50° and 3 mm. Recrystallization from ether–pentane gave 4.6 g. (55% yield) of the diketone as a yellow solid with an irritating odor. The melting point was 37–38°.

Anal. Calcd. for $C_5H_4O_2$: C, 62.5; H, 4.17; mol. wt., 96. Found: C, 62.3; H, 4.0; mol. wt., 96.

Its colorless di-O-methyloxime melted at 116–117° after recrystallization from ethanol.

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.60; H, 6.23; N, 18.35.

(ii) **Oxidation in Acetone.**—To a cold stirred solution of the diol (20 g., 0.20 mole) in 200 ml. of acetone was added dropwise with stirring a solution of chromic anhydride (30 g., 0.3 mole) in a mixture of 60 ml. of concentrated sulfuric acid and 142 ml. of water. The reaction flask was surrounded by an ice-bath, and the addition regulated so that the temperature in the flask did not rise above 0°. After the addition was complete the reaction mixture was stirred an additional two hours at 0°, allowed to warm to room temperature, diluted with 400 ml. of water and extracted three times with 300 ml. of methylene chloride. The combined extracts were washed with 100 ml. of water, dried over anhydrous sodium sulfate, and the dione isolated as above. Yields are generally about 8 g. (42%), but despite the lower yield this procedure is more convenient than the oxidation in acetic acid.

Cyclopentane-1,3-dione.—To a vigorously stirred mixture of 5 g. of zinc dust in 25 ml. of glacial acetic acid was added dropwise cyclopentene-3,5-dione (0.50 g.) in 25 ml. of acetic acid. The addition took 45 minutes, during which time the flask was immersed in an oil-bath at 85°. The reaction mixture was cooled, filtered and the acetic acid removed at room temperature under vacuum. The residue was extracted in a Soxhlet apparatus with chloroform, the chloroform removed and cyclopentane-1,3-dione sublimed at 120° (4 mm.); yield 0.23 g. (45%) m.p. 149–150° (reported[18] 150–151°).

Catalytic Hydrogenation of Cyclopentene-3,5-dione.—The dione (1.0 g.) in 25 ml. of ethyl acetate was hydrogenated at room temperature and atmospheric pressure using Adams catalyst.[27] Absorption stopped after 2.7 molar equivalents of hydrogen had been used. The solution was filtered and the solvent removed. Titration of an aliquot of the oily product showed that not more than 2% of acidic material was present. The infrared spectrum showed a single carbonyl peak at 5.75 μ and an intense hydroxyl band. Gas chromatography showed the presence of two compounds in about equal amounts, one of which had the same retention time as did cyclopentanone. The 2,4-dinitrophenylhydrazone of the mixture was prepared and chromatographed. Roughly equal amounts of the 2,4-DNP of cyclopentanone (m.p. 142–143°) and of cyclopentenone (m.p. 166–167°) were isolated.

Monotosylhydrazone of Cyclopentene-3,5-dione.—To 500 mg. (0.52 mole) of the dione in 10 ml. of hot methanol was added 915 mg. (0.049 mole) of tosylhydrazine. The mixture was allowed to stand and then cooled to 0° and filtered. Recrystallization from 95% ethanol gave 1.15 g. (90% yield) of the monotosylhydrazone, m.p. 185–186° dec.

Anal. Calcd. for $C_{12}H_{12}O_3N_2S$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.45; H, 4.68; N, 10.9.

This tosylhydrazone was readily soluble in dilute NaOH. It could be recovered in 90% yield by acidification after heating at 100° with base. Although some coloring of the solution took place, no evidence for the presence of a diazo grouping could be found.

Cyclopentadiene Adduct.—The adduct could be prepared in quantitative yield by mixing equimolar amounts of the dione and cyclopentadiene in four times their volume of benzene and allowing the mixture to stand at room temperature. The adduct begins to precipitate in a very short time. After a few hours the solution was filtered and the filtrate recrystallized from a mixture of chloroform–carbon tetrachloride and sublimed at 120–130° (1 mm.). The adduct had a melting point of 169.5–170.5°, and appeared to be 100% enolic.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.1; H, 6.2. Found: C, 73.9; H, 6.05.

Anthracene Adduct.—The dione (3.42 g., 0.036 mole) and anthracene (6.35 g., 0.036 mole) were refluxed in 40 ml. of benzene for four days. The precipitated adduct was filtered, dissolved in NaOH and again filtered, and precipitated by acidification with dilute HCl. The adduct weighed 8.7 g. (89% yield), m.p. 302–305° dec.

