product was isolated, m.p. 234–235° dec., that appeared to be XX, based on its infrared spectrum.

Methyl 2-Anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (XIV).—A solution of 130 mg. (0.325 mmole) of XVII in 3.2 ml. of methoxyethanol was added to a hot solution of 255 mg. (0.808 mmole) of barium hydroxide octahydrate in 3.2 ml. of water. After being refluxed for 18 hours, the mixture was cooled, diluted with about 10 ml. of water, then neutralized with solid carbon dioxide, causing evolution of hydrogen sulfide as evidenced by odor and a positive reaction with lead acetate paper. The solids were collected on a filter and washed with water. The mixture of barium carbonate and product was extracted with boiling ethanol (2 × 5 ml.). Evaporation of the combined ethanol extracts to dryness *in vacuo* gave 100 mg. (86%) of product, m.p. 148–150°. Recrystallization from alcohol–water afforded white crystals, m.p. 148–150°, $[\alpha]^{24}D$ −18° (2% in $CHCl_3$). In the infrared (KBr disk), this compound showed OH–NH absorption at 2.91, 2.95 and 3.03 μ, phenyl at 6.25 and 6.67 μ (only bands between 5 and 6.8 μ), C–O–C and C–O–H at 9.12, 9.34 and 9.95 μ, and monosubstituted phenyl at 13.3 and 14.3 μ.

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.2; H, 6.49; N, 3.92. Found: C, 67.2; H, 6.50; N, 4.06.

Methyl 2-Anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside 2,3-Carbonate (XXI).—To a warm solution of 200 mg. (0.501 mmole) of XVII in 200 ml. of absolute ethanol was added a warm solution of 162 mg. (0.508 mmole) of mercuric acetate in 10 ml. of absolute ethanol.[21] A white, gelatinous precipitate separated and gradually became dark gray. After standing for about 18 hours, the mixture was filtered. The filtrate was treated with excess hydrogen sulfide, then filtered through Celite and evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of hot absolute ethanol, filtered from some mercuric sulfide, then cooled at 3°. White needles separated gradually over 3 days. The product was collected and washed with cold ethanol; yield 54 mg. (28%), m.p. 168°. Crystals could be isolated from the mother liquor, but were obviously a mixture and were not investigated further.

Recrystallization of the 54 mg. from ethanol did not raise the m.p. The compound had $[\alpha]^{27}D$ −108° (0.1% in $CHCl_3$) and λ_{max}^{KBr} (μ) 5.65 (C=O of five-membered urethan ring), 8.28 (urethan C–O–C), 13.2 and 14.3 (mono substituted phenyl), no OH–NH near 3.0.

Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.8; H, 5.52; N, 3.65. Found: C, 65.1; H, 5.33; N, 3.80.

Acknowledgment.—The authors wish to thank Dr. Peter Lim and Dr. W. C. Coburn, Jr., for interpretation of the infrared spectra.

MENLO PARK, CALIF.

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

Potential Anticancer Agents.[1] XIV. The Thiourethan Neighboring Group. II. Synthesis of *cis*-2-Mercapto- and *cis*-2-Anilinocyclopentanols

