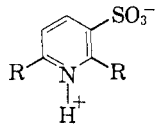
and 1 mole of sodium carbonate per liter of D_2O, so that the observed spectra are those of the sulfonate ions and of a small amount of H_2O formed when the acid is neutralized.

A usable sample of the 2,6-di-*t*-butylpyridinesulfonic acid could not be obtained in the analogous way because of the unexpectedly low water-solubility of the sodium salt. The solvent finally found most suitable was that used originally[1] in the sulfonation reaction, liquid sulfur dioxide. Sealed sample tubes containing liquid sulfur dioxide may safely be stored, and examined, at room temperature, and the solvent is ideal in that it produces no proton spectrum which would obscure that of the solute. Since the lutidinesulfonic acids are insoluble in liquid sulfur dioxide, the three spectra could not be compared in identical solvent, and therefore no attempt was made to measure the chemical shifts of the various peaks relative to a fixed standard. However, the spectrum of the 2,6-di-*t*-butylpyridinesulfonic acid, shown in Fig. 1(c), leaves no doubt that the material has structure I and not structure II.

An interesting feature of the latter spectrum is the apparent absence of a signal for the acid proton. The most likely explanation appears to be that structure I in liquid sulfur dioxide is in equilibrium with the dipolar ionic structure III, and that the



III

rate of migration of the proton is such as to result in a considerably broadened line[4] which would probably be undetected because of the small concentration of this species of proton.

Acknowledgment. All spectra were obtained with a Varian model 4311 high resolution NMR spectrometer operating at 56.4 mc. We should like to thank the Purdue Research Foundation, E. I. du Pont de Nemours and Co., and the National Science Foundation for grants which made the purchase of this equipment possible. We also wish to thank Professor H. C. Brown for calling this problem to our attention and providing the compounds.

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(4) See J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, New York, 1959, p. 63.

Potential Anticancer Agents.[1] XXI. 2-(Alkylthio)cyclopentene-1-carboxylic Acids and Derivatives

LEONARD O. ROSS, LEON GOODMAN, AND B. R. BAKER

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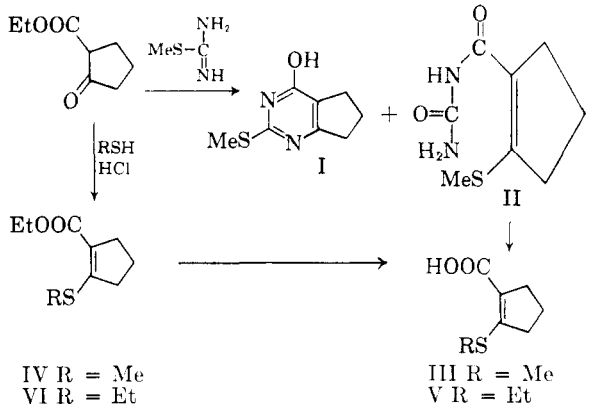
An earlier paper in this series[2] described the condensation of 2-methyl-2-thiopseudourea and 2-carbethoxycyclopentanone in aqueous alkali which led to the isolation of the expected 4-hydroxy-2-(methylthio)-5,6-trimethylenepyrimidine (I) and a product to which structure II was tentatively as-



IV R = Me
VI R = Et

III R = Me
V R = Et

signed. Some further work, which is reported in this note, has placed the structural assignment of II on firmer ground.

Alkaline hydrolysis of the compound assigned structure II gave a carboxylic acid which had strong ultraviolet absorption at 287 mμ, in good agreement with the absorption expected for compound III.[3] For comparison, the acid (III) was synthesized from 2-carbethoxycyclopentanone by the method used by Posner to synthesize 3-(ethylthio)crotonic acid.[4] Methanethiol, in large excess, on reaction with 2-carbethoxycyclopentanone in the presence of concentrated hydrochloric acid, furnished, as the directly isolated product, ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV). The ester IV was saponified to the acid III, which was identical with acid III derived from II as shown by nondepression of the mixed melting point, identical infrared spectra, and the same paper chromatographic behavior. It is interesting to note that the ester IV was the direct product from the reaction of

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* W. A. Skinner, H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) L. O. Ross, L. Goodman, B. R. Baker, paper XVII of this series, *J. Am. Chem. Soc.*, **81**, 3108 (1959).

