Table II
Results from the Correlation Equation[a]

| Biological system | $n$ | X: Log $P$ $r^2$ | Log $P$ $s$ | $\alpha$ $r^2$ | $\alpha$ $s$ | Mol wt $r^2$ | Mol wt $s$ | $F$* $r^2$ | $F$* $s$ | $P_r$ $r^2$ | $P_r$ $s$ | $P_r$* $r^2$ | $P_r$* $s$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Log $(1/C) = aX + b$ | | | | | | | | | | | | | |
| Tadpole narcosis[b] | 53 | 0.913 | 0.343 | 0.683 | 0.654 | 0.567 | 0.765 | 0.758 | 0.571 | 0.556 | 0.775 | 0.861 | 0.434 |
| Narcosis frog muscle[c] | 23 | 0.944 | 0.242 | 0.630 | 0.623 | 0.569 | 0.672 | 0.617 | 0.634 | 0.659 | 0.598 | 0.841 | 0.408 |
| 1:1 $M$ complex with bovine serum albumin[c] | 42 | 0.920 | 0.159 | 0.094 | 0.536 | 0.163 | 0.515 | Insufficient data | | 0.095 | 0.536 | 0.648 | 0.334 |
| Log $(1/C) = aX + bX^2 + c$ | | | | | | | | | | | | | |
| $I_{50}$ chick embryo hatching[d] | 10 | 0.965 | 0.112 | 0.909 | 0.179 | 0.856 | 0.226 | 0.933 | 0.155 | | | 0.923 | 0.165 |

[a] See text for definition of parameters represented by $X$. $n$ = number of data points used; $r^2$ = square of the correlation coefficient and can be taken as the per cent of the variance in the data "explained" by the regression; $s$ = the standard deviation from regression. [b-d] See corresponding footnotes in Table I.

tions do not allow us to include, we have found results like those of Table II.

In making comparisons of the above type, care must be taken to select meaningful data. As Meyer and Hemmi[4] pointed out in comparing different solvent reference systems for log $P$, nothing is to be gained by using homologous series for comparisons. One can also see from a comparative study of different sets of biological data that if, say, only relatively apolar changes are made in a parent molecule, quite similar results can be obtained using a variety of parameters. This would appear to account for the rather close agreement Ostrenga[9] obtained in comparing $F$ and $\pi$. The use of a variety of drugs as narcotics convinced Meyer and Hemmi that alcohols make better reference systems than esters such as olive oil. Our own studies[28] suggest that a variety of simple polar solvents would give reasonable results, but that hydrocarbons would not make good reference systems.[28] It still remains to be seen how close octanol–water fits the ideal for a reference system. In a study[5] of 54 different linear correlations based on log $P$ (octanol–water), 47 had $r$ values of 0.95 or better. This means that only 10% of the variance in the biological data is not accounted for. The 10% must be split between errors in determination of log $P$, errors in measuring log $(1/C)$, and the quality of the octanol–water model. It is not unreasonable to expect errors of 3–5% in even the best biological data and errors of 1–2% in log $P$. Thus it would seem that relatively little improvement could be obtained by selection of a better solvent reference system.

In extrathermodynamic correlations of the above type, the importance of choosing a reference system as close as possible to that of the one under study has been emphasized.[29] Thus it appears to us *a priori* that a model reference system such as octanol–water would be more able to account for drug distribution than a more abstract and artificial parameter such as parachor. It is our hope that log $P$ can be used with some confidence to account for what these days is termed the hydrophobic[30] character of drugs. Not only does log $P$ have the advantage of being relatively easily measured experimentally, it is also an additive and constitutive constant and thus may be estimated from known constants for the various constituents of a given drug.[5,31]

(28) C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).

(29) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, New York, N. Y., 1963, p 128.

(30) G. Némethy, *Angew. Chem.*, **6**, 195 (1967).

(31) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

# Potential Antitumor Agents. II. Effects of Modifications in the Side Chain of 1-Formylisoquinoline Thiosemicarbazone[1,2]

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A number of modifications have been made in the formyl thiosemicarbazone side chain of 1-formylisoquinoline thiosemicarbazone to ascertain the importance of this part of the molecule for antineoplastic activity; tumor-inhibitory potency and host toxicity of these compounds were assessed in mice bearing Sarcoma 180 ascites cells. Substitutions made on the different positions of the side chain resulted in either a diminution or a total loss of tumor-inhibitory activity, indicating that the intactness of this portion of the molecule was essential for 1-formylisoquinoline thiosemicarbazone to function as an inhibitor of the growth of malignant cells.