Reaction of Cyclopentene-3,5-dione with Aqueous Base.—To 500 mg. of the dione in 5 ml. of water was added 53 ml. of 0.1 *N* NaOH. After stirring at room temperature for 20 minutes the brownish-red solution was passed through an Amberlite IR 120 ion-exchange column to remove sodium ions. The aqueous solution of the polymer was then evaporated to dryness leaving a tan, highly enolic powder which was insoluble in organic solvents.

Anal. Calcd. for $C_5H_4O_2 \cdot {}^2/_3H_2O$: C, 55.55; H, 4.97. Found: C, 55.44; H, 4.87.

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[27] An apparatus which is especially convenient for this hydrogenation, and for others in which a relatively large amount of hydrogen is absorbed (in this case 620 ml.), is described by P. R. Story and C. H. DePuy, in press.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXII. The Conversion of Cyclopentene Oxide to Cyclopentene Sulfide

BY LEON GOODMAN AND B. R. BAKER

RECEIVED MARCH 31, 1959

Reaction of cyclopentene oxide (6-oxabicyclo[3.1.0]hexane) (Ia) with potassium thiocyanate led directly to cyclopentene sulfide (6-thiabicyclo[3.1.0]hexane) (Va) in 20% yield. On reaction of the epoxide with ammonium thiocyanate, an 11% yield of cyclopentene thiocyanohydrin (VI) was obtained, along with 3% of cyclopentene sulfide (Va). Treatment of *trans*-2-thiocyanatocyclopentyl methanesulfonate (VIII) with aqueous sodium hydroxide gave a 63% yield of cyclopentene sulfide (Va).

In a previous paper of this series,[2] a number of methods for the conversion of cyclopentene oxide to cyclopentene sulfide were reported which would proceed under conditions compatible with the chemistry of nucleosides. Additional methods have now been found and are the subject of this paper.

A number of sulfur-containing reagents cause the direct conversion of epoxides to episulfides,[3] alkali thiocyanates being the most frequently used. A mechanism for the thiocyanate reaction was advanced by Ettlinger[4] and given support by

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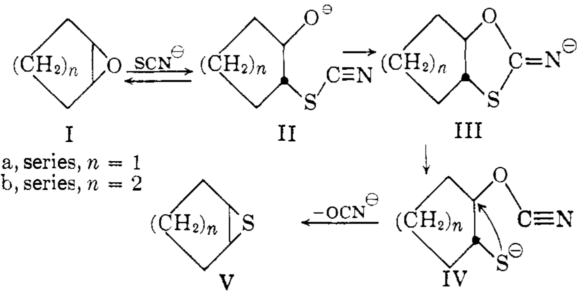
[1] This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* L. O. Ross, L. Goodman and B. R. Baker, *J. Org. Chem.*, **24**, in press (1959).

[2] L. Goodman, A. Benitez and B. R. Baker, THIS JOURNAL, **80**, 1680 (1958).

[3] C. C. Culvenor, W. Davies and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).

[4] M. G. Ettlinger, THIS JOURNAL, **72**, 4792 (1950).

van Tamelen[5] in his studies in the cyclohexane and cyclopentane systems and by Price and Kirk[6] in their study of the stereochemistry of the reaction. For the case of an alicyclic oxide the mechanism may be written

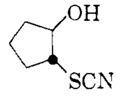


Ia, series, $n = 1$
b, series, $n = 2$

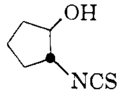
van Tamelen[5] reported that cyclopentene oxide (Ia) was not converted to cyclopentene sulfide (Va) with potassium thiocyanate at room temperature, conditions under which cyclohexene oxide (Ib) was converted to cyclohexene sulfide (Vb) in high yield. He also reported that cyclopentene oxide (Ia) was recovered in about 80% yield when it was heated with excess potassium thiocyanate at 60° for 15 hours. van Tamelen[5] rationalized these results by assuming that the intermediate IIIa represented a highly strained system of two *trans*-fused five-membered rings that would be expected to form with difficulty, if at all. In view of the fact that allobiotin and epiallobiotin contain two *trans*-fused five-membered rings[7] and the fact that thiocyanate ion should at least convert cyclopentene oxide (Ib) to the thiocyanate IIb, the reaction was reinvestigated.

