diphenyl ether was added to the oily residue and the resulting solution heated with stirring in an oil bath for 30 min after gas evolution had started. The temperature was maintained, as closely as possible, at the point at which the gas evolution had started, 206–217 °C.

Upon withdrawal from the oil bath, the reaction was cooled to 50 °C and diluted with 1–2 volumes of hexane. The crystalline product was collected and washed with ether. After the solid was dissolved in 200 mL of $CHCl_3$, it was passed through 250 mL of hydrous magnesium silicate in a 350-mL sintered-glass funnel followed by 800 mL of $CHCl_3$ wash. The filtrate was concentrated under vacuum and the residual crystals recrystallized from ca. 250 mL of EtOAc to give 48.2 g (65%) of off-white crystalline **4-16**, mp 154–155 °C.

6-Benzyl-8-bromoimidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-one (4-30). Method L. A stirred suspension of 1.13 g (0.005 mol) of 6-benzylimidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-one (**4-3**) in 15 mL of *t*-BuOH was treated with 1.54 mL (4.80 g, 0.300 mol) of Br_2. After 30 min, the mixture was added to 200 mL of water and the precipitated product collected. Washing the product with dilute aqueous sodium dithionate converted any *N*-bromo to *N*-H in the product, as determined by color and odor. The crude product, mp 181–183 °C, was recrystallized from acetonitrile to give 0.87

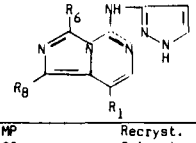
Table VIII. Preparation and Activities of 4-Aminoimidazo[1,5-*d*][1,2,4]triazines



Compound	R_4	R_6	R_8	Yield %	MP °C	Recryst. Solvent	Starting Material	Method of Synthesis	Amine	Bas[a] IC_{50}	Formula[b]
8-1	NHMe	H	H	Ref 3						1	$C_6H_7N_5$
8-2	Piperidinyl	H	H	Ref 3						1	$C_{10}H_{13}N_5$
8-3	$NHCH_2CH_2NMe_2$	H	H	Ref 3						1	$C_9H_{14}N_6$
8-4	NH-2-furfuryl	H	H	Ref 3						1	$C_{10}H_9N_5O$
8-5		H	H	27	160-161[c]	2-PrOH	7-1	E		1	$C_{10}H_{14}N_6$
8-6		H	H	35	189.5-192.5	EtOH	7-1	E		1	$C_{22}H_{22}N_6 \cdot C_2H_5OH$
8-7	$NHCH_2Ph$	H	H	56	270-274	MeOH	7-1	E	H_2NCH_2Ph	1	$C_{12}H_{11}N_5$
8-8	$NHCH_2CH_2NMe_2$	CH_2OCH_3	H	29	86-89	Cyhex	7-5	E	$H_2NCH_2CH_2NMe_2$	I	$C_{11}H_{18}N_6O$
8-9	$NHCH_2CH_2NMe_2$	Pr	Me	38	51-53[d]	EtOAc	7-7	E	$H_2NCH_2CH_2NMe_2$	1	$C_{13}H_{22}N_6 \cdot \frac{1}{2}H_2O$
8-10	NH-cyclopentyl	H	H	14	199.9-201[e]	EtOH	7-1	E	H_2N-cyclopentyl	I	$C_{10}H_{13}N_5$
8-11	NH-1-adamantyl	H	H	8	296-299	EtOH	7-1	E	H_2N-1-adamantyl	1	$C_{16}H_{21}N_5$
8-12		H	H	3	345d.		7-1	E[f]		46±28 (2)	$C_7H_6H_8 \cdot 1/8H_2O$
8-13	 $\cdot H_2SO_4$	H	H	37	250d.	EtOH	7-1	E[f]		10±9 (2)	$C_{14}H_{13}N_7O_4S \cdot \frac{1}{4}H_2O$
8-14	NHMe	H	Me	74	304-308d.	EtOH	2-41	S	$H_2NN{=}C(SMe)NHMe$	1	$C_7H_9N_5 \cdot \frac{1}{4}H_2O$
8-15	NMe_2	H	Me	48	162-163	Me_2CO-PE	7-4	S	$HNMe_2$	I	$C_8H_{11}N_5$
8-16	N(Ac) 	H	Me	26	223-224	H_2O	9-2	h		1	$C_{11}H_{11}N_7O$
8-17	NH-3-oyridyl	H	Me	20	227-229	DMF-$PhCH_3$	7-4	S	H_2N-3-pyridyl	1	$C_{11}H_{11}N_6 \cdot \frac{1}{4}H_2O$
8-18	NH-2-furfuryl	H	Me	29	209-210d.	H_2O	7-4	S	H_2N-2-furfuryl	1	$C_{11}H_{11}N_5O$
8-19	NH-2-thenyl	H	Me	33	222-224d.	H_2O	7-4	S	H_2N-2-thenyl	1	$C_{11}H_{11}N_5S$
8-20	$NHNH_2$	H	Me	95	208-210d.	DMF-EtOH	7-4	S	NH_2NH_2	I	$C_6H_8N_6 \cdot 1/8H_2O$

