

## New Compounds

### Synthesis of Thiocarbamate S-Ester Derivatives

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
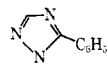
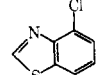



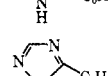
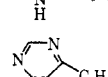
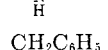
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We have synthesized a number of substituted thiocarbamates of the general formula  $R_1\text{SCONHR}_2$  (see Table I). Our attempt was to generate a thiocarbamate derivative of a tolinaftate-like compound having

TABLE I

No.	R <sub>1</sub>	R <sub>2</sub>	Mp, °C	Pro- cedure	Re- action solvent	Formulas <sup>b</sup>
1	C <sub>6</sub> H <sub>5</sub>		151–154	A	THF	C <sub>9</sub> H <sub>8</sub> N <sub>4</sub> S <sup>c</sup>
2	C <sub>6</sub> H <sub>5</sub>		209–210	A	THF	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> OS
3	C <sub>6</sub> H <sub>5</sub>		180–182	A	THF	C <sub>14</sub> H <sub>9</sub> ClN <sub>2</sub> OS <sub>2</sub>
4	C <sub>6</sub> H <sub>5</sub>	2-Naphthyl	145–147	A	THF	C <sub>17</sub> H <sub>13</sub> NOS
5	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> OH	148–150	A	THF	C <sub>13</sub> H <sub>11</sub> NO <sub>2</sub> S
6	C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Cl	127–129	A	THF	C <sub>14</sub> H <sub>12</sub> ClNOS
7	C <sub>6</sub> H <sub>5</sub>	<i>i</i> -Pr <sup>a</sup>	104–107	B	THF	C <sub>13</sub> H <sub>19</sub> NOS
8	Et		127–130	A	THF	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> OS <sup>c</sup>
9	<i>n</i> -Pr		103–105	A	THF	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> OS <sub>2</sub>
10	<i>i</i> -Pr		142–143	A	THF	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> OS <sub>2</sub>
11	Et		160–162	B	D <sup>d</sup>	C <sub>11</sub> H <sub>12</sub> N <sub>4</sub> OS
12	<i>n</i> -Pr		148–150	A	D	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> OS
13	<i>i</i> -Pr		189–191	A	D	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub> OS
14	Et	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	61–62	A	D	C <sub>10</sub> H <sub>13</sub> NOS

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

mate derivative of a tolinaftate-like compound having both antifungal and antibacterial<sup>1</sup> activity. The compounds were evaluated<sup>2</sup> in a primary *in vitro* screen (agar strip) against bacteria and fungi. None of them

demonstrated a zone of inhibition equal to tolinaftate when evaluated at the equiv concn.

### 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<sub>2</sub>O.

**Method B.**<sup>3</sup>—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<sub>2</sub>O, and recrystd from H<sub>2</sub>O or Me<sub>2</sub>CO–H<sub>2</sub>O.

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(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<sup>1,2</sup> 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<sup>1,3,4</sup> 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)<sub>0.5</sub> > 5.0) the corresponding alkylating analogs (X = Cl) were not prepared.

### Experimental Section<sup>5</sup>

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

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

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

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

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

(5) Melting points were recorded on a Thomas-Kofter 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.

(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.