

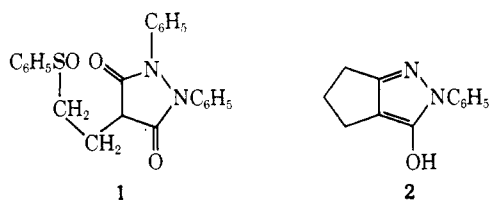
Synthesis, Alkylation, and Oxidation of Thieno[3,4-*c*]- and -[3,2-*c*]pyrazoles

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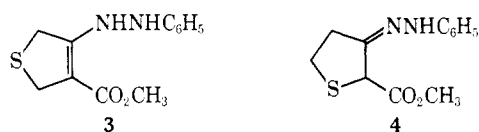
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Members of the pyrazole class of antiinflammatory-analgetic agents, especially phenylbutazone and oxyphenbutazone, are often employed in the management of rheumatoid arthritis, and sulfinpyrazone (**1**) has been used in the treatment of gout.¹ As an extension of our effort to prepare bicyclic analogs, such as the tetrahydrocyclopentapyrazolol **2**,² we now re-



port the synthesis, tautomeric behavior, and reactions of two series of new heterocyclic compounds, the thieno[3,4-*c*]- and -[3,2-*c*]pyrazolols (**5** and **6**).

Treatment of the known methyl tetrahydro-4-oxo-3- and -3-oxo-2-thiophenecarboxylates³ with phenylhydrazine provided the derivatives **3** and **4**. That compound **3**

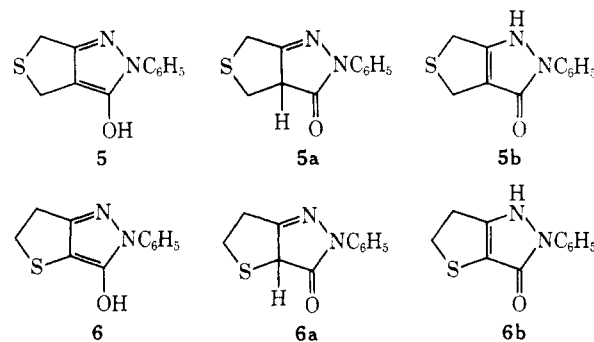


exists in the hydrazine tautomeric form in the solid state is shown by its ir spectrum, which exhibits a conjugated ester CO band at 6.04 μ . In contrast, compound **4** exists as the hydrazone, as indicated by its CO absorption at 5.78 μ . Similar products were obtained when the keto esters were allowed to react with *p*-methyl-, fluoro-, chloro-, and bromophenylhydrazines.

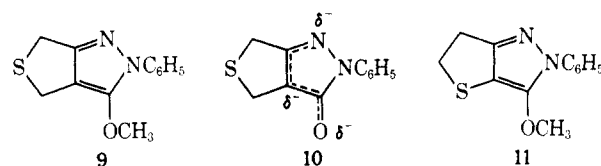
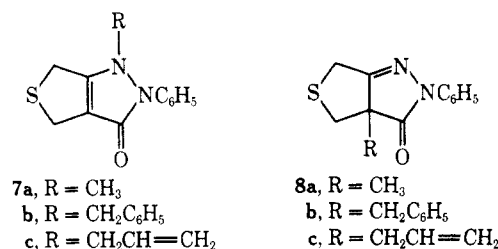
Cyclization of the phenylhydrazine derivatives **3** and **4** to the desired thienopyrazolols **5** and **6** was accomplished by heating in MeOH soln with a slight excess of NaOMe. Ring closures of the para-substituted phenylhydrazine products were also affected.

The bicyclic products exist in the solid state as the strongly H bonded OH tautomers **5** and **6**, as shown by the absence of CO absorption below 6.2 μ in the ir. In dil CHCl₃ soln, however, the pyrazolone tautomers **5a** and **6a** (ir 5.87 and 5.83 μ , respectively) are formed to the exclusion of OH forms **5** and **6** and conjugated pyrazolones **5b** and **6b**. This tautomeric behavior parallels that shown by **2**.²

In our earlier work with cyclopentapyrazolols,² it was obsd that alkylation of a tridentate anion formed from