In these laboratories it was shown that reaction of Ia with potassium thiocyanate at about 100° gave a 20% yield of cyclopentene sulfide (Va). This was accompanied by a non-distillable, viscous residue which contained 24% sulfur, showed no infrared absorption bands characteristic of –SH or –SCN groups, but did show distinct –OH absorption bands; this residue may have resulted from opening of the episulfide Va under the alkaline reaction conditions. When the reaction was carried out at 60–75°, approximating van Tamelen's[5] conditions, the distillable product was largely the episulfide Va, accompanied by some of the epoxide Ia. Clearly, the conversion (Ia → Va) is much more difficult than that of Ib to Vb, but, if the above mechanism is accepted, the formation of intermediate IIIa is possible; the presence of the two heterocyclic atoms in IIIa must make the system more flexible than a carbocyclic system.

When the reaction of cyclopentene oxide (Ia) and ammonium thiocyanate was carried out at 100°, only about 3% of episulfide Va was obtained. This was accompanied by about 11% of the thiocyanohydrin VI and a large, non-distillable residue whose infrared spectrum indicated it to be a low molecular weight polymer arising from the reaction of cyclopentene oxide and water.



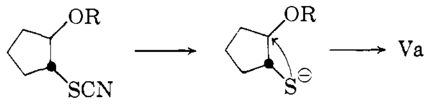
VI



VII

Aqueous potassium thiocyanate is much more basic than aqueous ammonium thiocyanate, and the conversion of Ia to Va seems to require that the intermediates be in the anionic form, as suggested by the proposed mechanism.[4,5] An authentic sample of the thiocyanohydrin VI was prepared in 63% yield by the reaction of the epoxide Ia thiocyanic acid, as described by van Tamelen.[5] The material prepared by this method showed strong infrared –SCN absorption at 4.65 μ which was accompanied by appreciable absorption at 4.75 μ, probably attributable to the presence of *trans*-2-hydroxycyclopentyl isothiocyanate (VII) in the distillate. The extraneous 4.75 μ band was present only in trace amounts in the thiocyanohydrin VI isolated fron the reaction of Ia with ammonium thiocyanate, and did not increase as a result of distillation; it is known that some thiocyano compounds rearrange to the more stable isothiocyanate isomers upon heating.[8] When VI was heated with aqueous potassium carbonate, a mixture of epoxide Ia and, predominantly, the episulfide Va resulted. The episulfide Va presumably resulted from the sequence IIa → IIIa → IVa → Va and the epoxide probably resulted from the reversion of IIa, as suggested by the mechanism. Under milder alkaline conditions, van Tamelen[3] converted VI to unidentified, undistillable products; it is surprising that he did not isolate cyclopentene oxide (Ia) from this transformation.

The thiocyanohydrin VI was converted in good yield to its mesylate VIII and its tosylate IX. The latter was a well-defined crystalline compound.



VIII, R = SO_2CH_3
IX, R = $SO_2C_6H_4CH_3$-*p*

When the mesylate was stirred at room temperature with aqueous sodium hydroxide, cyclopentene sulfide (Va) was obtained in 63% yield. Only a low yield of Va could be obtained from the tosylate IX under alkaline conditions, but this could be attributed to its low solubility and the necessity of carrying out the reaction at a temperature higher than the melting point of IX. Similar circumstances were responsible for the low yields of Va formed from a number of intermediates in the previous work.[2]

Several attempts to prepare Va by the reaction of Ia with thiourea[3,9] gave only traces of Va. Most of the epoxide Ia was converted to undistillable material, probably as a result of hydrolysis of the intermediate in that reaction which would correspond to IIa.

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[5] E. E. van Tamelen, THIS JOURNAL, **73**, 3444 (1951).

[6] C. C. Price and P. F. Kirk, *ibid.*, **75**, 2396 (1953).

[7] B. R. Baker, M. V. Querry, W. L. McEwen, S. Bernstein, S. R. Safir, L. Dorfman and Y. SubbaRow, *J. Org. Chem.*, **12**, 186 (1947); S. A. Harris, R. Mozingo, D. E. Wolf, A. N. Wilson and K. Folkers, THIS JOURNAL, **67**, 2102 (1945).

[8] Houben-Weyl, "Methoden der Organischen Chemie," Band IX, Georg Thieme Verlag, Stuttgart, 1955, p. 866.

[9] F. G. Bordwell and H. M. Andersen, THIS JOURNAL, **75**, 4959 (1953).