[a] See Table IV, footnote *a*. [b] Anal. *C*, H, N, S. [c] A sample was recrystallized again for analysis (2-PrOH); mp 163-166 °C. [d] Dimorphic. On standing, a sample melted and resolidified as a lump, mp 62-74 °C. [e] Dimorphic. Crystalline change at 189.5 °C. [f] A few milliliters of DMF was added until a solution formed at the reflux temperature. In the case of **8-13**, sulfuric acid was added in the recrystallization step to form a salt. [g] Grandberg, I. I.; Ting, W.; Kost, A. N. *Zh. Obshch. Khim.* **1961**, *31*, 2311; *Chem. Abstr.* 1962, *56*, 47470. [h] Prepared by refluxing **9-2** with Ac_2O and then concentrating under vacuum.

Table IX. Preparation and Activities of 4-(3-Pyrazolylamino)imidazo[1,5-*d*][1,2,4]triazines

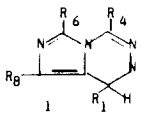


Compound	R_1	R_6	R_8	Yield %	MP °C	Recryst. Solvent	Starting[a] Material	Bas[b] IC_{50}	Formula[c]
9-1	H	H	H	Ref 3					
9-2	H	H	Me	69	288-292.5	DMF-EtOH	7-4	57±28 (7)	$C_9H_9N_7$
9-3	H	CH_2OCH_3	H	6	223.5-225.5	MeOH	7-5	31 (1)	$C_{10}H_{11}N_7O$
9-4	H	H	Pr	64	230-232	EtOH	7-24	I	$C_{11}H_{13}N_7$
9-5	H	Me	Me	4	328-329	EtOH	7-6	53±36 (2)	$C_{10}H_{11}N_7 \cdot 1/8H_2O$
9-6	H	Pr	Me	44	245-246.5	EtOH	7-7	25±8 (4)	$C_{12}H_{15}N_7$
9-7	H	H	Et	6	242-244	EtOH	d	36 (1)	$C_{10}H_{11}N_7 \cdot \frac{1}{4}H_2O$
9-8	H	H	2-Pr	88	246-248	EtOH	7-27	1	$C_{11}H_{13}N_7$
9-9	Ph	H	H	68	263.5-265	DMF-EtOH	7-28	1	$C_{14}H_{11}N_7 \cdot \frac{1}{4}H_2O$
9-10	2-Pr	Pr	Me	88	246-248	EtOH	7-30	1	$C_{11}H_{13}N_7$
9-11	Ph	Pr	Me	88	254-256	EtOH	7-31	1	$C_{18}H_{19}N_7$
9-12	Me	Pr	Me	73	274-277	MeOH	7-29	I	$C_{13}H_{17}N_7$
9-13	Et	Pr	Me	29	280-283	H_2O	7-32	1	$C_{14}H_{19}N_7$
9-14	Me	Pr	H	67	245-247	EtOH	7-33	39±21 (4)	$C_{12}H_{15}N_7$
9-15	H	Et	Me	72	291-294	H_2O	7-35	13±2 (3)	$C_{11}H_{13}N_7$
9-16	Ph	Et	Me	37	267-270	EtOAc-Hex	7-36	1	$C_{17}H_{17}N_7$[e]
9-17	Ph	2-Pr	Me	94	249-251	H_2O	7-37	1	$C_{18}H_{19}N_7 \cdot 1/8H_2O$
9-18	Pr	Pr	Me	66	248-251	H_2O	7-38	1	$C_{15}H_{21}N_7$
9-19	Me	Me	Me	71	338-340	DMF	7-39	1	$C_{11}H_{13}N_7$
9-20	Pr	Me	H	82	244-246.5	DMF-EtOH	7-40	1	$C_{12}H_{15}N_7$

[a] In each case the second reactant was 3-aminopyrazole and the method S. [b] See Table IV, footnote *a*. [c] Anal. C, H, N. [d] The *S*-Me derivatives of 6-15 could not easily be freed of NaI and was used crude. [e] M^+/e: calcd, 319.1544; found, 319.1546.