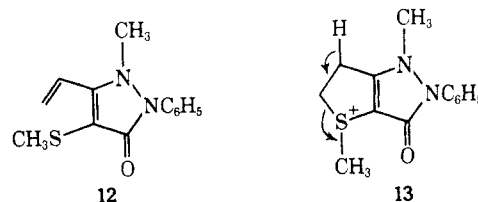


2 under basic conditions gave rise to products of C, N, and O substitution. A similar behavior was expected for thienopyrazolol **5**. Treatment of **5** with MeI and K₂CO₃ in Me₂CO did, indeed, afford a mixture of products. Chromatog sepn provided the *N*-Me (**7a**, ir 5.95 μ), the *C*-Me (**8a**, ir 5.83 μ), and the *O*-Me products (**9**, no C=O below 6.2 μ). The intermediacy of the tridentate anion **10** is therefore implicated. Compound **9** is



prepd more efficiently by treatment of **5** with MeOTs and NaOMe in DMF. Alkylation of **5** with PhCH₂Br gave the *N*-benzyl product **7b** and the *C*-benzyl isomer **8b**. Alkylation of **5** with allyl bromide yielded **7c** and **8c**.

Reaction of **6** with MeOTs and base gave a single methylation product, the *O*-Me compd **11** (no C=O ir absorption below 6.2 μ). Treatment of **6** with MeI and base failed to give the desired N, C, or O alkylation products, but instead provided, in low yield, a compd with the empirical formula C₁₃H₁₄N₂OS. The presence of one vinyl and two Me group signals in the nmr spec-



trum and a conjugated pyrazolone C=O band at 6.03 μ in the ir are consistent with formula **12**. This product can arise from double alkylation of **6** to the salt **13**, which then undergoes β elimination to **12**.

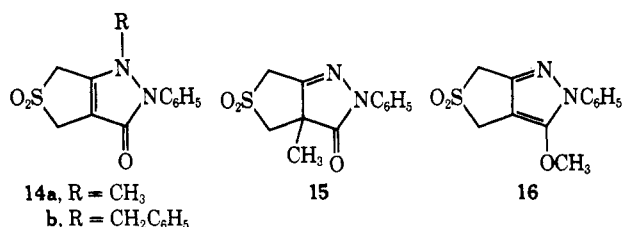
Oxidn of **7a**, **7b**, **8a**, and **9** with 2 equiv of *m*-chloroperoxybenzoic acid⁴ in CH₂Cl₂ at room temp provided the sulfones **14a**, **14b**, **15**, and **16**.

(1) W. C. Cutting, "Handbook of Pharmacology," 4th ed, Appleton-Century-Crofts, New York, N. Y., 1969, pp 619-621.

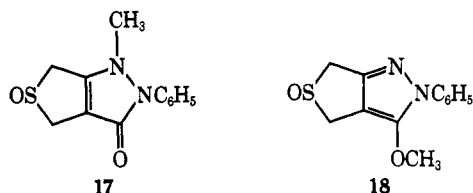
(2) R. P. Williams, V. J. Bauer, and S. R. Safir, *J. Med. Chem.*, **13**, 773 (1970).

(3) R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, **68**, 2229 (1946).

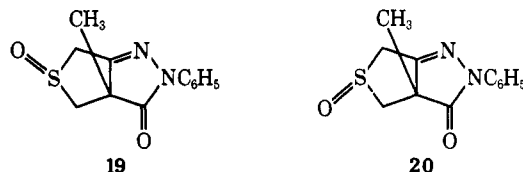
(4) L. A. Paquette, *ibid.*, **86**, 4383 (1964).



Oxidn of **7a** and **9** with 1 equiv of *m*-chloroperoxybenzoic acid⁵ in CH₂Cl₂ at 0° gave the sulfoxides **17** and **18**. Similar oxidn of **8a** gave a separable mixture of two



isomeric sulfoxides. Since **8a** contains an asymmetric C and the SO group is also asymmetric, diastereomers are possible, and the *cis* (**19**) and *trans* (**20**) compds are formed. The assignment of structures is based upon



the chemical shifts of the Me groups in **19** and **20**. The Me group of the parent **8a** resonates at δ 1.65 ppm. Oxidn to the sulfone **15**, in which an O atom must now be *cis* to the Me, effects a downfield shift to δ 1.75 ppm. A similar downfield shift to 1.86 ppm is shown by *cis*-sulfoxide **19**. In contrast, a shift to higher field (δ 1.52 ppm) is seen for the Me group of the other sulfoxide, which therefore must have the *trans* structure **20**. These observations are in accord with known deshielding effect of the sulfoxide bond on *cis*-situated γ -hydrogens.⁶