Experimental[10]

Reaction of Cyclopentene Oxide (Ia) with Potassium Thiocyanate.—A mixture of 10.2 g. (0.105 mole) of potassium thiocyanate, 3.90 g. (46.4 mmoles) of cyclopentene oxide (Ia)[2] and 30 ml. of water was heated, with stirring, at reflux for 2 hours. The resultant colorless mixture contained two layers and was extracted with four 30-ml. portions of pentane and one 30-ml. portion of methylene chloride. The combined extracts were dried over magnesium sulfate; the solvents were distilled from the filtrate through a short Widmer column and the residue was distilled *in vacuo* through a short Vigreux column to yield 0.95 g. (20%) of cyclopentene sulfide (Va), b.p. 68° (65 mm.), $n^{20}\text{D}$ 1.5240 (lit.[5] b.p. 69–70° (65 mm.), $n^{25}\text{D}$ 1.5222), whose infrared spectrum was identical with that of previous samples of Va.[2] The residue from the distillation (2.8 g.) was a viscous, yellow liquid, $\lambda_{\max}^{\text{film}}$ 3.00 (OH), no SH near 3.9 or SCN at 4.65 μ.

Anal. Found: C, 55.5; H, 8.11; S, 24.4.

Essentially the same yield of Va resulted when equimolar quantities of Ia and potassium thiocyanate were used in the above reaction.

When the reaction was carried out approximating van Tamelen's[5] conditions by heating a mixture of 6.05 g. (76.4 mmoles) of potassium thiocyanate, 4.20 g. (50.0 mmoles) of cyclopentene oxide (Ia) and 8.75 ml. of water at 60–75° for 15 hours, the final mixture had the same appearance as that described above. The mixture was worked up as above and distillation at atmospheric pressure through a short Vigreux column furnished two fractions as follows: (1) 0.12 g., b.p. 89–120°, $n^{20}\text{D}$ 1.4402; and (2) 1.10 g., b.p. 120–135°, $n^{20}\text{D}$ 1.4928. Fraction 1 was essentially pure cyclopentene oxide (Ia, $n^{20}\text{D}$ 1.4355) and fraction 2 was a mixture of about 65% of Va and 35% of Ia. The infrared spectra of these fractions corroborated the refractive index data. The residue from the distillation (1.8 g.) contained 23.1% sulfur and showed strong–OH and appreciable –SCN absorption in the infrared.

Reaction of Cyclopentene Oxide (Ia) with Ammonium Thiocyanate.—A mixture of 8.00 g. (0.105 mole) of ammonium thiocyanate, 3.90 g. (46.4 mmoles) of cyclopentene oxide (Ia) and 30 ml. of water was heated, with stirring, at reflux for 2 hours. The mixture was extracted with four 25-ml. portions of pentane and these extracts were dried over magnesium sulfate. The mixture then was extracted with three 25-ml. portions of methylene chloride; these extracts were washed with 15 ml. of water and then dried over magnesium sulfate.

The dried pentane extracts, after filtration, were distilled through a short Widmer column and the residue was evaporatively distilled at 88 mm. (bath temp. 50–85°) to yield 0.20 g. of product, $n^{20}\text{D}$ 1.5124, whose infrared spectrum showed it to be largely cyclopentene sulfide (Va) containing about 10% of the epoxide Ia.

The dried methylene chloride extracts, after filtration, were evaporated *in vacuo* to leave 4.05 g. of a viscous, red oil, which was evaporatively distilled twice to give 0.70 g. (11%) of colorless distillate collected at 1.0 mm. (bath temp. 90–100°), $n^{20}\text{D}$ 1.5272, whose infrared spectrum agreed well with that of VI prepared from thiocyanic acid (*cf.* below), $\lambda_{\max}^{\text{film}}$ 2.95 (OH), 4.64 (SCN), 9.10 and 9.27 (C–OH); only a trace of NCS absorption at 4.74 μ. The residue from the evaporative distillation was a viscous liquid whose infrared spectrum showed strong OH absorption and no other absorption bands readily attributable to other functional groups.

trans-**2-Hydroxycyclopentyl thiocyanate (VI)** was prepared from 12.6 g. (0.15 mole) of Ia as described by van Tamelen.[5] The distilled product was collected in two fractions: (1) 6.1 g., b.p. 106–111° (2.0 mm.), $n^{20}\text{D}$ 1.5265; and (2) 7.4 g., b.p. 111° (2.0 mm.), $n^{20}\text{D}$ 1.5257, for a total yield of 63%. Fraction 1 showed much stronger –NCS infrared absorption at 4.75 μ than did fraction 2; otherwise, both fractions had spectra very similar to that for VI isolated from the reaction of I and ammonium thiocyanate.