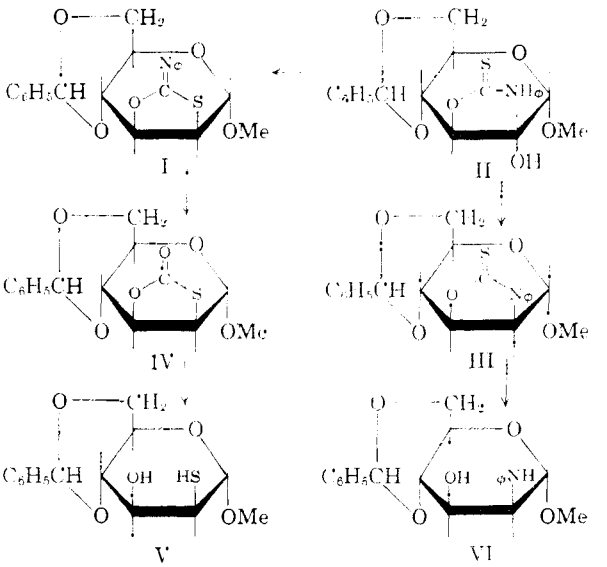
BY LEON GOODMAN, ALLEN BENITEZ, CHARLES D. ANDERSON AND B. R. BAKER

RECEIVED JULY 17, 1958

trans-1,2-Cyclopentanediol can be converted to either *cis*-2-mercaptocyclopentanol (X) or to *cis*-2-anilinocyclopentanol (XVI), depending upon the conditions selected for cyclization of the monophenylthiourethan VII of the diol. These transformations have been carried out under conditions that should be compatible with the stability of nucleosides and should allow synthesis of nucleosides containing 3′-deoxy-3′-mercapto- or 3′-anilino-3′-deoxy-D-ribofuranose moieties. In order to establish the structure of *cis*-2-mercaptocyclopentanol (X) prepared by the neighboring group method, this substance was also synthesized from 1-cyclopentenyl acetate through the addition of thiolacetic acid and subsequent hydrolysis.

In the preceding paper of this series,[2] the use of the thiourethan group for the synthesis of anilino sugars and mercapto sugars and nucleosides of such sugars was discussed. Mesylation of the thiourethan II followed by treatment with sodium methoxide afforded the crystalline cyclic thiourethan III, which in turn could be hydrolyzed to crystalline methyl 2-anilino-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranoside (VI). When the thiourethan II was treated with thionyl chloride, an oily product (I) was obtained that readily lost aniline to give another oil that was presumably the cyclic thiocarbonate IV. The presence of both I and IV in their respective reaction mixtures was highly probable in view of the characteristic infrared absorption bands. Since neither I nor IV could be adequately purified, this thionyl chloride ring closure has now been investigated with the simpler cyclopentane system. The successful conversion of a *trans*-1,2-glycol to a *cis*-2-mercaptoalcohol and to a *cis*-2-anilinoalcohol in the cyclopentane series is the subject of this paper.

The conversion of *trans*-1,2-cyclopentanediol to the monophenylthiourethan, *trans*-2-(phenylthiocarbamoyloxy)-cyclopentanol (VII), was best accomplished by refluxing the dried diol dissolved in toluene with an equimolar quantity of phenyl isothiocyanate.[3] Although the yield of VII was



(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research.

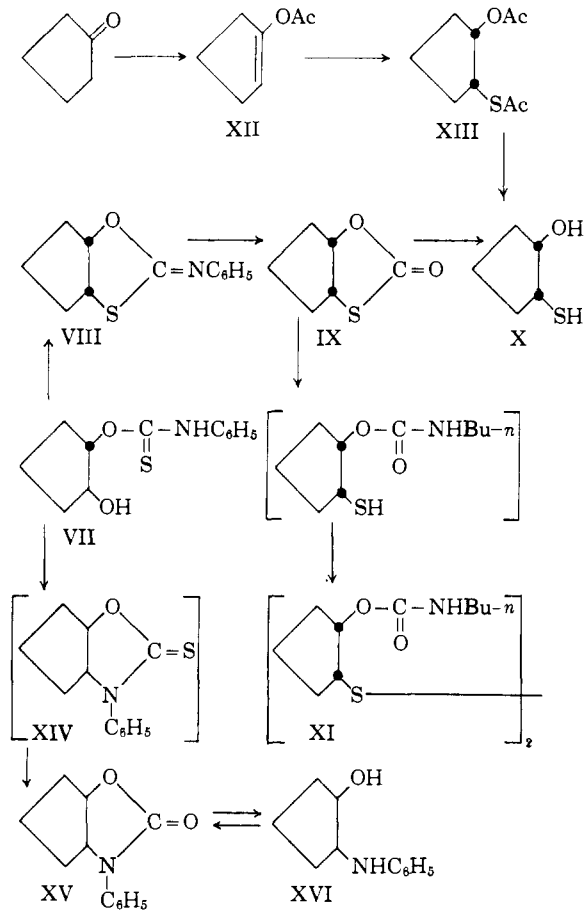
(2) B. R. Baker, K. Hewson, L. Goodman and A. Benitez, THIS JOURNAL, **80**, 6577 (1958).