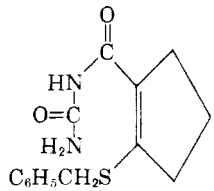
(3) B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org. Chem.*, **13**, 123 (1948).

(4) T. Posner, *Ber.*, **32**, 2801 (1899).

methanethiol and 2-carbethoxycyclopentanone, whereas Posner[4] showed that in the similar reaction of acetoacetic ester, the first product was the thioketal, which was converted to the 3-(alkylthio)-crotonic acid only after vigorous saponification.

Similarly, ethanethiol with 2-carbethoxycyclopentanone gave a good yield of the ester VI, which could be saponified to the acid V. Several attempts to effect a condensation between 2-ethyl-2-thiopseudourea and 2-carbethoxycyclopentanone, so as to obtain the ethyl analogs of I and II, were unsuccessful.

When the reaction of 2-methyl-2-thiopseudourea and 2-carbethoxycyclopentanone was carried out in the presence of benzyl mercaptide ion,[5] a compound was isolated whose analysis, infrared and ultraviolet absorption spectra, and paper chromatographic behavior indicated it to be the benzyl analog of II, [2-benzylthio)cyclopentene-1-carbonyl]-urea (VII). This strongly indicates that the compound II previously isolated[2] was not the product of an intramolecular rearrangement but resulted from the intervention of methyl mercaptide ion, which would be present in the alkaline reaction mixture containing 2-methyl-2-thiopseudourea.



VII

Although the detailed mechanism of formation of II would be of interest, the results have been presented here since no further work in this area is contemplated.

EXPERIMENTAL[6]

2-(Methylthio)cyclopentene-1-carboxylic acid (III). A. *By hydrolysis of* II. A mixture of 2.00 g. (10.0 mmoles) of II,[2] 4.0 g. (64 mmoles) of potassium hydroxide (85%), and 40 ml. of water was heated under reflux for 1 hr. The resulting solution was filtered and the filtrate was adjusted to *p*H 5 with glacial acetic acid. The precipitated product, 0.50 g. (31%), m.p. 190–200° (dec.), was dissolved in 50 ml. of saturated aqueous sodium bicarbonate, the solution was filtered, and the filtrate adjusted to *p*H 5 with glacial acetic acid. The purified product, 0.30 g. (19%), m.p. 234–237° (dec.), was homogeneous on paper chromatography,[7] with R_{Ad} = 1.38, and had $\lambda_{max(\mu)}^{KBr}$ 3.7–3.9 (carboxyl OH), 6.06 (carboxyl C=O), 6.41 (C=C), 7.02 and 10.59 (COOH), and $\lambda_{max(\mu)}$ 287 (ϵ 11,400) in 95% ethanol.

Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.1; H, 6.38; S, 20.2. Found: C, 53.0; H, 6.60; S, 19.9.

B. *By saponification of* IV. A mixture of 5.0 g. (27 mmoles) of ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV) (*cf.* below), 5.0 g. (78 mmoles) of potassium hydroxide (85%), and 75 ml. of water was heated under reflux for 1.5 hr. The resulting solution was filtered and the filtrate was adjusted to *p*H 5 with glacial acetic acid. The precipitated product, 2.0 g. (46%), m.p. 170–210° (dec.), was dissolved in 30 ml. of saturated aqueous sodium bicarbonate, the solution filtered, and the filtrate acidified to *p*H 5 with glacial acetic acid. The purified product, 0.60 g. (14%), m.p. 232–237° (dec.), had m.p. 234–237° (dec.) when mixed with acid prepared by hydrolysis of II. Its infrared spectrum was identical with that described above and it showed the identical paper chromatographic behavior.

No effort was made to increase the yield in the above reaction.

Ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV). A mixture of 10.0 g. (64 mmoles) of 2-carbethoxycyclopentanone, 11.5 g. (0.24 mole) of methanethiol, and 10 ml. of concentrated hydrochloric acid was stirred for 4 hr. at −5 to 0°. The solution was extracted with 100 ml. of methylene chloride. The extract was chilled, causing the precipitation of 0.20 g. of acid III, m.p. 235–237° (dec.), which was removed by filtration. The filtrate was evaporated *in vacuo*, leaving a solid residue, 4.0 g. (34%), m.p. 45–48°. This product was recrystallized twice from methanol with the use of Norit, giving the analytical product, 3.8 g (32%), m.p. 68–70°; $\lambda_{max(\mu)}^{KBr}$ 5.97 (carbonyl C=O), 6.39 (C=C), 7.75–8.45 (several bands which probably represent ester C—O—C).