A number of $\alpha$-N-heterocyclic aldehyde thiosemicarbazones, possessing the potential to form coordination compounds with certain transition metals, have been shown to be potent inhibitors of the growth of a variety of transplanted rodent neoplasms.[3] The meta-

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(2) This work was supported by Grant T-23 from the American Cancer Society and Grant CA-02817 from the National Cancer Institute, U. S. Public Health Service.

(3) (a) R. W. Brockman, J. R. Thomson, M. J. Bell, and H. E. Skipper, *Cancer Res.*, **16**, 167 (1956); (b) F. A. French and E. J. Blanz, Jr., *J. Med. Chem.*, **9**, 585 (1966); (c) F. A. French and E. J. Blanz, Jr., *Cancer Res.*, **25**, 1454 (1965).

bolic alterations produced by one of the most active compounds in this series, 1-formylisoquinoline thiosemicarbazone, have been studied; this agent caused marked inhibition of the synthesis of DNA by preventing the conversion of ribonucleotides to deoxyribonucleotide forms.[4] Blockade of the formation of RNA and protein also occurred, but these sites were considerably less sensitive to drug-induced inhibition. A similar mechanism of action appears to be operative with both 2-formyl-3-hydroxypyridine thiosemicarbazone and 2-formyl-5-hydroxypyridine thiosemicarbazone,[5] two thiosemicarbazone derivatives of the pyridine ring system with relatively high therapeutic indices as antineoplastic agents.[6]

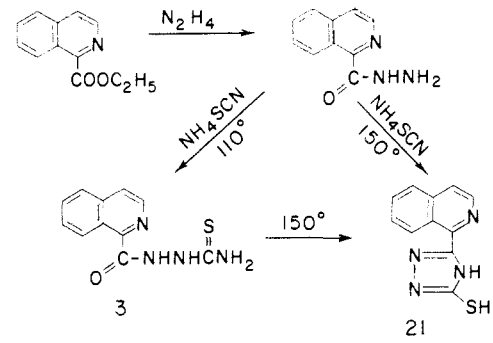
As part of an investigation designed to (a) develop new antineoplastic agents and (b) define the structural requirements for tumor-inhibitory activity, 1-formylisoquinoline thiosemicarbazone has been subjected to systematic structural modification. The initial approach employed was the synthesis of a series of 5-substituted 1-formylisoquinoline thiosemicarbazones.[7] These studies indicated that the dimensions of the 1-formylisoquinoline thiosemicarbazone system at the 5 position could be modified with the retention of high antineoplastic activity, since substituents such as 5-hydroxy or 5-acetoxy did not appear to lessen carcinostatic potency of the parent compound.

Soluble derivatives of several of these extremely insoluble agents have also been synthesized and were found to have tumor-inhibitory activity equal to or better than the parent compounds.[8]

In the present investigation a number of alterations in the formyl thiosemicarbazone side chain ($RCH{=}NNHCSNH_2$) have been made to determine the effect of such substitutions on both tumor-inhibitory potency and host toxicity in mice bearing Sarcoma 180 ascites cells. Such modifications in the formyl thiosemicarbazone side chain are of importance to an understanding of the role of chelation in the biological action of these agents, since a conjugate N*-N*-S* tridentate ligand system was reported to be a common feature of compounds with carcinostatic potency.[9b]

**Chemistry.**—Substitution of the H atom in the formyl group of the side chain by a methyl function was accomplished by synthesizing 1-isoquinolyl methyl ketone by the procedure of Padbury and Lindwall;[9] the ketone was then treated with thiosemicarbazide to produce **2**. A further modification was made by synthesizing isoquinaldinoylthiosemicarbazide (**3**), in which the aldehyde hydrogen was replaced by a carbonyl oxygen (Chart I). Compound **3** was obtained by treating ethyl isoquinaldinate with hydrazine to give isoquinaldinic acid hydrazide, which subsequently, on reaction with $NH_4SCN$ at 110°, yielded the desired compound. If the reaction temperature was increased to 150°, however, 1 mole of $H_2O$ was lost and cyclization to form 3-mercapto-5-(1-isoquinolyl)-1,2,4(H)-triazole (**21**) occurred; compound **21** was also obtained by heating **3** at 150°.