(3) The benzoylthiourethan group was regarded as another interesting neighboring group whose utility could be visualized as similar to

only 31%, the conversion to VII was 71%; most of the unreacted diol could be recycled. The use of refluxing xylene in the above preparation led to extensive decomposition; the preparation of VII from the monosodium salt[2] of *trans*-1,2-cyclopentanediol and phenyl isothiocyanate gave inferior yields. Attempts to carry out the reaction between diol and phenyl isothiocyanate in the presence of pyridine containing tri-*n*-butylamine led to the formation of some diphenylthiourea, a high yield of triphenylguanidine and only traces of VII.

Reaction of the monophenylthiourethan VII with cold thionyl chloride led to a complex mixture. When an ether extract of the hydrolyzed product was added to an ethereal picric acid solution, however, the picrate of the anil VIII precipitated in a high state of purity, as shown by comparison with an analytically pure sample of the anil VIII picrate. A variety of conditions were studied in the reaction of thionyl chloride with the thiourethan VII. It was shown that the best yields (54-58%) of the anil VIII picrate resulted when the urethan VII was mixed with thionyl chloride at 0° in a mole ratio of 1:12 and left at 0° for 24 hours before the excess thionyl chloride was decomposed with a large excess of cold aqueous sodium bicarbonate solution. Smaller or larger mole ratios of thionyl chloride gave lower yields, as did shorter reaction times or the use of lower temperatures. Regeneration of the anil VIII from its picrate was readily accomplished in high yield by the aqueous ethanolamine procedure described by Weiner and Kaye.[4] It is interesting that the infrared absorption frequency of the C=N bond in the anil VIII appears at 6.12 μ, whereas the $C{=}\overset{+}{N}H$ absorption in both the anil VIII picrate and hydrochloride occurs at 6.15 μ (all spectra obtained by the potassium bromide pellet method). Generally the acquisition of a positive charge by a C=N bond causes a marked hypsochromic shift in the infrared frequency[5] but, in the examples cited, the carbon of the azomethine group has been at the aldehyde oxidation level. In the anil VIII the azomethine carbon is at the carbonic acid oxidation level; a recent paper by Bradsher and co-workers[6] cites another example where the protonation of 4-phenethyl-5-phenethylimino-1,2,4-dithiazolidin-3-one causes practically no shift of the C=N infrared frequency at 6.12 μ. The azomethine carbon in this latter case is also at the carbonic acid oxidation level.

Conversion of the anil VIII to the cyclic thiolcarbonate, tetrahydro-3aH-cyclopenta-1,3-oxathiolan-2-one (IX), was carried out in 55-65% yield by heating the anil VIII with 50% aqueous acetic acid at 80° for 4 hours. Compound IX had a strong carbonyl band at 5.76 μ. The thiolcarbonate IX was converted in 57% yield to *cis*-2-mercaptocyclopentanol (X) by treatment with methanolic sodium methoxide at room temperature. When the anil VIII was converted to the mercaptoalcohol X without isolation of the thiolcarbonate IX, the yield of X was 63%. Several attempts were made to convert the anil VIII directly to the *cis*-mercaptoalcohol IV. The anil VIII was recovered unchanged after treatment with methanolic sodium methoxide at reflux. An attempt to convert the thiolcarbonate IX to the mercaptoalcohol X with refluxing methanolic *n*-butylamine resulted instead in cleavage at the sulfur–carbonyl bond to give, undoubtedly as the result of oxidation during the long period of heating, the disulfide XI of *cis*-2-(*n*-butylcarbamoyloxy)-cyclopentanethiol.