Anal. Calcd. for $C_9H_{14}O_2S$: C, 58.0; H, 7.55; S, 17.2. Found: C, 58.0; H, 7.86; S, 17.5.

Ethyl 2-(ethylthio)cyclopentene-1-carboxylate (VI). A mixture of 15.0 g. (96 mmoles) of 2-carbethoxycyclopentanone, 11.9 g. (0.19 mole) of ethanethiol, and 30 ml. of concentrated hydrochloric acid was stirred at room temperature for 2 hr. The mixture was extracted with 50 ml. of methylene chloride, the extract was evaporated *in vacuo*, and the residue was distilled using a short Vigreux column. The product, 13.3 g. (77%), was collected at 110° (0.3 mm.); n_D^{20} 1.5341; $\lambda_{max(\mu)}^{film}$ 5.90 (ester C=O), 6.36 (C=C), 7.92 (probably ester C—O—C).

Anal. Calcd. for $C_{10}H_{16}O_2S$: C, 59.9; H, 8.04; S, 16.0. Found: C, 59.9; H, 8.10; S, 15.9.

2-(Ethylthio)cyclopentene-1-carboxylic acid (V). A mixture of 5.0 g. (20.9 mmole) of VI, 5.0 g. (0.13 mole) of sodium hydroxide, and 50 ml. of water was heated, with stirring, on the steam bath for 1.5 hr. The cooled solution was extracted with 30 ml. of methylene chloride and the extract was discarded. The aqueous solution was decolorized with Norit and filtered. The filtrate was adjusted to *p*H 5 with glacial acetic acid, precipitating 0.40 g. (9.3%) of product, m.p. 157–162°. The product was dissolved in 30 ml. of saturated aqueous sodium bicarbonate, treated with Norit, filtered, and the filtrate adjusted to *p*H 5 with glacial acetic acid, precipitating 0.30 g. (6.9%) of solid, m.p. 174–175°; $\lambda_{max(\mu)}^{KBr}$ 3.95 (carboxyl OH), 6.11 (carboxyl C=O), 6.49 (C=C), 7.77 and 10.58 (COOH); $\lambda_{max(\mu)}$ (ϵ 11,600) in 95% ethanol.

Anal. Calcd. for $C_8H_{12}O_2S$: C, 55.7; H, 7.01; S, 18.6. Found: C, 55.5; H, 7.03; S, 18.3.

The yield of acid V could probably be improved by the use of more severe hydrolytic conditions.

[*2-(Benzylthio)cyclopentene-1-carbonyl*]*urea* (VII). To a stirred solution of 27.8 g. (0.100 mole) of 2-methyl-2-thiopseudourea sulfate, 13.2 g. (0.200 mole) of potassium hydroxide (85%), and 150 ml. of water was added, dropwise during 1 hr., a mixture of 15.6 g. (0.100 mole) of 2-carbethoxycyclopentanone and 24.8 g. (0.200 mole) of α-toluenethiol. The reaction mixture was stirred for 8 hr. more and the solid present was removed by filtration. The solid was stirred with 200 ml. of methylene chloride, the resulting sus-

(5) This experiment was suggested by Mr. J. I. DeGraw, Jr., of These Laboratories.

(6) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus.

(7) Paper chromatograms were run by the descending technique on Whatman No. 1 paper in the solvent system 1-butanol/acetic acid/water (5/2/3).[8] The spots were detected with ultraviolet light and are located relative to adenine, *i.e.*, $R_{Adenine}$ = 1.00.

(8) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

pension was filtered, and the solid was extracted with 100 ml. of hot (90°) methyl Cellosolve, some insoluble inorganic material being filtered. To the methyl Cellosolve filtrate was added 50 ml. of water and the solution was chilled yielding 1.0 g. (3.6%) of product, m.p. 188–190° (dec.). The solid was crystallized twice from 100 ml. of methanol with the aid of Norit to give 0.80 g. (2.9%) of pure VII, m.p. 190–193° (dec.), which was homogeneous on paper chromatography[8] with R_{Ad} = 1.47, and had $\lambda^{KBr}_{max(\mu)}$ 2.95–3.10 (NH), 5.90 and 6.12 (amide and urea carbonyls), 6.02 (NH_2), 6.48 (NH and C=C), 13.03 and 14.15 (monosubstituted phenyl), and $\lambda_{max(m\mu)}$ 307 (ϵ 12,500) in 95% ethanol.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.8; H, 5.83; S, 11.6. Found: C, 60.6; H, 5.71; S, 10.6, 10.7.

