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The free radical addition of thioacetic acid to 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazines gave high yields of 1,2-dicarbethoxy-4-*S*-thiolacetoxypiperidazines. The latter compounds served as the key intermediates in the preparation of 4-piperidazinethiols. The thiolacetoxy derivatives were partially hydrolyzed to afford the related 1,2-dicarbethoxy-4-piperidazinethiols. Complete hydrolysis of the thiolacetates gave rise to 4-piperidazinethiols. Finally, lithium aluminum hydride reduction of the thiolacetoxy esters produced a series of 1,2-dimethyl-4-piperidazinethiols. Only 4-piperidazinethiol hydrochloride showed appreciable antiradiation activity.

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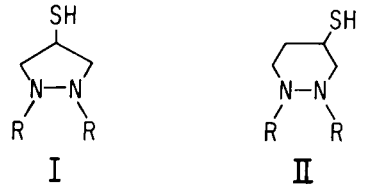
A recent report (2) from these laboratories described the synthesis and antiradiation activity of a series of 1,2-dialkyl-4-pyrazolidinethiols (I). In order to gain further insight regarding structure-activity relationships, the next higher homologs, the 4-piperidazinethiols (II), were required. The latter compounds also contain the 2-aminoethylmercaptan pharmacophoric group.



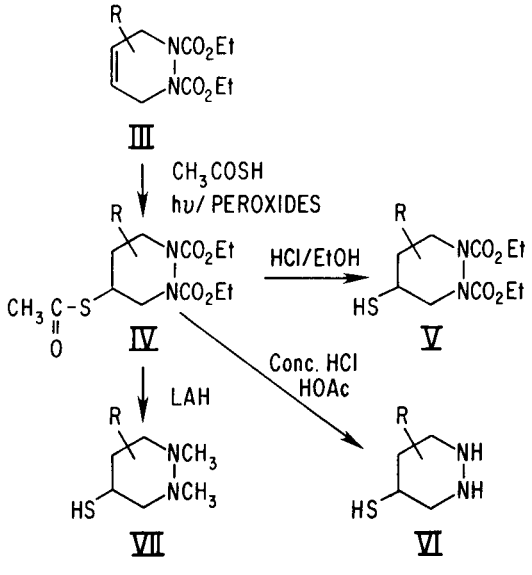
I II

The sequence involved in the preparation of II began with a Diels-Alder reaction. Six different 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazines (III) were prepared as described in the literature by the reaction of diethyl azodicarboxylate and the following dienes: 1,3-butadiene (3); isoprene (4); 2,3-dimethyl-1,3-butadiene (4); cyclopentadiene (3); 1,4-diphenyl-1,3-butadiene (5); and chloroprene (6). These adducts were obtained in yields of 75-100%.

The second step of the sequence involved a free radical addition of thioacetic acid to the alkene functional group of III to produce 1,2-dicarbethoxy-4-*S*-thiolacetoxypiperidazines (IV) (Scheme I). While such additions to 1,2,3,6-tetrahydropyridazines have not been reported previously, this type of free radical addition to alkenes (7) and to cyclohexenes (8) in particular have been successful.

When benzoyl peroxide was used as the free radical initiator, the addition failed and starting materials were recovered. By contrast, *t*-butyl hydroperoxide proved to be an effective initiator and the addition of thioacetic acid to 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine occurred readily and provided an 83% yield of the thiolacetate (IV). In a similar fashion, both 1,2-dicarbethoxy-3,6-endomethylene-1,2,3,6-tetrahydropyridazine and 1,2-dicarbethoxy-4-methyl-1,2,3,6-tetrahydropyridazine readily under-

SCHEME I




SCHEME II

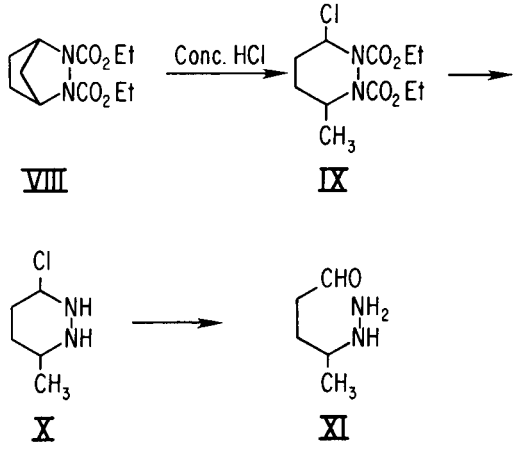



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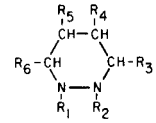
Table I