The sequence from *trans*-1,2-cyclopentanediol to the mercaptoalcohol X represents a synthesis which should be compatible with the chemistry of purine nucleosides. The extension of this model synthesis to the preparation of a nucleoside which contains a 2′,3′-*cis*-mercaptoalcohol moiety, such as 3′-deoxy-3′-mercaptoadenosine,[2] is in progress.

Proof of structure of the *cis*-2-mercaptocyclopentanol (X) was carried out by synthesis of X using the procedure employed by Behringer and Kley[7] for the syntheis of *cis*-2-mercaptocyclohexanol. The enol acetate XII of cyclopentanone was prepared in 76% yield using the isopropenyl acetate procedure described by Hagemeyer and

that of the phenylthiourethan group. When the reaction of one mole of benzoyl isothiocyanate with one mole of *trans*-1,2-cyclopentanediol was carried out, both the monobenzoylthiourethan and the bis-benzoylthiourethan were isolated. In view of the successful work with the monophenylthiourethan VII, the similar cyclization reactions of the monobenzoylthiourethan of *trans*-1,2-cyclopentanediol were not investigated.

(4) N. Weiner and I. A. Kaye, *J. Org. Chem.*, **14**, 868 (1949).

(5) B. Witkop, THIS JOURNAL, **76**, 5597 (1954); B. Witkop, *Experientia*, **10**, 420 (1954).

(6) C. K. Bradsher, F. C. Brown, E. F. Sinclair and S. T. Webster, THIS JOURNAL, **80**, 414 (1958).

(7) H. Behringer and W. Kley, *Ann.*, **595**, 160 (1955).

Hull[8] for other enol acetates. The addition of freshly distilled thiolacetic acid to cyclopentenyl acetate XII proceeded exothermically (the necessity of using "activated" enol acetate as had been reported for the addition of thiolacetic acid to cyclohexenyl acetate[7] was not experienced) and gave the diacetate XIII in 91% yield. It will be noted that the addition of the elements of thiolacetic acid to the double bond of XII must be stereospecifically *trans* in order to give pure *cis*-diacetate XIII. Behringer and Kley[7] considered that their 2-(acetylthio)-cyclohexyl acetate was the pure *cis*-diacetate and, although no intensive investigation of the stereochemical purity of XIII was made, it seems probable that it also was essentially pure *cis*-diacetate. Treatment of XIII with one equivalent of dilute aqueous base caused hydrolysis of only the S-acetate group of XIII. Under these conditions any *trans*-2-(acetylthio)-cyclopentyl acetate would have been converted to cyclopentene episulfide[9] but none of the episulfide could be detected in the product when an isolation procedure was used which would have permitted easy separation. Bordwell and Hewett[10] recently have reported a careful study of the additions of thiolacetic acid to 1-methylcyclohexene and 1-methylcyclopentene and showed them to give stereoselectively, but not stereospecifically, *trans* addition of the elements of thiolacetic acid.

The hydrolysis of the *cis*-diacetate XIII to the mercaptoalcohol X could be carried out in rather low yield using refluxing aqueous sodium hydroxide or methanolic sodium methoxide at room temperature; large amounts of unidentified residues accompanied the desired product. The acid-catalyzed methanolysis of XIII proved to be the best procedure for the preparation of X; it gave consistent yields of 62–65%. The mercaptoalcohol X was characterized by the preparation of the 2,4-dinitrophenyl sulfide derivative, which was shown to be identical with that from X prepared *via* the anil VIII, but isomeric with the same derivative of *trans*-2-mercaptocyclopentanol. The infrared spectra of the samples of X prepared by the two routes were identical and showed significant differences from the infrared spectrum of *trans*-2-mercaptocyclopentanol.[9] In addition, the di-N-phenylurethan of X was prepared and was shown to be different in melting point and infrared spectrum from the derivative of *trans*-2-mercaptocyclopentanol.