Oral administration of these thienopyrazoles at 250 mg/kg failed to inhibit significantly the carrageenin-induced rat-paw edema⁷ when assayed by the method of Winter, *et al.*⁸

Experimental Section⁹

Methyl 4-(2-*p*-X-Phenylhydrazino)-2,5-dihydro-3-thiophenecarboxylates and Methyl Tetrahydro-3-oxo-2-thiophenecarboxylate *p*-X-Phenylhydrazones.—To 16.0 g (0.1 mole) of methyl tetrahydro-4-oxo-3- or -3-oxo-2-thiophenecarboxylate⁹ was added 0.1 mole of *p*-X-phenylhydrazine. An exothermic reaction

(5) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(6) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *Chem. Commun.*, 552 (1967); A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 881 (1967).

(7) Animal testing was carried out by Dr. A. E. Sloboda of the Experimental Therapeutics Research Section of these laboratories.

(8) C. A. Winter, E. A. Risely, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(9) Melting points, determined with a Hershberg apparatus, are uncorrected. Microanalyses were performed for C, H, N, S, and halogen on every compd by Mr. L. M. Brancone and staff; for each compd, found values were within $\pm 0.4\%$ of theoretical. Ir spectra (KBr discs for solids, neat for liquids) and nmr spectra (CDCl₃ soln, TMS internal standard, Varian Associates A-60 spectrometer) were detd by Mr. W. Fulmor and staff. Partition chromatography was carried out on Celite 560 (Johns-Manville) using a heptane-*n*-BuOH-H₂O mixt by Dr. C. Streuli and staff.

occurred, and H₂O sepd. The mixt was heated 0.5 hr on a steam bath, cooled, and triturated with MeOH. The solid which sepd was collected and recrystd; details are included in Tables I and II.

TABLE I

METHYL 4-(2-*p*-X-PHENYLHYDRAZINO)-2,5-DIHYDRO-3-THIOPHENECARBOXYLATES

X	Mp, °C	Recrystn solvent	Formula
H	137-138	Me ₂ CO	C ₁₂ H ₁₄ N ₂ O ₂ S
CH ₃	131-132	MeOH	C ₁₃ H ₁₆ N ₂ O ₂ S
F	125-126	MeOH	C ₁₂ H ₁₃ FN ₂ O ₂ S
Cl	147-148	MeOH	C ₁₂ H ₁₃ ClN ₂ O ₂ S
Br	155-156	C ₆ H ₆	C ₁₃ H ₁₃ BrN ₂ O ₂ S

TABLE II

METHYL TETRAHYDRO-3-OXO-2-THIOPHENECARBOXYLATE *p*-X-PHENYLHYDRAZONES

X	Mp, °C	Recrystn solvent	Formula
H	128-130	<i>c</i> -C ₆ H ₁₂	C ₁₂ H ₁₄ N ₂ O ₂ S
CH ₃	153-154	MeOH	C ₁₃ H ₁₆ N ₂ O ₂ S
F	115-116	EtOH-H ₂ O	C ₁₂ H ₁₃ FN ₂ O ₂ S
Cl	143-144	MeOH	C ₁₂ H ₁₃ ClN ₂ O ₂ S
Br	151-152	EtOH	C ₁₂ H ₁₃ BrN ₂ O ₂ S

2-*p*-X-Phenyl-2,6-dihydro-4*H*-thieno[3,4-*c*]pyrazol-3-ols and 2-*p*-X-Phenyl-5,6-dihydro-2*H*-thieno[3,2-*c*]pyrazol-3-ols.—A soln of 0.01 mole of methyl 4-(2-*p*-X-phenylhydrazino)-2,5-dihydro-3-thiophenecarboxylate or methyl tetrahydro-3-oxo-2-thiophenecarboxylate *p*-X-phenylhydrazones, 0.62 g (0.011 mole) of NaOMe, and 50 ml of MeOH was heated under reflux for 1 hr and poured into 250 ml of H₂O. The soln was acidified with HOAc and the solid which sepd was collected and recrystd. Details are included in Tables III and IV.