The Piperidazines



| No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | B.p./mm Hg | $n_D$(°C) | Yield % | Derivative M.p.°C |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $-CO_2Et$ | $-CO_2Et$ | H | $-SCCH_3$ (O) | H | H | 140/0.02 | 1.4940 (32) | 83 | |
| 2 | $-CO_2Et$ | $-CO_2Et$ | | $-SCCH_3$ (O), $CH_2$ | H | | (a) | ---- | 71 | |
| 3 | $-CO_2Et$ | $-CO_2Et$ | H | $-SCCH_3$ (O) | $-CH_3$ | H | 140/0.08 | 1.4959 (24) | 80 | |
| 4 | $-CO_2Et$ | $-CO_2Et$ | H | -SH | H | H | 112/0.045 | 1.4929 (29) | 76 | |
| 5 | $-CO_2Et$ | $-CO_2Et$ | | -SH, $CH_2$ | H | | 134-136/0.1 | 1.5040 (29) | 56 | |
| 6 | $-CO_2Et$ | $-CO_2Et$ | H | -SH | $-CH_3$ | H | 110-112/0.02 | 1.4887 (34) | 74 | |
| 7 | H | H | H | -SH | H | H | 60/0.15 | 1.5569 (3) | 43 | 108-110 (b) |
| 8 | H | H | H | -SH | $-CH_3$ | H | 113/7 | 1.5446 (24) | 50 | 140-142 (b) |
| 9 | $-CH_3$ | $-CH_3$ | H | -SH | H | H | 90/12 | 1.5155 (30) | 54 | 155.5-157 (c) |
| 10 | $-CH_3$ | $-CH_3$ | | -SH, $CH_2$ | H | | 100/15 | 1.5230 (25) | 56 | 179-180 (c) |
| 11 | $-CH_3$ | $-CH_3$ | H | -SH | $-CH_3$ | H | 104/15 | 1.5121 (32) | 60 | |

(a) M.p. 62.5-64.5°. (b) Hydrochloride. (c) Picrate.

Table II

Analytical Data for Piperidazines

| Compound Number | Formula | Carbon | | Hydrogen | | Nitrogen | | Sulfur | | Chlorine | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| 1 | $C_{12}H_{20}N_2O_5S$ | 47.35 | 47.50 | 6.62 | 6.70 | 9.20 | 9.33 | 10.54 | 10.38 | | |
| 2 | $C_{13}H_{20}N_2O_5S$ | 49.35 | 49.30 | 6.37 | 6.31 | 8.86 | 8.98 | 10.14 | 10.16 | | |
| 3 | $C_{13}H_{22}N_2O_5S$ | 49.04 | 49.08 | 6.97 | 6.83 | 8.80 | 8.99 | 10.07 | 9.97 | | |
| 4 | $C_{10}H_{18}N_2O_4S$ | 45.78 | 45.83 | 6.92 | 6.88 | 10.68 | 10.59 | 12.22 | 12.09 | | |
| 5 | $C_{11}H_{18}N_2O_4S$ | 48.16 | 48.35 | 6.61 | 6.46 | 10.21 | 10.31 | 11.69 | 11.56 | | |
| 6 | $C_{11}H_{20}N_2O_4S$ | 47.80 | 47.91 | 7.30 | 7.37 | 10.14 | 9.97 | 11.60 | 11.55 | | |
| 7 | $C_4H_{10}N_2S$ | 40.64 | 40.82 | 8.53 | 8.66 | 23.70 | 23.41 | 27.13 | 26.82 | | |
| 7·HCl | $C_4H_{11}N_2SCl$ | 31.06 | 31.16 | 7.17 | 6.96 | 18.11 | 18.05 | 20.73 | 20.66 | 22.92 | 23.05 |
| 8 | $C_5H_{12}N_2S$ | 45.41 | 45.39 | 9.15 | 9.23 | 21.19 | 20.93 | 24.25 | 23.89 | | |
| 8·HCl | $C_5H_{13}N_2SCl$ | 35.60 | 35.59 | 7.77 | 7.83 | 16.61 | 16.46 | 19.01 | 19.15 | 21.02 | 21.35 |
| 9 | $C_6H_{14}N_2S$ | 49.27 | 49.06 | 9.65 | 9.75 | 19.16 | 18.84 | 21.92 | 21.77 | | |
| 9·picrate | $C_{12}H_{17}N_5O_7S$ | 38.39 | 38.39 | 4.57 | 4.95 | 18.66 | 18.63 | 8.54 | 8.45 | | |
| 10 | $C_7H_{14}N_2S$ | 53.12 | 53.13 | 8.92 | 8.95 | 17.70 | 17.67 | 20.26 | 20.13 | | |
| 10·picrate | $C_{13}H_{17}N_5O_7S$ | 40.30 | 40.48 | 4.42 | 4.48 | 18.08 | 18.15 | 8.28 | 8.40 | | |
| 11 | $C_7H_{16}N_2S$ | 52.45 | 52.58 | 10.06 | 10.11 | 17.47 | 17.42 | 20.01 | 19.75 | | |