The reaction of phenylthiourethan VII with *p*-toluenesulfonyl chloride (or with methanesulfonyl chloride) in pyridine also gave a very complex mixture of products after treatment of the reaction mixture with water. Infrared examination of the crude product showed that no unreacted hydroxyl remained, but it was not possible to identify clearly any major cyclization product. A careful examination of the mixture resulted in the isolation of small amounts of carbanilide XVII and diphenylcarbodiimide XVIII (whose presence in the reaction mixture was apparent from a strong infrared absorption at 4.68 μ). The diimide XVIII formation can be attributed to the reaction of carbanilide with *p*-toluenesulfonyl chloride in pyridine. This general method of synthesis of carbodiimides has been reported recently.[11]

$$C_6H_5NHCNHC_6H_5 \xrightarrow[\text{pyridine}]{RSO_2Cl} C_6H_5NHC(OSO_2R)=NC_6H_5 \longrightarrow$$

XVII

$C_6H_5N=C=NC_6H_5$

XVIII

Vigorous alkaline hydrolysis of the crude tosylation product of VII led to a dark product which gave a positive sodium nitroprusside test indicative of the presence of mercaptans; infrared absorption near 3.90 μ also indicated the presence of the mercaptan group. The acid-soluble fraction of the hydrolysis mixture was separated into aniline (59% yield based on VII) and a non-steam-distillable fraction (31%) which has been assigned the structure *cis*-2-anilinocyclopentanol (XVI) on the basis of analysis, analysis of the picrate and the ready formation of the cyclic urethan, hexahydro-3-phenyl-2H-cyclopenta[d]oxazol-2-one (XV). Compound XV was formed in good yield by the base-catalyzed transesterification of the anilinoalcohol XVI with diethyl carbonate according to the procedure of Homeyer.[12] The possibility that compound XVI is a 1,3-anilinoalcohol has not been ruled out, but it would be difficult to rationalize such a product mechanistically; the 1,2-structure seems to represent the logical choice. The carbonyl infrared absorption of XV at 5.77 μ seems more compatible with a 5-membered cyclic urethan than with a 6-membered cyclic urethan. Small quantities (*ca.* 5%) of the anil VIII have also been noted in the crude product from the reaction of VII and *p*-toluenesulfonyl chloride and it seems likely that the presence of the mercaptan group in the crude hydrolysis product of that reaction results from VIII.

Although the yields of anil VIII and anilinoalcohol XVI obtained from the reactions of VII with thionyl chloride and with *p*-toluenesulfonyl chloride in pyridine, respectively, make it certain that the reactions are more complex than the simple representation below, nevertheless the difference in the direction of ring closure in the two cases is clear. The situation seems comparable to that encountered with the 1-aryl-3-(2-bromoethyl)-ureas where solvolysis under neutral conditions led to O–5 closure to anilinoöxazolines and under basic conditions led to N$^-$–5 closure to N-arylimidazolidinones.[13] Similar reactions have also been observed by Heine, *et al.*[14] Analogously, the reactions of VII may be written as shown.

The sequence XIV→XV→XVI then follows logically. The cyclic thionourethan XIV was proabably present in material isolated by evaporative distillation of the crude reaction product of

(8) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

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

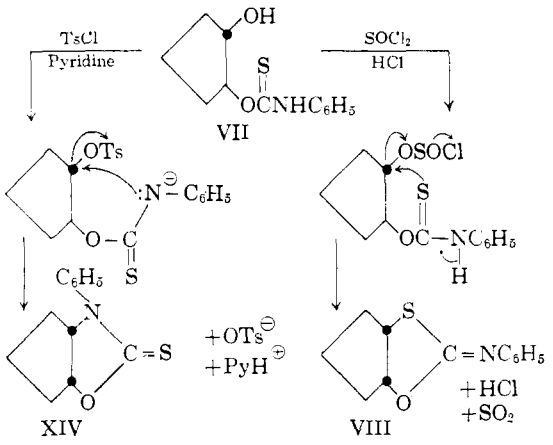
(10) F. G. Bordwell and W. A. Hewett, *ibid.*, **79**, 3493 (1957).