g (57%) of **4-30**, mp 185-187 °C. A sample for analysis was recrystallized from EtOH (results in Table IV). The bromine was located by NMR. **4-30** ($CDCl_3$): (CH-1, 1 H) δ 7.95 (s), (NH-3, 1 H), 9.37 (s), (Ph-5′, 5 H), 7.35 (m), (CH_2-5, 2 H), 4.70 (s). **4-3**

Table X. Preparation and Activities of Miscellaneous Imidazo[1,5-*d*][1,2,4]triazines



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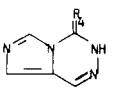

II

Compound	Structure	R_1	R_4	R_6	R_8	Yield %	MP °C	Recryst. Solvent	Starting Material	Method of Synth.	Reactant	Bas[a] IC_{50}	Formula[b]
10-1	I	Ph	SMe	H	H	40	142-144	PhH-PE	7-1	M	PhMgBr	-	$C_{12}H_{12}N_4S$
10-2	II	$NHCH_2CH_2NMe_2$	$NHCH_2CH_2NMe_2$	CH_2OCH_3	H	4	133.5-135.5	Me_2CO	7-5	E	$NH_2CH_2CH_2NMe_2$	1	$C_{15}H_{30}N_8O$
10-3	I	NH cyclopentyl	NH cyclopentyl	H	H	4	200-201	EtOH	7-1	E	NH-cyclopentyl	1	$C_{15}H_{24}N_6 \cdot \frac{1}{4}H_2O$
10-4	I	Ph	SMe	Pr	Me	54	149-151	Cyhex	7-7	M	PhMgBr	1	$C_{16}H_{20}N_4S$[c]
10-5	I	Pr	SMe	Me	H	3	134.5-136	Me_2CO	7-2	M	PrMgBr	1	$C_{10}H_{16}N_4$
10-6	I	Ph	SMe	Et	Me	14	157-159	Et_2O	7-35	M	PhMgBr	-	$C_{15}H_{18}N_4S$[d]
10-7	I	Ph	SMe	2-Pr	Me		oil		7-34	M	PhMgBr	-	$C_{16}H_{20}N_4S$[d]
10-8	II		$CHCO_2Et$			9	149-151	EtOAc-Et_2O[e]	7-9	T		1	$C_9H_{10}N_4O_2 \cdot \frac{1}{4}H_2O$
10-9	II		CHCOPh			8	206-210	CH_3CN	7-11	T		38	$C_{13}H_{10}N_4O \cdot \frac{1}{4}H_2O$
10-10	II		$C(CO_2Et)_2$			14	103-105	EtOAc-Cyhex	6-1	R	$BrCH(CO_2Et)_2$	1	$C_{12}H_{14}N_4O_4$

[a] See Table IV, footnote *a*. [b] Anal. C, H, N, S. [c] S: calcd, 10.67; found, 9.96. [d] Used crude in the next step. [e] Column chromatographed on silica gel first.

Table XI. Comparison of the Most Active Imidazotriazines

compd	basophil[a] IC_{50}, μM	mouse PCA[b] ED_{50}, mg/K	guinea pig[c] anaphylaxis
4-16	14 ± 1	109 ± 12	act.[d]
4-17	16 ± 3.5	146 ± 23	act.[e]
4-18	16 ± 7	114 ± 20	borderline[f]
theophylline	335 ± 88	140 ± 25	inact.[g]

[a] Reference 13. [b] Friedman, H. In "Animal and Clinical Pharmacologic Techniques in Drug Evolution"; Siegler, P. E., Moyer, J. H., Eds.; Yearbook Medical Pubisher: New York, 1967; Vol. II, pp 548-568. Female CFW mice were given 50 μL of diluted IgE-containing homologous serum iv. Two days later the animals were dosed with compound po 1 h before an iv injection of antigen (ovalbumin) and Evan's Blue Dye. After 20 min, the animals were sacrificed and lesion areas scored as a product of two normal diameters. [c] Female Hartley strain guinea pigs were passively sensitized by ip adminstration of hyperimmune serum, raised in other guinea pigs by a single injection of an emulsion of 50 mg of ovalbumin in Freund's complete adjuvant with sacrifice at 28 days. Test compounds were given given ip at 50 mg/kg, 1 h before an iv dose of ovalbumin usually sufficient to cause death in more than 8/10 animals. The fraction of animals collapsed was compared to control. [d] Fraction of guinea pigs in collapse: treated, 41/105; control, 86/106. [e] Treated 21/70; control, 45/62. [f] Treated, 45/74; control, 78/97. [g] Treated, 12/19; control, 16/20.