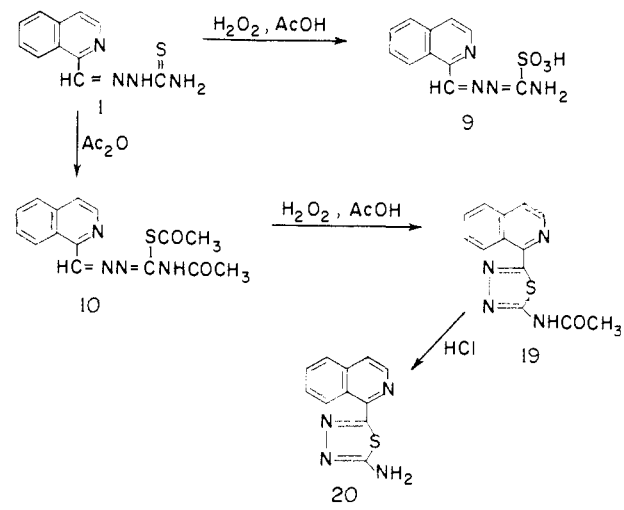
CHART I




Substitution of the 2′-nitrogen atom of the side chain was accomplished by fabricating the 2′-methyl (**4**) and 2′-phenyl thiosemicarbazones (**5**). These compounds were prepared by the reaction of isoquinoline-1-carboxaldehyde (1-A) with either 2-methylthiosemicarbazide[10] or 2-phenylthiosemicarbazide,[11] respectively. The S atom of 1-formylisoquinoline thiosemicarbazone (**1**) was replaced by either =NH (**6**), =O (**7**), or $-SCH_3$ (**8**). These compounds were obtained by treating 1-A with either aminoguanidine, semicarbazide, or 3-methylthiosemicarbazide, respectively. The intermediate 3-methylthiosemicarbazide was fabricated by refluxing equimolar amounts of thiosemicarbazide and MeI.[12]

Oxidation of **1** with $H_2O_2$ and AcOH formed 1-amino-4-isoquinolyl-2,3-diazabuta-1,3-diene-1-sulfonic acid (**9**), in which the S atom is replaced by an $SO_3H$ group (Chart II). This reaction has previously been reported[13] for the oxidation of aromatic aldehyde thiosemicarbazones. Characterization of **9** was accomplished by ir and elemental analyses. Comparison of ir spectra of **1** and **9** showed that the absorption from C=S at 835 $cm^{-1}$ in **1** was absent in **9**. In addition, **9** had strong absorptions in the 1220–1155-$cm^{-1}$ region which

CHART II




(1) (a) A. C. Sartorelli, *Biochem. Biophys. Res. Commun.*, **27**, 26 (1967); (b) A. C. Sartorelli, *Pharmacologist*, **9**, 192 (1967); (c) A. C. Sartorelli, M. S. Zedeck, K. C. Agrawal, and E. C. Moore, *Fed. Proc.*, **27**, 650 (1968).

(5) (a) A. C. Sartorelli and B. A. Booth, *Proc. Am. Assoc. Cancer Res.*, **9**, 61 (1968); (b) A. C. Sartorelli, B. A. Booth, and E. C. Moore, *ibid.*, **10**, 299 (1969).

(6) (a) F. A. French and E. J. Blanz, Jr., *Cancer Res.*, **26**, 1638 (1966); (b) F. A. French and E. J. Blanz, Jr., *Gann* (Monograph 2), 51 (1967); (c) E. J. Blanz, Jr., and F. A. French, *Cancer Res.*, **28**, 2419 (1968).

(7) K. C. Agrawal, B. A. Booth, and A. C. Sartorelli, *J. Med. Chem.*, **11**, 700 (1968).

(8) K. C. Agrawal and A. C. Sartorelli, *J. Pharm. Sci.*, **57**, 1948 (1968).

(9) J. J. Padbury and H. G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945).

(10) E. Cattelain, *Compt. Rend.*, **209**, 799 (1939).

(11) H. G. Mautner and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 97 (1956).

(12) E. Cattelain, *Bull. Soc. Chim. France*, **11**, 249 (1944).

(13) E. Hoggarth, *J. Chem. Soc.*, 2202 (1951).

was attributed to the $SO_3H$ group. Acetylation of **1** produced 1-formylisoquinoline $N^4$,S-diacetylthiosemicarbazone (**10**), which on oxidation with $H_2O_2$ and AcOH followed by acid hydrolysis produced 2-amino-5-(1-isoquinolyl)-1,3,4-thiadiazole (**20**).