went homolytic addition of thioacetic acid and afforded the corresponding adducts (Scheme I).

In contrast to these facile homolytic addition reactions, 1,2-dicarbethoxy-4,5-dimethyl-1,2,3,6-tetrahydropyridazine and 1,2-dicarbethoxy-3,6-diphenyl-1,2,3,6-tetrahydropyridazine failed to react under conditions which had proved successful previously, and a quantitative recovery of starting materials was achieved. The refractory nature of these derivatives may arise from a steric effect of the substituent groups.

When 1,2-dicarbethoxy-4-chloro-1,2,3,6-tetrahydropyridazine and thioacetic acid were irradiated in the presence of a *t*-butyl hydroperoxide catalyst, a vigorous reaction ensued. However, attempts to isolate the product by distilla-

tion gave rise to extensive decomposition and characterization of the product could not be accomplished.

It was possible to effect the stepwise hydrolysis of these thiolacetates. By refluxing IV in 1*N* ethanolic hydrogen chloride, the corresponding 1,2-dicarbethoxy-4-piperidazinethiols (V) were prepared. Prolonged refluxing of the thiolacetates in a mixture of concentrated hydrochloric acid and glacial acetic acid led to complete hydrolysis along with the expected decarboxylation of the intermediary carbamic acid and the 4-piperidazinethiols (VI) were formed (Scheme I). This reaction required reflux periods up to forty-eight hours to effect hydrolysis of the refractory carbamate functional groups. Attempts to hydrolyse 1,2-dicarbethoxy-3,6-endomethylene-4-*S*-thiolacetoxypiperidazine under these conditions led to the formation of an intractable tar. This is not wholly unexpected since a closely related bridge compound VIII undergoes cleavage of the bridge to afford IX when refluxed for two hours in concentrated hydrochloric acid (9) (Scheme II). It is probable that the more severe conditions required to hydrolyze the carbamate groups yields an intermediate X which would suffer further cleavage to XI (Scheme II). In a strong acid medium such cleavage products may undergo extensive condensation reactions.

Lithium aluminum hydride reduction of the 1,2-dicarbethoxy-4-*S*-thiolacetoxypiperidazines (IV) at room temperature produced the desired 1,2-dimethyl-4-piperidazinethiols (VII) (Scheme I). Isolation of the amphoteric products was achieved by decomposing the reaction complexes with water followed by the addition of an equimolar amount of concentrated hydrochloric acid (based on the amount of lithium aluminum hydride) (10).

The 4-piperidazinethiols (compounds **4-11**) were tested for antiradiation activity as reported previously (11). The compounds were administered to mice intraperitoneally 15-30 minutes before whole body lethal radiation. Only compound **7** had appreciable activity, but this was at very high doses. At 800 mg./kg., it produced 83% 30-day survivors.

## EXPERIMENTAL

The melting points and boiling points are uncorrected. The analyses were performed by Dr. Kurt Eder, Geneva, Switzerland and Drs. Weiler and Strauss, Oxford, England. The infrared spectra were determined on a Beckman IR-4 spectrophotometer using sodium chloride optics.

1,2-Dicarbethoxy-4-*S*-thiolacetoxypiperidazines (IV) (1-3, Table I,II).