TABLE III

2-*p*-X-PHENYL-2,6-DIHYDRO-4*H*-THIENO[3,4-*c*]PYRAZOL-3-OLS

X	Mp, °C	Recrystn solvent	Formula
H	226-227	EtOH	C ₁₁ H ₁₀ N ₂ OS
CH ₃	204-205	MeOH	C ₁₂ H ₁₂ N ₂ OS
F	224-225	MeOH	C ₁₁ H ₉ FN ₂ OS
Cl	222-223	MeOH	C ₁₁ H ₉ ClN ₂ OS
Br	232-233	MeCN	C ₁₁ H ₉ BrN ₂ OS

TABLE IV

2-*p*-X-PHENYL-5,6-DIHYDRO-2*H*-THIENO[3,2-*c*]PYRAZOL-3-OLS

X	Mp, °C	Recrystn solvent	Formula
H	165-167	EtOH	C ₁₁ H ₁₀ N ₂ OS
CH ₃	171-172	MeCN-H ₂ O	C ₁₂ H ₁₂ N ₂ OS
F	213-214	MeCN	C ₁₁ H ₉ FN ₂ OS
Cl	181-182	MeOH-H ₂ O	C ₁₁ H ₉ ClN ₂ OS
Br	180-182	MeOH-H ₂ O	C ₁₁ H ₉ BrN ₂ OS

Alkylation of 2,6-Dihydro-2-phenyl-4*H*-thieno[3,4-*c*]pyrazol-3-ol (5). **A. With MeOTs.**—A soln of 4.36 g (0.02 mole) of **5**, 1.3 g (0.021 mole) of NaOMe, and 100 ml of anhyd DMF was heated to 80° with stirring, and 3.7 g (0.02 mole) of MeOTs was added. The mixt was heated at 120° for 2 hr, cooled, and poured into 1500 ml of H₂O. The solid which sepd was collected and recrystd from *c*-C₆H₁₂ to provide 1.8 g (39%) of tan crystals, mp 84-85°. Another recrystn gave colorless crystals, mp 83-84°, of **5,6-dihydro-3-methoxy-2-phenyl-4*H*-thieno[3,4-*c*]pyrazole (9)**; ir, no C=O below 6.2 μ ; nmr δ 3.90 (t, *J* = 1.5 Hz, 2 CH₂), 4.00 (s, 3, OCH₃), 4.08 (t, *J* = 1.5 Hz, 2, CH₂).

B. With MeI.—A mixt of 11.0 g (0.05 mole) of **5**, 30 g of K₂CO₃, 10 ml of MeI, and 250 ml of Me₂CO was stirred 24 hr at room temp and filtered, and the filtrate was coned to an oil. Trituration with Et₂O gave 2.85 g (25%) of colorless solid, mp 124-126°. Recrystn from C₆H₆ gave colorless needles of **1,2,4,6-**

tetrahydro-1-methyl-2-phenyl-3H-thieno[3,4-c]pyrazolone (7a): mp 136–137°; ν 5.95 μ ; nmr δ 3.03 (s, 3, NCH₃), 3.95 (m, 4, CH₂CH₂). Partition chromatog of the mother liquors provided two additional compds. Eluted first from the column was 1.42 g (12%) of colorless cryst, mp 109–111°. Recrystn from hexane gave colorless cryst of **2,3a,4,6-tetrahydro-3a-methyl-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one (8a)**: mp 115–116°; ν 5.83 μ ; nmr δ 1.67 (s, 3, CCH₃), 2.72 and 3.02 (dd, J = 10.6 Hz, 2, CH₂ AB), 3.66 and 3.75 (dd, J = 13.5 Hz, 2, CH₂ AB). Further elution gave 0.3 g (3%) of **9** as colorless cryst, mp 86–87°.

C. With PhCH₂Br.—A mixt of 2.2 g (0.01 mole) of **5**, 6 g of K₂CO₃, 50 ml of Me₂CO, and 1.5 ml (0.013 mole) of PhCH₂Br was stirred at room temp for 24 hr and filtered. The filtrate was coned to an oily solid which was chromatog on basic alumina. Eluted with C₆H₆–hexane (1:1) was 0.8 g (26%) of colorless oil. Evaporative distn at 150° (0.1 mm) gave **3a-benzyl-2,3a,4,6-tetrahydro-2-phenyl-3H-thieno[3,4-c]pyrazole-3-one (8b)** as a viscous colorless liq, ν 5.83 μ .

