New Compounds

Synthesis of Thiocarbamate S-Ester Derivatives

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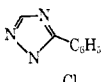
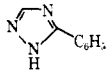
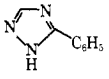
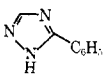
We have synthesized a number of substituted thiocarbamates of the general formula $R_1SCONHR_2$ (see Table I). Our attempt was to generate a thiocarbamate derivative of a tolnaftate-like compound having both antifungal and antibacterial[1] activity. The compounds were evaluated[2] in a primary *in vitro* screen (agar strip) against bacteria and fungi. None of them demonstrated a zone of inhibition equal to tolnaftate when evaluated at the equiv concn.

TABLE I

No.	R_1	R_2	Mp, °C	Procedure	Reaction solvent	Formulas[b]
1	C_6H_5		151–154	A	THF	$C_9H_8N_4S$[c]
2	C_6H_5		209–210	A	THF	$C_{15}H_{12}N_4OS$
3	C_6H_5		180–182	A	THF	$C_{14}H_9ClN_2OS_2$
4	C_6H_5	2-Naphthyl	145–147	A	THF	$C_{17}H_{13}NOS$
5	C_6H_5	C_6H_4OH	148–150	A	THF	$C_{13}H_{11}NO_2S$
6	C_6H_5	$CH_2C_6H_4Cl$	127–129	A	THF	$C_{14}H_{12}ClNOS$
7	C_6H_5	*i*-Pr_2[a]	104–107	B	THF	$C_{13}H_{19}NOS$
8	Et		127–130	A	THF	$C_5H_8N_4OS$[c]
9	*n*-Pr		103–105	A	THF	$C_7H_{10}N_2OS_2$
10	*i*-Pr		142–143	A	THF	$C_7H_{10}N_2OS_2$
11	Et		160–162	B	D[d]	$C_{11}H_{12}N_4OS$
12	*n*-Pr		148–150	A	D	$C_{12}H_{14}N_4OS$
13	*i*-Pr		189–191	A	D	$C_{12}H_{14}N_4OS$
14	Et	$CH_2C_6H_5$	61–62	A	D	$C_{10}H_{13}NOS$

[a] Disubstituted amide resulted as shown by elemental analysis and spectral data. [b] All compds were analyzed for C, H, N unless otherwise noted. [c] Also S anal. [d] D, dioxane.

Experimental Section

Thiocarbamates. Method A.—To a soln of the amine in the reaction solvent (see Table I) was added dropwise 0.5 equiv of the appropriate chlorothioformate dissolved in the reaction solvent. The mixt was allowed to stir for 18 hr. The amine salt was isolated by filtration and the thiocarbamate by evapn of the filtrate under reduced pressure. The product was recrystd from EtOH or PhH–Et_2O.

Method B.[3]—To a soln of amine in the reaction solvent (see Table I) was added dropwise 0.5 equiv of the appropriate chlorothioformate dissolved in the reaction solvent. After stirring overnight the mixt was poured into ice water. The solid thiocarbamate was collected by filtration, washed successively with 2 *N* HCl and H_2O, and recrystd from H_2O or Me_2CO–H_2O.

Acknowledgments.—Grateful acknowledgment is made of the valuable assistance of John D. Hansard.

(1) R. E. Orth, W. I. Darby, and N. F. Billups, *Can. J. Pharm. Sci.*, **2**, 48 (1968).

(2) M. Harris, "Pharmaceutical Microbiology," Bailliere, Tindall, and Cox, London, 1964, p 171.

(3) D. G. Crosby and C. Niemann, *J. Amer. Chem. Soc.*, **76**, 4458 (1954).

Potential Folic Acid Antagonists. 6. Potential Irreversible Folate Reductase Inhibitors Derived from 2,4-Diamino-5-arylazopyrimidines

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Previous studies[1,2] have described the irreversible inhibition of folate reductase produced by 5-arylazopyrimidines bearing an alkylating function at the 6 position (I). It appeared of interest in the light of our previous[1,3,4] rationalizations of the structure–activity relationships of 5-arylazopyrimidines to prepare and examine the activities of related compounds in which the alkylating function is attached to the 5-aryl group (II). In view of the pronounced lack of activity of the compounds listed in Table III $(I)/(S)_{0.5} > 5.0$) the corresponding alkylating analogs (X = Cl) were not prepared.