The procedure used for the free radical addition reaction of thioacetic acid was similar to that described by Neureiter and Bordwell (12). A magnetically stirred mixture of 22.8 g. (0.10 mole) of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine and 15.2 g. (0.20 mole) of thioacetic acid was illuminated by a 150 watt bulb placed two cm. from the flask. Twenty drops of *t*-butylhydroperoxide were added through the top of the condenser. After five to ten minutes the temperature of the reaction mixture rose rapidly until a maximum of 94° was reached. The irradiation was continued for one and one-half hours. Excess thioacetic acid was evaporated under reduced pressure and the residue was distilled.

1,2-Dicarbethoxy-4-piperidazinethiols (V) (4-6, Table I,II).

A mixture of 1,2-dicarbethoxy-4-*S*-thiolacetoxypiperidazine (**1**) and 190 ml. of 1*N* ethanolic hydrogen chloride was refluxed under a nitrogen atmosphere for four hours. The ethanol was evaporated under reduced pressure. The residue was dissolved in 100 ml. of ether and washed once with 50 ml. of 5% sodium bicarbonate solution and twice with 100 ml. portions of water. After drying (magnesium sulfate) and removal of the ether *in vacuo*, the residue was distilled.

4-Piperidazinethiols (VI) (7-8, Table I,II).

A mixture of 18.7 g. (0.0615 mole) of 1,2-dicarbethoxy-4-*S*-thiolacetoxypiperidazine (**1**), 30 ml. of glacial acetic acid, and 150 ml. of concentrated hydrochloric acid was refluxed under nitrogen for 48 hours. The volatile components were evaporated *in vacuo*. The residue was dissolved in 25 ml. of water and basified to *p*H ~ 7-8 (*p*Hydrion paper). The resulting mixture was extracted with ether continuously for 18 hours and the ether extract was concentrated. The residue was dissolved in 80 ml. of tetrahydrofuran and dried (magnesium sulfate). After removal of the tetrahydrofuran, the residue was distilled.

1,2-Dimethyl-4-piperidazinethiols (VII) (9-11, Table I,II).

A solution of 12.5 g. (0.0411 mole) of 1,2-dicarbethoxy-4-*S*-thiolacetoxypiperidazine in 35 ml. of anhydrous ether was added dropwise to a solution of 6.24 g. (0.164 mole) of lithium aluminum hydride in 215 ml. of anhydrous ether over a period of 40 minutes. Stirring at room temperature was continued for an additional hour. The mixture was cooled in an ice-bath and decomposed by the cautious, dropwise addition of 11.9 ml. of water followed by 13.65 ml. of concentrated hydrochloric acid. The inorganic salts were filtered and extracted four times with 100 ml. portions of boiling 1,2-dimethoxyethane. The combined organic extracts were dried (magnesium sulfate) and the solvents were evaporated under reduced pressure. The remaining residue was distilled.

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## REFERENCES AND NOTES

(1) Abstracted in part from the Ph.D. dissertation submitted by M. J. Kornet to the Graduate College of the University of Illinois at the Medical Center, 1963.

(2) M. J. Kornet and R. Daniels, *J. Pharm. Sci.*, **68**, 1331 (1979).

(3) J. C. J. MacKenzie, A. Rodgman, and G. F. Wright, *J. Org. Chem.*, **17**, 1666 (1952).

(4) P. Baranger, J. Levisalles, and M. Vuidart, *Compt. Rend.*, **236**, 1365 (1953).

(5) S. G. Cohen, S. Hsiao, E. Saklad, and C. H. Wang, *J. Am. Chem. Soc.*, **79**, 4404 (1957).

(6) H. R. Snyder and J. G. Michels, *J. Org. Chem.*, **28**, 1144 (1963).

(7) F. W. Stacey and J. F. Harris, Jr., *Org. React.*, **13**, 150 (1963).

(8) J. I. Cunneen, *J. Chem. Soc.*, 134 (1947).

(9) O. Diels, J. H. Blom, and W. Koll, *Ann. Chem.*, **443**, 242 (1925).

(10) W. C. McCarthy and B. T. Ho, *J. Org. Chem.*, **26**, 4110 (1961).

(11) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(12) N. P. Neureiter and F. G. Bordwell, *J. Am. Chem. Soc.*, **82**, 5354 (1960).