Replacement of the terminal amide group in **1** by an acid (**11**) or an ester (**14**) was accomplished by reaction of 1-A with sodium dithiocarbazate or methyl dithiocarbazate, respectively. Both intermediates were synthesized utilizing the procedure of Audrieth, *et al.*[14] To determine the requirement for the two terminal H atoms of the amide group for biological activity, the $NH_2$ group was replaced by hydrazino (**12**), methylhydrazino (**13**), ethanolamino (**15**), isobutylamino (**16**), morpholino (**17**), and pyrrolidino (**18**) groups. These compounds were synthesized by treating 1-A with the respective 4′-substituted thiosemicarbazides, which were prepared by a general reaction of primary and secondary amines with dithiocarbazate esters.[15]

## Biological Results and Discussion

The parent compound **1** has been shown[7] to cause a pronounced lengthening of the life span of mice bearing Sarcoma 180 ascites cells; thus, administration of **1** to tumor-bearing mice at the maximum effective daily dose of 30 mg/kg for 6 consecutive days resulted in an average survival time of 39.9 days, as compared to 12.8 days for untreated control tumor-bearing animals. The effects of modifications in the side chain of **1** on antineoplastic activity are shown in Table I. Substitution of

TABLE I

EFFECT OF 1-FORMYLISOQUINOLINE THIOSEMICARBAZONES SUBSTITUTED IN THE SIDE CHAIN ON THE SURVIVAL TIME OF MICE BEARING SARCOMA 180 ASCITES CELLS

| Compd[a] | Max effective daily dose, mg/kg[b] | Av Δ wt, %[c] | Av survival days ± SE |
|---|---|---|---|
| None | | +18.8 | 12.8 ± 0.5 (30)[d] |
| 2 | 40 | +3.4 | 21.0 ± 1.2 (7)[e] |
| 6 | 80 | −6.6 | 29.6 ± 3.8 (10) |
| 12 | 20 | −4.6 | 17.5 ± 0.8 (10) |
| 13 | 2.5 | −0.9 | 18.6 ± 0.7 (10) |

[a] Compounds **3–5**, **7–11**, and **14–21** were inactive in this test system. [b] Administered once daily for 6 consecutive days, beginning 24 hr after tumor implantation. [c] Average weight change from onset to termination of drug treatment. [d] The values in parentheses indicate the number of animals employed. [e] Three of ten animals treated with this agent died during therapy; these mice were omitted in the calculation of the average survival time.

the H atom in the formyl group of the side chain by Me (**2**) resulted in a compound with reduced tumor-inhibitory potency. Conversion of **1** to isoquinaldinoylthiosemicarbazide (**3**) and cyclization of **3** to give **21** yielded compounds which were essentially inactive as inhibitors of the growth of Sarcoma 180. The requirement for the proton on N-2′ seemed to be critical since both **4** and **5**, substituted with either Me or Ph, respectively, were inactive biologically. This finding is in agreement with the postulated involvement of a chelation mechanism, involving a conjugate N*–N*–S* tridentate ligand system,[3b] for antineoplastic activity, since 2′-substituted thiosemicarbazones would not be expected to form the lactim form.

$$=N-NH-\underset{\displaystyle S}{\underset{|}{C}}- \rightleftharpoons =N-N=\underset{\displaystyle SH}{\underset{|}{C}}-$$

The lactim form as a resonance-hybrid anion $=N-N=C(S^-)-$ would be essential for chelation of a metal ion.

Replacement of S by NH (**6**) resulted in an active growth inhibitor which produced an optimum prolongation of the survival time of Sarcoma 180 tumor-bearing mice of 29.6 days. Compound **7**, in which S was replaced with O, was inactive in the test system employed. These results are also in accord with the involvement of a chelation mechanism in the biological mode of action of these agents, since the semicarbazone is much less active than the thiosemicarbazone as a metal-binding agent. Other modifications made at S, such as in **8–10** and **20**, gave agents that were completely ineffective in prolonging the survival time of mice bearing Sarcoma 180.