(11) G. Amiard and R. Heymès, *Bull. soc. chim.*, 1360 (1956).

(12) A. H. Homeyer, U. S. Patent 2,399,118, April 23, 1946.

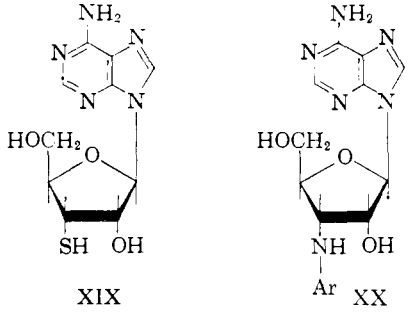
(13) F. L. Scott, R. E. Glick and S. Winstein, *Experientia*, **13**, 183 (1957).

(14) H. W. Heine, P. Love and J. L. Bove, THIS JOURNAL, **77**, 5420 (1955); H. W. Heine, *ibid.*, **78**, 3708 (1956).



VII and *p*-toluenesulfonyl chloride in pyridine after treatment with water. Efforts were made to synthesize the thionourethan XIV by reaction of XVI with thiophosgene and by preparation of the methyl xanthate ester of XVI followed by ring closure. These attempts were unsuccessful and probably gave crude samples of XV as a result of hydrolysis of XIV to XV. In the case of the benzylidene sugar quoted in the previous paper,[2] the thionourethan related XIV was a stable, isolable compound.

The successful conversion of VII (and therefore of *trans*-1,2-cyclopentanediol) to X and to XVI by paths which should be compatible with the chemistry of nucleosides makes it likely that such procedures will allow the synthesis of the nucleosides XIX and XX which could have interesting biological properties.



Experimental[15]

trans-2-(**Phenylthiocarbamoyloxy**)-cyclopentanol (**VII**).—A solution of 51.0 g. (0.50 mole) of *trans*-1,2-cyclopentanediol in 250 ml. of toluene was dried by refluxing the solution, using a Dean–Stark trap, until removal of water was complete. After the addition of 60.0 ml. (0.50 mole) of phenyl isothiocyanate, the resulting solution, protected from moisture, was heated under reflux for 50 hours. The toluene was evaporated at water-pump vacuum and the unreacted phenyl isothiocyanate was removed at 1 mm. and 40°. The residue, a waxy solid, was thoroughly triturated with four 80-ml. portions of water. The remaining solid was dried and dissolved in about 2 liters of a boiling mixture of ligroin (65–110°) and benzene (85:15), decanting from any insoluble solid. The crystalline monophenylthiourethan VII separated on cooling; yield 36.6 g. (31% conversion), m.p. 89.5–93.5°; the product was suitable for further transformations. An an lytical sample was obtained by one recrystallization from the ligroin–benzene mixture and a final recrystallization from carbon tetrachloride gave white crystals, m.p. 93–94°; λ_{max}^{KBr} μ 2.98 (OH), 3.13, 6.48 (NH), 7.17 (C=S), 13.30 (monosubstituted phenyl); λ_{max} (mμ) 277 (ϵ 17,400) in 95% ethanol and 0.1 *N* ethanolic hydrogen chloride, 225 (ϵ 12,400) and 272 (ϵ 6,010) in 0.1 *N* ethanolic potassium hydroxide.

Anal. Calcd. for $C_{12}H_{15}NO_2S$: C, 60.7; H, 6.37; N, 5.91; S, 13.5. Found: C, 60.6; H, 6.31; N, 5.92; S, 13.9.

By evaporation of the water extracts of the crude thiourethan, 29.2 g. of *trans*-1,2-cyclopentanediol was recovered; the yield of VII based on unrecovered diol was therefore 71%.