Elution of the column with C₆H₆–MeOH (49:1) gave a yellow oil. Trituration with Et₂O provided 1.18 g (38%) of colorless cryst, mp 134–135°. Recrystn from EtOH gave colorless crystals, mp 134–135°, ν 5.92 μ , of **1-benzyl-1,2,4,6-tetrahydro-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one (7b)**.

D. With Allyl Bromide.—A mixt of 7.9 g (0.036 mole) of **5**, 22 g of K₂CO₃, 180 ml of Me₂CO, and 5.4 ml of allyl bromide was stirred at room temp for 24 hr and was filtered. The filtrate was coned to an oily solid. Trituration with Et₂O provided 2.8 g (30%) of colorless cryst, mp 132–133°. Recrystn from C₆H₆ gave colorless cryst, mp 135–136°, ν 6.00 μ , of **1-allyl-1,2,4,6-tetrahydro-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one (7c)**.

The mother liquors were subjected to partition chromatog. Eluted from the column was 4.1 g (44%) of pale yellow liq. Evaporative dist at 170° (20 mm) gave **3a-allyl-2,3a,4,6-tetrahydro-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one (8c)**, as a viscous colorless oil, ν 5.83 μ .

5,6-Dihydro-3-methoxy-2-phenyl-2H-thieno[3,2-c]pyrazole (11).—A stirred soln of 1.09 g (5.0 mmoles) of 5,6-dihydro-2-phenyl-2H-thieno[3,2-c]pyrazol-3-ol (**6**), 0.28 g (5.0 mmoles) of NaOMe, and 25 ml of anhyd DMF was heated to 80°, and 0.93 g (5.0 mmoles) of MeOTs was added. The soln was heated at 120° for 2 hr, cooled, dil with H₂O, and extd with Et₂O. The Et₂O soln was dried (MgSO₄) and coned to a yellow oil which was chromatog on alumina. Eluted with *c*-C₆H₁₂–EtOAc (9:1) was 0.32 g (27%) of pale yellow crystals, mp 62–65°. Recrystn from *c*-C₆H₁₂ gave colorless crystals; mp 68–69°; ν , no C=O below 6.2 μ ; nmr δ 2.93 (t, J = 7.5 Hz, 2, CH₂), 3.65 (t, J = 7.4 Hz, 2, CH₂), 3.90 (s, 3, OCH₃).

2-Methyl-4-methylthio-1-phenyl-3-vinyl-3-pyrazolin-5-one (12).—A mixt of 1.09 g (5.0 mmoles) of **6**, 2.8 g of K₂CO₃, 1 ml of MeI, and 25 ml of Me₂CO was stirred at room temp for 20 hr and was filtered. The filtrate was coned to a brown oil, which was chromatog on basic alumina. Eluted with C₆H₆–MeOH (99:1) was 50 mg (4%) of colorless solid, mp 87–88°. Recrystn from *c*-C₆H₁₂ gave colorless cryst; mp 89–90°; ν 6.03 μ ; nmr (CDCl₃) δ 2.40 (s, 3, SCH₃), 3.08 (s, 3, NCH₃), 5.71–6.97 (3, vinyl ABC system), and 7.44 (m, 5, phenyl-H).

2,6-Dihydro-3-methoxy-2-phenyl-4H-thieno[3,4-c]pyrazole 5,5-Dioxide (16).—To a stirred soln of 2.32 g (0.01 mole) of **9** and 100 ml of CH₂Cl₂ was added 3.60 g (0.021 mole) of *m*-chloroperoxybenzoic acid. After 1 hr at room temp, the soln was washed with NaHCO₃, dried (K₂CO₃), and coned to a solid. Recrystn from C₆H₆–hexane provided 2.0 g (76%) of tan crystals, mp 148–149°, finally 149–150°.

1,2,4,6-Tetrahydro-1-methyl-2-phenyl-3H-thieno[3,4-c]pyrazole 5,5-dioxide (14a) was prepd from 0.93 g (4.0 mmoles) of **7a** by the above method. Recrystn of the crude solid from MeCN gave 0.50 g (47%) of yellow cryst, mp 159–160°. Recrystn from EtOH gave colorless cryst, mp 159–160°.