The presence of an intact terminal $NH_2$ group on the side chain of the parent compound **1** also appeared to be critical for maximum antineoplastic activity. Thus, replacement of the amide group by an acid (**11**) or an ester (**14**) resulted in inactive compounds. The requirement for the two terminal H atoms for biological activity was shown by the inactivity of **15–18** in the test system. Compounds **12** and **13**, in which the $NH_2$ group was replaced by $NHNH_2$ or $NHNHCH_3$, showed weak carcinostatic activity, producing survival times of 17.5 and 18.6 days, respectively.

## Experimental Section

Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses[16] were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

**Biological Methods.**—Compounds were tested for antineoplastic activity in mice bearing Sarcoma 180 ascites cells. Complete details of the biological methods have been described earlier.[7] Transplantation of the neoplasm was accomplished by innoculating mice intraperitoneally with approximately $4 \times 10^6$ ascites cells. Drugs were administered 24 hr later as fine suspensions by intraperitoneal injection; such therapy was continued once daily for 6 consecutive days. Determination of the sensitivity of the tumor to these agents was based upon the prolongation of survival time afforded by the drug treatment. Compounds were tested up to nontolerated doses at levels of 2.5, 5, 10, 20, 40, 60, 80, 120 and 160 mg/kg/day; the results of the maximum effective doses of the active tumor-inhibitory agents are presented in Table I.

**Chemical Methods.**—Thiosemicarbazones were prepared, in general, by treating the corresponding aldehyde and ketone derivatives of isoquinoline with the appropriately substituted thiosemicarbazide. EtOH solutions of each compound were mixed, acidified with a few drops of dilute AcOH, and warmed for a few minutes. The resulting thiosemicarbazones, which precipitated on cooling, were filtered and purified by washing with $H_2O$, EtOH, and $Et_2O$. Relevant data concerning these compounds are listed in Table II.

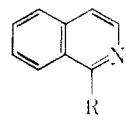
**Isoquinaldinic Acid Hydrazide.**—Ethyl isoquinaldinate was prepared according to the procedure of Padbury and Lindwall[9] except that the period of hydrolysis of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline with dilute $H_2SO_4$ was increased to 3 hr to accomplish complete hydrolysis. To a solution of 2.01 g of ethyl isoquinaldinate in 15 ml of absolute EtOH was added 5 ml of $N_2H_4 \cdot H_2O$. The mixture was heated at 100° for 1 hr,

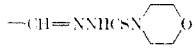
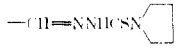
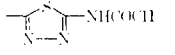
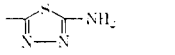
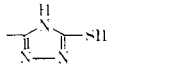
(14) L. F. Audrieth, E. S. Scott, and P. S. Kippur, *J. Org. Chem.*, **19**, 733 (1954).

(15) R. S. McElhinney, *J. Chem. Soc., C*, 950 (1966).

(16) Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE II



| Compd | R | Mp, °C dec | Formula | Analyses |
|---|---|---|---|---|
| 1 | $-CH{=}NNHCSNH_2$ | 224–226 | $C_{11}H_{10}N_4S$ | |
| 2 | $-(CH_3)C{=}NNHCSNH_2$ | 202–204 | $C_{12}H_{12}N_4S$ | C, H, N, S |
| 3 | $-CONHNHCSNH_2$ | 213–214 | $C_{11}H_{10}N_4SO$ | C, H, N, S |
| 4 | $-CH{=}NN(CH_3)CSNH_2$ | 175–176 | $C_{12}H_{12}N_4S$ | C, H, N |
| 5 | $-CH{=}NN(C_6H_5)CSNH_2$ | 176–179 | $C_{17}H_{14}N_4S$ | C, H, N, S |
| 6 | $-CH{=}NNHC(=NH)NH_2$ | 256–257 | $C_{11}H_{11}N_5$ | N |
| 7 | $-CH{=}NNHCONH_2$ | 199–200 | $C_{11}H_{10}N_4O$ | N |
| 8 | $-CH{=}NN{=}C(SCH_3)NH_2$ | 195–196 | $C_{12}H_{12}N_4S$ | C, H, N |
| 9 | $-CH{=}NN{=}C(SO_3H)NH_2$ | 200–201 | $C_{11}H_{10}N_4O_3S$ | C, H, N |
| 10 | $-CH{=}NN{=}C(SCOCH_3)NHCOCH_3$ | 274–275 | $C_{15}H_{14}N_4O_2S$ | C, H, S |
| 11 | $-CH{=}NNHCS_2Na$ | 266–268 | $C_{11}H_8N_3S_2Na$ | C, H, N |
| 12 | $-CH{=}NNHCSNHNH_2$ | 190–191 | $C_{11}H_{11}N_5S$ | C, H, N |
| 13 | $-CH{=}NNHCSNHNHCH_3$ | 163–164 | $C_{12}H_{13}N_5S$ | C, H, N, S |
| 14 | $-CH{=}NNHCS_2CH_3$ | 213–214 | $C_{12}H_{11}N_3S_2$ | C, H, N |
| 15 | $-CH{=}NNHCSNHCH_2CH_2OH$ | 160–161 | $C_{13}H_{14}N_4OS$ | C, H, N, S |
| 16 | $-CH{=}NNHCSNHCH_2CH(CH_3)_2$ | 169–171 | $C_{15}H_{18}N_4S$ | C, H, N, S |
| 17 |  | 178–179 | $C_{16}H_{16}N_4OS$ | C, H, N, S |
| 18 |  | 211–212 | $C_{15}H_{16}N_4S$ | C, H, N |
| 19 |  | 365–370 | $C_{13}H_{10}N_4OS$ | C, H, S |
| 20 |  | 223–224 | $C_{11}H_8N_4S$ | C, H, N |
| 21 |  | 303–305 | $C_{11}H_8N_4S$ | C, H, N, S |