(Me_2SO-d_6) (CH-1, 1 H) δ 8.23 (s), (NH-3, 1 H), 12.12 (s), (Ph-5′, 5 H), 7.24 (m), (CH_2-5, 2 H), 4.62 (s), (CH-8 1 H), 7.51 (s). **4-12** (Me_2SO-d_6) (CH-1, 1 H) δ 8.22 (s), (NH-3, 1 H), 11.95 (s), (Ph-5′, 5 H), 7.21 (m), (CH_2-5, 2 H), 4.58 (s), (CH_3-8, 3 H), 2.35 (s).

1,2-Dihydro-4-(methylthio)-1-phenylimidazo[1,5-*d*][1,2,4]triazine (10-1). Method M. A suspension of 9.96 g (0.0600 M) of 4-(methylthio)imidazo[1,5-*d*][1,2,4]triazine (**7-1**) in 120 mL of THF was stirred at 0 °C under N_2 while 200 mL (0.46 mol) of 2.3 M phenylmagnesium bromide in Et_2O was added over 30 min. The mixture turned green and then black, forming two layers and a gum ball. After the mixture was refluxed for 4.5 h, during which time the gum ball disintegrated, it was cooled to 0 °C and 90 mL of saturated aqueous NH_4Cl was slowly added. The pH of the resulting dark red mixture was adjusted to 5.5 with HOAc, and enough water was added to get a solution. Next the solution was extracted with EtOAc and the extracted back-washed with aqueous $KHCO_3$. After the extract was dried over Na_2SO_4, it was concentrated under vacuum to 17.1 g of a red oil. The oil was taken up in 80 mL of CCl_4, some insoluble material filtered off, and the filtrate cooled to give 8.51 g of salmon-colored crystals, mp 116–122 °C. Two recrystallizations from 2-PrOH gave 5.81 g (40%) of salmon-colored crystals of **10-1**, mp 139–142 °C. A sample, recrystallized for analysis from benzene–petroleum ether, had a melting point of 142–144 °C.

4-(Methylthio)-1-phenylimidazo[1,5-*d*][1,2,4]triazine (7-28). Method N. To a stirred solution of 5.81 g (0.0238 mol) of 1,2-dihydro-4-(methylthio)-1-phenylimidazo[1,5-*d*][1,2,4]triazine (**10-1**) in 238 mL of $CHCl_3$ was added 6.49 g (0.0286 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. There was an immediate color change and a slight exotherm. The reaction was stirred for 2 h and then filtered through hydrous magnesium silicate. On evaporation of the filtrate under vacuum, 5.70 g of light yellow crystals remained. Recrystallization from 2-PrOH gave 5.21 g of **10-1**, mp 136–137 °C.

8-Methyl-1-phenyl-6-propylimidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-one (4-22). Method O. To a solution of 2.44 g (8.18 mmol) of **7-31** in 25 mL of glacial HOAc was added 9.3 mL (82 mmol) of 30% hydrogen peroxide. After a mild exotherm, the yellow solution was permitted to stand at ambient temperature for 7 h. The solution was cooled in an ice bath and the excess peroxide cautiously decomposed with saturated aqueous $NaHSO_3$ until a KI-starch paper test was negative. Then, the mixture was concentrated under vacuum and the residue taken up in water and neutralized with aqueous $KHCO_3$. A precipitate formed that was collected, washed with water, and air-dried to give 2.24 g of solid. Recrystallization from acetone–petroleum ether gave 1.26 g (58%) of **4-22**, mp 210–211 °C.

3-Allyl-8-methyl-6-propylimidazo[1,5-*d*][1,2,4]triazin-4-(3*H*)-one (5-3). Method P. 8-Methyl-6-propylimidazo[1,5-*d*][1,2,4]triazin-4(3*H*)-one (**4-15**) (4.08 g, 0.0200 mol) was dissolved in 20 mL of DMF and the resultant solution added to 1.06 g (0.022 mol) of 50% sodium hydride in oil that had been thrice washed with petroleum ether to remove the oil. When the effervescence had ceased (45 min), 1.90 mL (0.0220 mol) of allyl bromide was added and the reaction stirred, with moisture exclusion, for 2 h. Stirring was continued for another hour while the reaction was heated on a steam bath. The reaction mixture was then poured into 250 mL of water and extracted with 2 × 100 mL of CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated to leave an oil. Trituration with 50 mL of hexane gave a yellow solid that was filtered off, the product being recovered from the filtrate by evaporation. The residual yellow oil was distilled in a Kugelrohr apparatus to give 3.4 g (73%) of a colorless liquid **5-3**, bp 125–130 °C (0.05 mm).