Experimental Section[5]

2-Nitro-ω-bromoalkylbenzenes (IV, *n* = 2–5).—These compds were prepared by nitration and fractional distillation of 2-bromo-

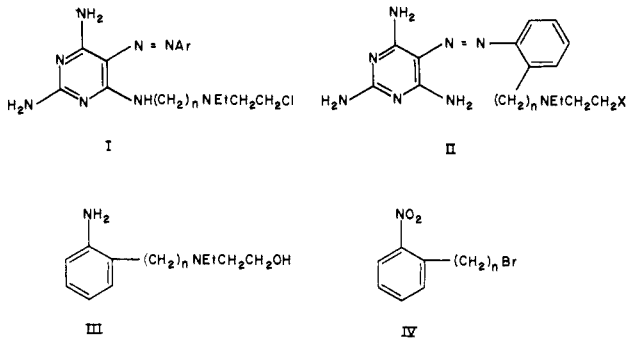
(1) J. Hampshire, P. Hebborn, A. M. Triggle, and D. J. Triggle, *J. Med. Chem.*, **8**, 745 (1965).

(2) J. Hampshire, P. Hebborn, A. M. Triggle, and D. J. Triggle, *J. Pharm. Sci.*, **55**, 453 (1966).

(3) S. S. Chatterjee, D. R. Garrison, R. Kaprove, J. F. Moran, A. M. Triggle, D. J. Triggle, and A. Wayne, *J. Med. Chem.*, **14**, 499 (1971).

(4) S. S. Chatterjee, S. Ludwig, J. F. Moran, D. J. Triggle, and A. Wayne, *ibid.*, **14**, 1237 (1971).

(5) Melting points were recorded on a Thomas-Kofler hot stage and are corrected. Analyses were performed by Dr. A. E. Bernhardt and, where indicated only by symbols of the elements, were within 0.4% of the theoretical values.



ethyl-, 3-bromopropyl-, 4-bromobutyl-, and 5-bromopentylbenzene according to lit. procedures.

2-Nitro-(ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkyl)benzenes.—A soln of IV (0.1 mole) and *N*-ethylethanolamine (0.2 mole) in C_6H_6 (150 ml) was refluxed for 24 hr. The PhH layer was washed thoroughly (H_2O) and then extd with 10% HCl. The acid ext was basified and extd with Et_2O, dried, and distd *in vacuo* (Table I).

Table I
2-Nitro-(ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkyl)benzenes

n	Bp (mm), °C	Yield, %	Formula[a]
1	145 (0.05)	72	$C_{11}H_{16}N_2O_3$
2	138 (0.10)	68	$C_{12}H_{18}N_2O_3$
3	152 (0.10)	70	$C_{13}H_{20}N_2O_3$
4	116 (0.05)	66	$C_{14}H_{22}N_2O_3$
5	165 (0.10)	52	$C_{15}H_{24}N_2O_3$

[a] All compds were analyzed for C, H, N.

2-Amino-(ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkyl)benzenes (III, *n* = 1–5).—Solns of the nitro compd (0.05 mole) in EtOH (100 ml) were reduced at 50° with 5% Pd/C catalyst (200 mg). The amines were isolated and characterized as the dihydrochlorides (Table II).

Table II
2-Amino-(ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkyl)-benzene Dihydrochlorides

n	Mp, °C[a]	Yield, %	Formula[b]
1	151	85	$C_{11}H_{20}Cl_2N_2O_3$
2	132	95	$C_{12}H_{22}Cl_2N_2O_3$
3	169	90	$C_{13}H_{24}Cl_2N_2O_3$
4	142	91	$C_{14}H_{26}Cl_2N_2O_3$
5	172	82	$C_{15}H_{28}Cl_2N_2O_3$

[a] Recrystn from *i*-PrOH–Et_2O. [b] All compds were analyzed for C, H, Cl, N.

2,4,6-Triamino-5-(2-ω-*N*-ethyl-*N*-2-hydroxyethylaminoalkylphenyl)azopyrimidines (II, *n* = 1–5) were prepd by the coupling procedure previously described[1,3,4] and are listed in Table III.