allowing most of the EtOH to be removed by distillation. The resulting solution was diluted with 10 ml of $H_2O$ and neutralized with dilute AcOH. On cooling, white crystals, 1.5 g (80%), were obtained, mp 114°. *Anal.* ($C_{10}H_9N_3O$) C, H, N.

**Isoquinaldinoylthiosemicarbazide (3).**—Isoquinaldinic acid hydrazide (0.56 g) and 0.68 g of $NH_4SCN$ were mixed in 5 ml of $H_2O$ and heated at 110° for 1 hr. During the course of the reaction isoquinaldinic acid hydrazide went into solution and **3** slowly precipitated. The white precipitate was filtered, washed ($H_2O$), and crystallized from EtOH to yield 0.25 g (40%).

**1-Amino-4-isoquinolyl-2,3-diazabuta-1,3-diene-1-sulfonic Acid (9).**—Compound 1 (0.46 g) was added in small portions with stirring over a period of 15 min to a mixture of 2.5 ml of $H_2O_2$ (30%) and 10 ml of glacial AcOH at 0°; the stirring was continued for 2 hr at 0°. The reaction mixture was then stored at 4° for 48 hr. Yellow crystals of **9** were filtered and washed (EtOH). Recrystallization from dilute AcOH gave 0.45 g (80%).

**1-Formylisoquinoline $N^4$,S-Diacetylthiosemicarbazone (10).**—Compound 1 (1.15 g) was refluxed with $Ac_2O$ (10 ml) for 1 hr. The yellow color of the compound turned white during the reaction. The mixture was cooled and the white insoluble product was filtered, washed (EtOH), and dried to yield 1.25 g (80%), mp 272–274°. Crystallization from DMF raised the melting point to 274–275°.

**2-Amino-5-(1-isoquinolyl)-1,3,4-thiadiazole (20).**—Compound **10** (0.628 g) was added in small portions to a mixture of 10 ml of AcOH and 10 ml of $H_2O_2$ (30%) at 0°. The reaction mixture was allowed to warm to room temperature and then was heated at 70° for 15 min. On cooling, the product crystallized. It was collected by filtration, washed ($H_2O$, EtOH), and dried to yield 0.50 g (92%) of 2-acetamido-5-(1-isoquinolyl)-1,3,4-thiadiazole (**19**); it was recrystallized from DMF. Compound **19** (0.27 g) was refluxed in 10 ml of 50% HCl for 1 hr. The reaction mixture was cooled and made alkaline with a solution of NaOH to give 0.12 g (53%) of **20**, mp 220–221°. Crystallization from EtOH and $H_2O$ raised the melting point to 223–224°.

**3-Mercapto-5-(1-isoquinolyl)-1,2,4(H)-triazole (21).**—Isoquinaldinic acid hydrazide (0.374 g) and 0.304 g of $NH_4SCN$ in 5 ml of $H_2O$ were heated at 100° for 1 hr; the temperature was then increased to 150° for 15 min. The residue was washed ($H_2O$) and crystallized from EtOH to yield 0.20 g (44%).

**Acknowledgment.**—The authors wish to thank Miss Andrea F. Gorske and Miss Lynn A. Bon Tempo for excellent assistance.