3-Allyl-8-ethylimidazo[1,5-*d*][1,2,4]triazine-4(3*H*)-thione (6-18). Method Q. Upon heating of 400 mg (1.82 mmol) of 4-(thioallyl)-8-ethylimidazo[1,5-*d*][1,2,4]triazine (**7-12**) to 185 °C (oil bath) for 2 h, the material darkened. On cooling, the reaction material was taken up in 20 mL of $CHCl_3$ and filtered through an anhydrous magnesium silicate pad. On evaporation of the filtrate, crystals were obtained that differed in R_f from starting material, on TLC. Recrystallization from cyclohexane gave 120 mg of white crystalline **6-18**, mp 74–77 °C (30%). The product was identified by NMR, IR, and UV spectroscopies. NMR: **7-12** (Me_2SO-d_6) (CH-1, 1 H) δ 8.47 (s), ($SCH_2CH{=}CH_2$-3, 2 H), 4.18 (d), (1 H), 6.06 (m), (1 H cis), 5.50 (d), (1 H trans), 5.24 (d), (CH-6, 1 H), 9.26 (s), (CCH_2CH_3-8, 2 H), 2.94 (q), (3 H), 1.32 (t); **6-18** (Me_2SO-d_6) (CH-1, 1 H) δ 8.76 (s), ($NCH_2CH{=}CH_2$-3, 2 H), 5.18 (m), (1 H), 6.00 (m), (2 H), 5.20 (m), (CH-6, 1 H), 8.88 (s), (CCH_2CH_3-8, 2 H), 2.90 (q), (3 H), 1.30 (t). UV: **7-12** (MeOH)

λ 206 (ε 15200), 246 (10200), 272 (7610), 327 (4460); **6-18** (MeOH) λ (17900), 280 (12400, C=S), 327 (6720). IR: **7-12**, 1279, 950, 734, 614 cm^{-1}; **6-18**, 1538, 1176, 1538 cm^{-1}.

Ethyl (Imidazo[1,5-*d*][1,2,4]triazin-4-ylthio)acetate (7-9). Method R. After a mixture of 1.52 g (0.0100 mol) of imidazo-[1,5-*d*][1,2,4]triazine-4(3*H*)-thione (**6-1**), 10 mL of DMF and 0.53 g (0.011 mol) of 50% sodium hydride in oil was stirred for an hour or until the bubbling ceased, 1.11 mL (1.62 g, 0.0100 mol) of ethyl bromoacetate was added. The reaction was stirred overnight, and then the solvent was removed at 60 °C under vacuum. After 50 mL of water was added to the reddish brown residue, the mixture was extracted with 3 × 50 mL of CH_2Cl_2. Drying (Na_2SO_4) the combined extract, passing it through hydrous magnesium silicate, and evaporation gave a brown oil. Upon three triturations with petroleum ether, crystallization occurred, giving 500 mg of light yellow solid, mp 103–106 °C. Recrystallization from toluene–cyclohexane gave 400 mg (17%) of product **7-9**, mp 114–117 °C.

8-Methyl-6-propyl-4-(3-pyrazolylamino)imidazo[1,5-*d*]-[1,2,4]triazine (9-6). Method S. A solution of 5.44 g (0.0656 mol) of 3-aminopyrazole in 15 mL of water was added to 2.38 g (0.0103 mol) of 8-methyl-4-(methylthio)-6-propylimidazo[1,5-*d*][1,2,4]triazine (**7-7**). The resulting mixture was stirred under reflux for 9 h. On cooling, a precipitate appeared that was collected: 1.43 g of white crystals; mp 244–247 °C. Further reflux of the filtrate for 8 h gave a little more product. The combined crude products were recrystallized from MeOH to give 1.16 g (44%) of crystalline **9-6**, mp 246–248.5 °C.

Ethyl Imidazo[1,5-*d*][1,2,4]triazine-Δ⁴(3*H*)-acetate (10-8). Method T. To a solution of 2.1 g (8.83 mmol) of ethyl (imidazo[1,5-*d*][1,2,4]triazin-4-ylthio)acetate (**7-9**) in 30 mL of DMF was added 3.06 g (0.045 mol) of sodium ethoxide, forming a reddish brown solution. After standing overnight, the solution was concentrated under vacuum to leave an oil. This oil was partitioned between water and EtOAc. Drying the organic extract (Na_2SO_4) and reconcentrating left a semisolid. Crystallization from 10 mL of MeOH gave 0.16 g (9%) light brown crystals of **10-8**, mp 147–150 °C. The NMR agreed with the assigned structure: NMR **10-8** ($CDCl_3$) (CH-1, 1 H) δ 7.96 (s), (CH-6, 1 H), 8.10 (s), (CH-8, 1 H), 7.55 (s), (=CH, 1 H), 5.05, (CH_2, 2 H), 4.24 (q), (CH_3, 3 H), 1.32 (t).