Table III
2,4,6-Triamino-5-(2-ω-*N*-ethyl-*N*-2[1]-hydroxyethylaminophenyl)azopyrimidines (II, *n* = 1–5)

n	Mp, °C[a]	Solvent	Yield, %	Formula[b]
1	185	EtOH	70	$C_{15}H_{22}N_8O$
2	175	EtOH	75	$C_{16}H_{24}N_8O$
3	165	*i*-PrOH	65	$C_{17}H_{26}N_8O$
4	170	*i*-PrOH	80	$C_{18}H_{28}N_8O$
5	*a*		67	

[a] Very hygroscopic: a satisfactory anal. could not be obtd. [b] All compds except **5** were analyzed for C, H, N.

Enzyme Procedure.—Chicken liver dihydrofolate reductase (partially purified) was employed with the protocol previously described.[3,4]

Pyrazoles. 4. Analogs of 3-(3,3-Dimethyl-1-triazeno)pyrazole-4-carboxamide[1]

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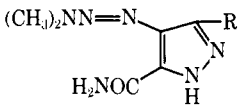
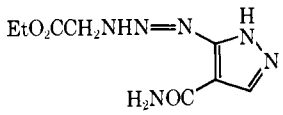
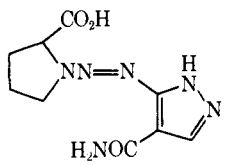
The antileukemic activity exhibited by 3-(3,3-dimethyl-1-triazeno)pyrazole-4-carboxamide[2] and its stability toward light and heat[2] prompted a synthesis of closely related compounds for continued study. The isomeric 4-(3,3-dimethyl-1-triazeno)pyrazole-3-carboxamide (Ia) and a homolog of Ia, 4-(3,3-dimethyl-1-triazeno)-5-methylpyrazole-3-carboxamide (Ib), as well as two amino acid derivatives of 3-diazopyrazole-4-carboxamide,[3] II and III, were prepared as described in the Experimental Section.



Ia, R = H
b, R = Me



II



III

Experimental Section[4]

4-Diazopyrazole-3-carboxamide.—To a suspension of 10 g of finely divided 4-aminopyrazole-3-carboxamide[5] in 100 ml of H_2O was added 6 ml of concd HCl. To the resulting soln was added dropwise, at 5°, 5.4 g of $NaNO_2$ in 30 ml of H_2O. A tan-colored ppt formed gradually. The mixt was stirred for 30 min, and the solid was filtered off, washed with cold H_2O and Me_2CO, and dried at 80° to yield 7.5 g (69% yield) of product, which decompd violently with a sharp sound at 220° upon rapid heating, ν 4.5 μ (diazo). *Anal.* ($C_4H_3N_5O$) C, H, N.

4-Diazo-5-methylpyrazole-3-carboxamide was prepd in a similar fashion from 4-amino-5-methylpyrazole-3-carboxamide[6] in 47% yield. In contrast to 4-diazopyrazole-3-carboxamide, this light yellow solid[7] decompd gradually upon heating above 200°. *Anal.* ($C_5H_5N_5O$) C, H, N.

4-(3,3-Dimethyl-1-triazeno)pyrazole-3-carboxamide (Ia).—To 125 ml of EtOAc, satd with anhyd Me_2NH at 20° was added 5 g of finely powdered 4-diazopyrazole-3-carboxamide. The mixt was stirred for 3 hr at room temp. The solid was collected by filtration, washed with EtOAc, and recrystd from MeOH to give 1.6 of Ia, mp 215–216°. *Anal.* ($C_6H_{10}N_6O$) C, H, N.

4-(3,3-Dimethyl-1-triazeno)-5-methylpyrazole-3-carboxamide (Ib), mp 193–194° (MeOH), was prepd in 25% yield from 4-

(1) This investigation was supported by Contract No. PH 43-65-94 with Chemotherapy, National Cancer Institute of the National Institutes of Health, Public Health Services.

(2) C. W. Noell and C. C. Cheng, *J. Med. Chem.*, **12**, 545 (1969).

(3) C. C. Cheng, R. K. Robins, K. C. Cheng, and D. C. Lin, *J. Pharm. Sci.*, **57**, 1044 (1968).

(4) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

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(6) R. A. Long, J. F. Gerster, and L. B. Townsend, *J. Heterocycl. Chem.*, **7**, 863 (1970).

(7) Although not isolated, the existence of this compd was commented on in ref 6.