When the preparation of VII was similarly attempted in refluxing xylene, extensive darkening occurred and the tarry residue had only weak C=S absorption at 7.2 μ. When the reaction of phenyl isothiocyanate with the sodium salt of the diol (prepared by the use of one mole of sodium methoxide) was carried out in dimethylformamide at room temperature for 18 hours,[2] a 17% yield of VII was obtained and appreciable amounts of thiocarbanilide (m.p. 166–167°) were also obtained. The reaction of phenyl isothiocyanate with the sodium salt of the diol in toluene led to the isolation of a small quantity of carbanilide in addition to a low yield of I. The reaction of phenyl isothiocyanate with a pyridine solution of the diol containing a few drops of tri-*n*-butylamine yielded about 70% of 1,3-triphenylguanidine and traces of thiocarbanilide and VII.

trans-2-(**Benzoylthiocarbamoyloxy**)-cyclopentanol.—A mixture of 0.62 g. (6.1 mmoles) of dry *trans*-1,2-cyclopentanediol, 0.99 g. (6.1 mmoles) of benzoyl isothiocyanate[16] and 7 ml. of methylene dichloride was stirred under nitrogen at room temperature for 50 hours. The solution was evaporated *in vacuo* and the residue was dissolved in boiling 80% methanol. On cooling, 177 mg. of solid, m.p. 147–151°, precipitated and was recrystallized twice from 80% methanol to yield the di-N-benzoylthiourethan of *trans*-1,2-cyclopentanediol, m.p. 161–162°; λ_{max}^{KBr} (μ) 3.07, 6.58 (NH), 5.90 (C=O), 7.60, 7.72 (C=S), 14.11 (monosubstituted phenyl); λ_{max} (mμ) 237 (ϵ 17,400), 273 (ϵ 21,800) in 95% ethanol and 0.1 *N* ethanolic hydrogen chloride, 236 (ϵ 28,400) and 313 (ϵ 5,550) in 0.1 *N* ethanolic potassium hydroxide.

Anal. Calcd. for $C_{21}H_{20}N_2O_4S_2$: C, 58.9; H, 4.70; N, 6.54; S, 15.0. Found: C, 58.6; H, 4.77; N, 6.02; S, 15.0.

The mother liquors from the crude diurethan, on partial evaporation, deposited a yellow oil (0.98 g.) which crystallized after trituration with water, m.p. 77–82°. After recrystallization from 5 ml. of benzene–hexane (80:20), 0.86 g., m.p. 81–82°, was obtained; a second recrystallization from 5 ml. of benzene yielded 0.64 g., m.p. 82.5–83.5°. The analytical sample had m.p. 83.0–83.5°; λ_{max}^{KBr} (μ) 3.07, 6.50 (NH), 7.61, 7.77 (C=S), 14.08 (monosubstituted phenyl); λ_{max} (mμ) 237 (ϵ 11,800) and 274 (ϵ 15,600) in ethanol and 0.1 *N* ethanolic hydrogen chloride, 238 (ϵ 19,400) and 309 (ϵ 4,500) in 0.1 *N* ethanolic potassium hydroxide.

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.9; H, 5.70; N, 5.28; S, 12.1. Found: C, 59.2; H, 6.00; N, 5.35; S, 11.8.

Tetrahydro-2-phenylimino-3aH-cyclopenta-1,3-oxathiolane (VIII) Picrate.—To 7.14 g. (60 mmoles) of thionyl chloride maintained at 0° was added 1.18 g. (5.0 mmoles) of the thiourethan VII and the solution was stored at 0° for 24 hours. The reaction mixture was added to a cold (0°) stirred suspension of 25 g. of sodium bicarbonate and 80 ml. of water. The resulting mixture was stirred for 2.25 hours while it warmed to room temperature. The aqueous mixture was extracted with six 30-ml. portions of ether and the combined extracts were washed with two 40-ml. portions of water, dried over magnesium sulfate, and filtered. To the filtrate was added a solution of 1.28 g. (5 mmoles) of 90% picric acid in 200 ml. of ether. The anil VIII picrate, 1.22 g. (54%), m.p. 117–122°, slowly crystallized on standing overnight at 20°. The picrate of VIII, prepared in an earlier run and purified, had m.p. 119–120° after two recrystallizations from Skellysolve B–benzene (1:1). Its infrared spectrum was identical with that of the picrate, m.p. 117–122°, described above and had λ_{max}^{KBr} (μ) 3.70 (NH^+), 6.15 ($C{=}NH^+$), 6.55, 7.50 (NO_2), 12.67 (trisubstituted phenyl), 13.42 (monosubstituted phenyl).