Acknowledgment. The authors thank L. Brancone and group for the elemental analyses, Dr. W. E. Gore and group for the spectral data, and G. O. Morton for NMR interpretation.

Registry No. **1-1**, 68282-42-8; **1-2**, 53292-67-4; **1-3**, 68282-46-2; **1-4**, 68282-45-1; **1-5**, 94887-76-0; **1-6**, 97749-51-4; **1-7**, 80304-45-6; **1-8**, 97749-52-5; **1-9**, 38603-80-4; **1-10**, 97749-53-6; **1-11**, 97749-54-7; **1-12**, 97749-55-8; **1-13**, 97749-56-9; **1-14**, 84227-31-6; **1-15**, 84227-34-9; **1-16**, 84227-37-2; **1-17**, 97749-57-0; **1-18**, 97749-58-1; **1-19**, 97749-59-2; **1-20**, 97749-60-5; **1-21**, 97749-61-6; **1-22**, 97749-62-7; **1-23**, 97749-63-8; **1-24**, 97749-64-9; **1-25**, 97749-65-0; **1-26**, 97749-66-1; **1-27**, 97749-67-2; **1-28**, 97749-68-3; **1-29**, 97749-69-4; **1-30**, 97749-70-7; **1-31**, 43002-56-8; **1-32**, 43002-54-6; **1-33**, 68283-57-8; **1-34**, 68282-39-3; **1-35**, 68282-41-7; **2-1**, 68282-54-2; **2-2**, 68282-55-3; **2-3**, 68282-47-3; **2-4**, 68282-52-0; **2-5**, 97749-71-8; **2-6**, 68282-57-5; **2-7**, 68282-61-1; **2-8**, 88634-80-4; **2-9**, 97749-72-9; **2-10**, 97749-73-0; **2-11**, 97749-74-1; **2-12**, 97749-75-2; **2-13**, 97749-76-3; **2-14**, 97749-77-4; **2-15**, 97749-78-5; **2-16**, 97749-79-6; **2-17**, 84227-32-7; **2-18**, 84227-35-0; **2-19**, 84227-38-3; **2-20**, 97749-80-9; **2-21**, 97749-81-0; **2-22**, 97749-82-1; **2-23**, 56536-44-8; **2-24**, 97749-83-2; **2-25**, 97749-84-3; **2-26**, 97749-85-4; **2-27**, 97749-86-5; **2-28**, 97749-87-6; **2-30**, 97749-88-7; **2-31**, 97749-89-8; **2-32**, 84694-92-8; **2-33**, 97749-90-1; **2-34**, 97749-91-2; **2-35**, 38603-77-9; **2-36**, 97749-92-3; **2-37**, 35034-22-1; **2-38**, 68282-59-7; **2-39**, 68282-48-4; **2-40**, 68282-50-8; **2-41**, 68282-53-1; **3-1**, 68282-78-0; **3-2**, 68282-79-1; **3-3**, 68282-76-8; **3-4**, 68282-77-9; **3-5**, 68282-74-6; **3-6**, 97749-93-4; **3-7**, 68282-82-6; **3-8**, 68282-83-7; **3-9**, 68282-84-8; **3-10**, 68282-85-9; **3-11**, 97749-94-5; **3-12**, 97749-95-6; **3-13**, 97749-96-7; **3-14**, 97749-97-8; **3-15**, 97749-98-9; **3-16**, 97749-99-0; **3-17**, 68282-69-9; **3-18**, 68282-64-4; **3-19**, 68282-65-5; **3-20**, 97750-00-0; **3-21**, 97750-01-1; **3-22**, 68282-70-2; **3-23**, 68282-68-8; **3-24**, 97750-02-2; **3-25**, 97750-03-3; **3-26**, 97750-04-4; **3-29**, 97750-05-5; **3-30**, 97750-06-6; **3-31**, 97763-73-0; **4-1**, 70258-50-3; **4-2**, 68282-99-5; **4-3**, 68283-00-1; **4-4**, 68283-01-2; **4-5**, 68283-02-3; **4-6**, 68283-03-4; **4-7**, 68283-04-5; **4-8**, 97763-74-1; **4-9**, 