No effort was made to recover compound I from the filtrate from VII.

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Preparation of Quinone Sulfenimines

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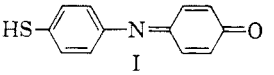
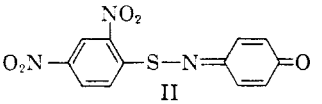
As a part of an investigation of the preparation of compounds of the thio indophenol series, attempts were made to prepare compound I



I

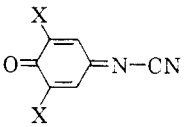
following the procedure of Hirsch[1] by reaction of *N*-chloro-*p*-quinoneimine with aromatic thiols unsubstituted in the para position. The desired compound was not obtained; but instead the reaction took another course to yield quantitatively, quinone sulfenimines. Since this method offers a simple procedure for the preparation of sulfenimines, the results are reported here. Gebauer-Fülnegg and Beatty[2] prepared a metallic complex of 4-chloro-2-nitrophenyl quinone sulfenimine by oxidation of the corresponding sulfenamide with sodium dichromate in acetic acid. By a similar oxidation procedure, Burmistrov and Glazkov[3] reported the preparation of a dinitro sulfenimine (II).



II

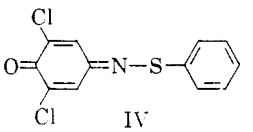
Other workers[4] noted that the reaction of thiols with *N*-chloroquinoneimine yielded colored products which could serve as quantitative estimations of the thiol in solution. Although the formation of quinone sulfenimines was postulated, no attempts were made to isolate or characterize the colored products.

When one equivalent of *N*-chloroquinoneimine was added, with rapid stirring, to the aryl thiol dissolved in sodium carbonate solution, a vigorous reaction occurred yielding a deep red insoluble precipitate. The product was insoluble in dilute alkali and dilute mineral acid and soluble in organic solvents. When treated with alkaline sodium cyanide, the quinone sulfenimine decomposed with the liberation of the thiol which could be detected by odor. Concomitantly, a deep green, unstable water soluble dye was formed, presumably, compound III.



III. X = H, Cl, Br

The infrared spectrum of compound IV



IV

shows absorption maxima at 6.05, 6.45, 6.85 (doublet), 7.85 (doublet), 9.55, 11.1, 12.27, and 13.53μ indicative of quinoid carbonyl and *p*-substituted aromatics. The absence of an absorption peak at 4.0μ due to SH indicates that no free thiol is present.

Similar reactions of *N*-chloroquinoneimines with a variety of thiols such as ethyl potassium xanthate, 2-mercaptobenzothiazole yielded the corresponding sulfenimine (see Table I).

In an attempt to obtain an intramolecular rearrangement of the quinone sulfenimine to the corresponding thio indophenol similar to I, it was found that the reaction was effected by refluxing in glacial acetic acid. Other Lewis acids and bases either cleaved the molecule or had no effect upon it. The course of the rearrangement could be followed by treating sequential aliquots of the glacial acetic acid solution with dilute alkali and noting the appearance of the characteristic blue color of indophenols. The results of these studies will be reported at a later date.

(1) A. Hirsch, *Ber.* **13**, 1903 (1880).

(2) E. Gebauer-Fülnegg and H. A. Beatty, *J. Am. Chem. Soc.* **49**, 1361 (1927).

(3) S. I. Burmistrov and V. I. Glazkov, *J. Gen. Chem. (USSR)*, **22**, 1901 (1952) Consultants Bureau Translation; *Chem. Abstr.*, **47**, 6367 (1953).

(4) W. R. Fearon, *Biochem. J.*, **38**, 399 (1944); R. A. McAllister, *J. Pharm. and Pharmacol.*, **3**, 506 (1951); R. A. McAllister, *J. Clin. Path.*, **4**, 432 (1952); R. A. McAllister and K. W. Howells, *J. Pharm. and Pharmacol.*, **4**, 259 (1952); C. E. Searle, *J. Appl. Chem.*, **5**, 313 (1955).