Reaction of VI with Aqueous Potassium Carbonate.—A mixture of 5.8 g. (40 mmoles) of thiocyanohydrin VI (fraction 2, above), 16.56 g. (0.120 mole) of potassium carbonate and 40 ml. of water was refluxed, with stirring, for 2 hours. The solution was extracted with three 25-ml. portions of pentane and one 25-ml. portion of methylene chloride and the combined extracts were dried over magnesium sulfate. After filtration, the solvents were removed by distillation through a short Widmer column. The residue was evaporatively distilled at 90 mm. (bath temp. 48–90°); yield 0.70 g., $n^{20}\text{D}$ 1.5045. Vapor-phase chromatography[11] indicated the presence of 82% episulfide Va and 18% epoxide Ia, in fair agreement with the proportions calculated from the refractive index. In addition, vapor-phase chromatography[11] of the distilled solvents showed that almost 0.07 g. of a mixture of Va and Ia was present in the pentane–methylene chloride distillate.

trans-**2-Thiocyanatocyclopentyl *p*-Toluenesulfonate (IX).**—To a chilled (0°) solution of 1.43 g. (10.0 mmoles) of thiocyanohydrin VI (fraction 2, above) in 6 ml. of reagent-grade pyridine was added 2.86 g. (15.0 mmoles) of *p*-toluenesulfonyl chloride. The mixture was left 18 hours at 0° protected from moisture, then was poured onto 50 g. of a mixture of ice and water, yielding a tan oil. The oil was dissolved in 60 ml. of methylene chloride; the solution was washed with 75 ml. of cold 1 *N* hydrochloric acid and with 100 ml. of water. After being dried over magnesium sulfate, the solution was filtered and the filtrate evaporated *in vacuo*, leaving 2.80 g. (94%) of oil which slowly solidified to a solid, m.p. 42–52°. Two recrystallizations from 67% aqueous ethanol gave an analytical sample, m.p. 53.5–54.5°; $\lambda_{\max}^{\text{KBr}}$ 4.66 (SCN), 7.35–7.40 (CH$_3$ and –OSO$_2$), 8.41 and 8.54 (-OSO$_2$), 12.31 μ (*p*-disubstituted phenyl).

Anal. Calcd. for $C_{13}H_{15}NO_3S_2$: C, 52.5; H, 5.09; S, 21.6. Found: C, 52.6; H, 5.18; S, 21.7.

When 5.94 g. (20 mmoles) of the tosylate IX was heated, with stirring, at 55–65° for 8.5 hours in 100 ml. of water containing 1.65 g. (40 mmoles) of sodium hydroxide, only 0.20 g. (10%) of cyclopentene sulfide (Va) could be isolated from the reaction mixture a large distillation residue (2.9 g.) remained. Titration of the reaction mixture showed that 15 mmoles of base was present at the end of the reaction period.

trans-**2-Thiocyanatocyclopentyl Methanesulfonate (VIII).**—The mesylate VIII was prepared from 5.0 g. (35 mmoles) of VI and 5.0 g. (53 mmoles) of methanesulfonyl chloride in 21 ml. of pyridine according to the procedure described for the preparation of IX. The product was a yellow liquid yield 6.8 g. (88%); $\lambda_{\max}^{\text{film}}$ 4.65 (SCN), 7.35–7.48 and 8.49 μ (-OSO$_2$); a small amount of absorption at 4.77 (NCS) was present due to the impurity in the VI used. This material was made without further purification.

A mixture of the crude mesylate (6.67 g., 30.0 mmoles), 2.48 g. (60.0 mmoles) of sodium hydroxide and 110 ml. of water was stirred at room temperature for 28 hours. The final basic solution was adjusted to *p*H 7 with 8.0 ml. of 1 *N* hydrochloric acid and then extracted with two 40-ml. portions of methylene chloride. The extract was dried over magnesium sulfate, filtered and the solvent removed from the filtrate by distillation through a short Vigreux column at atmospheric pressure. Distillation of the residue *in vacuo* yielded 1.90 g. (63.3%) of cyclopentene sulfide (Va), b.p. 67–68° (62 mm.), $n^{20}\text{D}$ 1.5246, whose infrared spectrum was in complete agreement with that of authentic Va.

Acknowledgments.—The authors are indebted to Dr. Peter Lim for interpretation of infrared spectra and to Mr. O. P. Crews, Jr., and his group for the preparation of the large amounts of cyclopentene oxide used.

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[10] Boiling points and melting points are uncorrected; the latter were obtained with the Fisher–Johns apparatus.

[11] The vapor-phase chromatography was performed on a 6-foot LAC column (Wilkens Instrument Co., Walnut Creek, Calif.) at a temperature of 123° by Mrs. H. H. Johnson of the Analytical Chemistry Section of Stanford Research Institute.