2,3a,4,6-Tetrahydro-3a-methyl-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one 5,5-dioxide (15) was prepd from 0.46 g (2.0 mmoles) of **8a** by the above method. Recrystn of the crude solid from C₆H₆ gave 0.30 g (57%) of colorless cryst, mp 198–199°.

1-Benzyl-1,2,4,6-tetrahydro-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one 5,5-dioxide (14b) was prepd from 0.31 g (1.0 mmole) of **7b** by the above method. Recrystn of the crude solid from C₆H₆–hexane gave 0.20 g (59%) of colorless cryst, mp 137–139°, finally 139–140°.

2,6-Dihydro-3-methoxy-2-phenyl-3H-thieno[3,4-c]pyrazole 5-Oxide (18).—To a cold, stirred soln of 2.32 g (0.01 mole) of **9** and 50 ml of CH₂Cl₂ was added dropwise during 1 hr a soln of 1.72 g

(0.01 mole) of *m*-chloroperoxybenzoic acid in CH₂Cl₂. The soln was washed with NaHCO₃, dried (K₂CO₃), and coned to a solid. Recrystn from C₆H₆–hexane gave 1.80 g (73%) of tan cryst, mp 120–121°. Recrystn gave colorless cryst, mp 122–123°.

1,2,4,6-Tetrahydro-1-methyl-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one 5-oxide (17) was prepd from 0.93 g (4.0 mmoles) of **7a** by the above method. Crystn of the crude product from EtOAc gave 0.50 g (51%) of yellow crystals, mp 129–130°, finally pale yellow cryst, mp 136–137°.

cis- (**19**) and *trans*-**2,3a,4,6-tetrahydro-3a-methyl-2-phenyl-3H-thieno[3,4-c]pyrazol-3-one 5-oxide (20)** were prepd from 1.09 g (4.7 mmoles) of **8a** by the above method. The crude product, 1.12 g of colorless cryst, mp 125–126°, was subjected to preparative tlc (Analtech, Inc. silica gel GF, 1000- μ plates) with a C₆H₆–EtOH (9:1) solvent. Eluted farthest from the origin was 0.41 g of colorless solid. Recrystn from C₆H₆–hexane gave 0.34 g (30%) of **19** as colorless cryst, mp 142–143°.

A second fraction consisted of 0.35 g of colorless solid. Recrystn from C₆H₆ provided 0.31 g (27%) of **20** as colorless cryst, mp 164–165°.

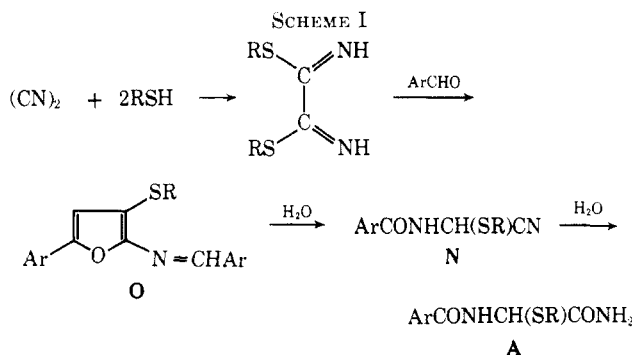
Synthesis and Biological Study of a Series of S-Substituted α -Mercaptohippuramides and Nitriles¹

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S,S'-Disubstituted dithiooxaldiimides react with aromatic aldehydes to form 5-arylidene-4-substituted-mercapto-2-phenyloxazoles (**O**).² As part of the structural proof it was shown that one of these (**1-O**) could be hydrolyzed to α -methylmercaptohippuronitrile (**1-N**) and the hippuramide **1-A**. This amide was evaluated for its somnifacient properties because of its structural relationship to trimethylamide and thalidomide.³ We are now reporting the synthesis and biological evaluation of a series of these amides and nitriles having modifications in both the aryl group and the S substituent. The oxazoles were also included in the studies since their facile chemical hydrolysis should make them easily degraded in biological systems as well. The reactions are outlined in Scheme I; the data for the synthesis of new compounds are in Table I.



(1) Supported in part by a grant (NIMH 08787) from the U. S. Public Health Service.

(2) A. R. Martin and R. Ketcham, *J. Org. Chem.*, **31**, 3612 (1966).

(3) A. R. Martin, F. H. Meyers, and R. Ketcham, *J. Pharm. Sci.*, **56**, 753 (1967).