68283-05-6; **4-10**, 68283-07-8; **4-11**, 68283-08-9; **4-12**, 68283-09-0; **4-13**, 68283-10-3; **4-14**, 68283-13-6; **4-15**, 68283-12-5; **4-16**, 84227-33-8; **4-17**, 84227-36-1; **4-18**, 84227-39-4; **4-19**, 97750-07-7; **4-20**, 97750-08-8; **4-21**, 97750-09-9; **4-22**, 97750-10-2; **4-23**, 97750-11-3; **4-24**, 97750-12-4; **4-25**, 97750-13-5; **4-26**, 97750-14-6; **4-27**, 97750-15-7; **4-28**, 97750-16-8; **4-29**, 97750-17-9; **4-30**, 97750-18-0; **4-31**, 97750-19-1; **4-32**, 97750-20-4; **4-33**, 97763-75-2; **4-34**, 97750-21-5; 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**5-34**, 97750-68-0; **5-35**, 97750-69-1; **5-36**, 97750-70-4; **5-37**, 97750-71-5; **5-38**, 97750-72-6; **5-39**, 97750-73-7; **5-40**, 97750-74-8; **5-41**, 97750-75-9; **5-42**, 97750-76-0; **5-43**, 97750-77-1; **6-1**, 68282-88-2; **6-2**, 68282-89-3; **6-3**, 68282-90-6; **6-4**, 68282-91-7; **6-5**, 68282-92-8; **6-6**, 97750-78-2; **6-7**, 97750-79-3; **6-8**, 68282-94-0; **6-9**, 68325-00-8; **6-10**, 68282-97-3; **6-11**, 68282-98-4; **6-12**, 69195-50-2; **6-13**, 97750-80-6; **6-14**, 97750-81-7; **6-15**, 97750-82-8; **6-16**, 97750-83-9; **6-17**, 97750-84-0; **6-18**, 97750-85-1; **6-19**, 97750-86-2; **6-20**, 97750-87-3; **6-21**, 97763-77-4; **6-22**, 97750-88-4; **6-23**, 97750-89-5; **6-24**, 97750-90-8; **6-25**, 97750-91-9; **6-26**, 97750-92-0; **6-27**, 97750-93-1; **6-28**, 97750-94-2; **7-1**, 97750-95-3; **7-2**, 69195-39-7; **7-3**, 69195-40-0; **7-4**, 69195-41-1; **7-5**, 69195-48-8; **7-6**, 97750-96-4; **7-7**, 69195-49-9; **7-8**, 97750-97-5; **7-9**, 97750-98-6; 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$PhCH_2C(NH_2)$=NH·HCl, 2498-46-6; *t*-$BuC(NH_2)$=NH·HCl, 18202-73-8; EtC(NH_2)=NH·HCl, 3599-89-1; $PrC(NH_2)$=NH·HCl, 3020-81-3; $CH_3(CH_2)_{16}C(NH_2)$=NH·HCl, 63979-63-5; 3-$ClC_6H_4C(OEt)$=NH·HCl, 60612-87-5; $CH_3OCH_2C(NH_2)$=NH·HCl, 1903-91-9; MeBr, 74-83-9; EtBr, 74-96-4; PrBr, 106-94-5; BuBr, 109-65-9; *i*-PrBr, 75-26-3; c-PrBr, 4333-56-6; *t*-$BuCH_2C(NH_2)$=NH·HCl, 61457-23-6; $EtCH(CH_3)C(NH_2)$=NH·HCl, 61457-22-5; $EtCOCHClCO_2Et$, 24045-73-6; H_2NCH_2Ph, 100-46-9; $H_2NCH_2CH_2NMe_2$, 811-93-8; H_2N-cyclopentyl, 1003-03-8; H_2N-1-adamantyl, 768-94-5; H_2NN=C(SMe)NHMe, 57561-23-6; $HNMe_2$, 124-40-3; H_2N-3-pyridyl, 462-08-8; H_2NCH_2-2-furyl, 617-89-0; H_2NCH_2-2-thienyl, 27757-85-3; NH_2NH_2, 302-01-2; $BrCH(CO_2Et)_2$, 685-87-0; ethyl butyrylacetate, 3249-68-1; ethyl 2-chloro-3-oxohexanoate, 67271-32-3; formamide, 75-12-7; *o*-propoxybenzamide, 59643-84-4; fluorosulfonate, 421-20-5; ethyl

carbazate, 4114-31-2; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 84-58-2; 3-aminopyrazole, 1820-80-0; benzyl bromide, 100-39-0; allyl bromide, 106-95-6; iodomethane, 74-88-4; ethyl bromoacetate, 105-36-2; cyclopropanemethanol methanesulfonate, 696-77-5; ethyl 4-bromocrotonate, 6065-32-3; iodoethane, 75-03-6; propargyl bromide, 106-96-7; iodopropane, 107-08-4; 2-bromoacetic acid, 79-08-3; 3-chloro-1,2-propanediol, 96-24-2; phenacyl bromide, 70-11-1; 1-bromo-3-methylbutane, 107-82-4; ethyl 2-bromopropionate, 535-11-5; 1,4-dibromo-2-butene, 6974-12-5; *N*-methylpiperazine, 109-01-3; *N*-(diphenylmethyl)piperazine, 97763-80-9; 3-amino-2,3-dihydro-1*H*-1,2,4-triazole, 97751-70-7; 3-amino-4-phenyl-2,3-dihydropyrazole, 97763-80-9.

Synthesis, Absolute Configuration, and Conformation of the Aldose Reductase Inhibitor Sorbinil

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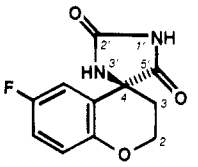
The aldose reductase inhibitor 2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione was resolved into its enantiomers. Sorbinil, the *S* isomer, was found to be a better inhibitor of the enzyme in vitro and in vivo than the corresponding *R* isomer. X-ray data on sorbinil, which were used to determine its absolute configuration, are presented. NMR studies of sorbinil in solution indicate the existence of two conformers with a low energy barrier for interconversion.

Aldose reductase inhibitors are potentially of therapeutic interest because they may play a role in preventing or treating chronic complications of diabetes mellitus. Sorbinil, the *S* isomer of 2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (1), is an aldose

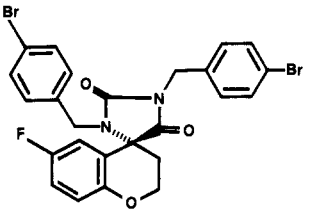


sorbinil (1)

reductase inhibitor that shows excellent in vivo activity in animal models[1,2] and is currently in clinical trials. Interestingly, sorbinil is considerably more potent than its *R* enantiomer in inhibiting aldose reductase, as shown in Table I. Analogous results were observed in an in vivo model (Table I), and this apparently highly stereospecific interaction of sorbinil with aldose reductase made it important to determine its absolute configuration and solution conformation.

Sorbinil and its enantiomer were synthesized by the reaction sequence shown in Scheme I, involving a brucine resolution of the racemic hydantoin precursor.[3] The free base of brucine forms a crystalline complex with sorbinil, whereas the enantiomer of sorbinil only forms a crystalline complex with brucine hydrochloride. Since this resolution technique does not work with certain congeners of sorbinil, a synthesis via an asymmetric induction sequence has also developed that seems generically applicable to optically active spiro hydantoins.[4]

The absolute configuration of sorbinil was established by single-crystal X-ray analyses. In an attempt to simplify the problem by the presence of a heavy atom we prepared the N_1',N_3'-bis(*p*-bromobenzyl) derivative **7** of the enantiomer of sorbinil. However, crystals of **7** proved unsuitable for X-ray analysis. On the other hand, the corresponding bis(*m*-bromobenzyl) derivative **8** yielded readily to X-ray analysis and, as depicted in Figure 1, showed that the absolute configuration of this derivative is *R* and that, therefore, the absolute configuration of sorbinil is *S*.



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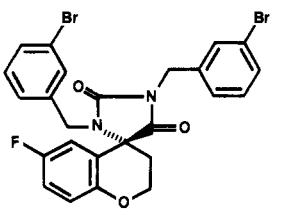
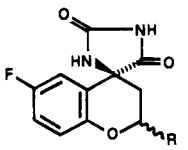


8



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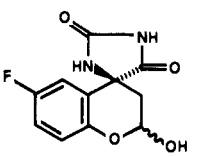

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Subsequently, an X-ray analysis of sorbinil itself confirmed this result.

The problem of solution conformations was approached by using both theoretical and NMR analyses. Molecular mechanical energy computations[5] of sorbinil yield two potential energy minima with torsion angles about the C_2–C_3 bond of approximately ±60°. These minima correspond to the pseudochair forms **9a**, with the N_3' nitrogen of the spiro hydantoin ring in a pseudoequatorial position and **9b** with a pseudoaxial N_3' nitrogen. The energy computations predict that **9a** is more stable than **9b** by 570 cal/mol^{-1}.

Inspection of the X-ray structure of **8** (figure 1) shows that this sorbinil derivative indeed crystallizes in a form corresponding to **9a**, with the N_3' nitrogen in a pseudoequatorial position. Similarly, the X-ray analysis of sorbinil itself (Figure 2) shows that the unsubstituted compound

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(2) M. J. Peterson, R. Sarges, C. E. Aldinger, and D. P. MacDonald, *Metab. Clin. Exp.*, *28* (Suppl. 1), 456 (1979).
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(4) R. Sarges, H. R. Howard, Jr., and P. R. Kelbaugh, *J. Org. Chem.*, **47**, 4081 (1982).
(5) These energy calculations were carried out by using the MMI program (N. L. Allinger, et al., *QCPE* 11, 318 (1976). The authors will provide parameters on request.

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