Anal. Calcd. for $C_{18}H_{16}N_4O_8S$: C, 48.2; H, 3.60. Found: C, 48.4; H, 3.79.

(15) Boiling and melting points are uncorrected. The latter were obtained with the Fisher–Johns apparatus.

(16) J. C. Ambelang and T. B. Johnson, THIS JOURNAL, **61**, 632 (1939).

When the reaction of VII and thionyl chloride was conducted with the same ratio of reagents but with the mixing of the reagents at −80° and storage at −20° for 4 hours, the yield of picrate was 13%. When the reaction was conducted as described in the detailed procedure above except that the thionyl chloride was removed *in vacuo* before treatment with sodium bicarbonate, the yield of picrate was 52%. When the reaction mixture was stored at 20–25° for 24 hours before hydrolysis, the yield of picrate was 44%. Changing the ratio of VII to thionyl chloride to 1:6 and using the detailed procedure described above gave a 42% yield of picrate; a ratio of 1:24 resulted in a 48% yield of picrate.

Tetrahydro-2-phenylimino-3aH-cyclopenta-1,3-oxathiolane (VIII).—A mixture of 2.3 g. (5.13 mmoles) of the anil VIII picrate, 5 ml. (83.6 mmoles) of 2-aminoethanol, 20 ml. of water and 30 ml. of ether was shaken in a separatory funnel. The ether phase was separated and the aqueous phase was extracted with four 17-ml. portions of ether. The total ether extracts were combined, washed with five 15-ml. portions of ethanolamine–water (1:5) and three 15-ml. portions of ethanolamine–water (1:2), yielding a colorless ether phase. The ether solution was dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo*, finally at 0.5 mm. and room temperature, to give 1.0 g. (89%) of crystalline anil VIII, m.p. 55–61°, whose infrared spectrum was essentially identical with that of authentic anil VIII. Previously a sample of anil had been recovered from the reaction of VII and thionyl chloride and had been crystallized from Skellysolve B to furnish an analytical sample, m.p. 65–67°; λ_{max}^{KBr} (μ) 6.12 (C=N), 13.01, 14.35 (monosubstituted phenyl).

Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.7; H, 5.98; N, 6.35. Found: C, 65.9; H, 6.16; N, 6.84, 6.50.

The anil VIII hydrochloride was prepared by mixing an ether solution of VIII with a saturated solution of hydrogen chloride in ether. The hydrochloride had m.p. 76–79° and in the infrared had λ_{max}^{KBr} (μ) 3.95–4.30 (NH), 6.17 ($C=\overset{+}{N}H$), 13.14, 14.43 (monosubstituted phenyl).

Tetrahydro-3aH-cyclopenta-1,3-oxathiolan-2-one (IX).—A mixture of 6.81 g. (31.1 mmoles) of the anil VIII, 50 ml. of glacial acetic acid and 50 ml. of water was stirred at 80° for 4 hours and then evaporated *in vacuo*. The liquid residue was dissolved in 30 ml. of methylene chloride and the solution was washed with four 20-ml. portions of 1 *N* hydrochloric acid and five 25-ml. portions of water. After being dried over magnesium sulfate, the methylene chloride solution was filtered and the filtrate evaporated *in vacuo*. The residue was distilled through a short Vigreux column to give (1) 0.17 g., b.p. 62–65° (1 mm.), $n^{20}D$ 1.5255, and (2) 2.75 g., b.p. 65–66° (1 mm.), $n^{20}D$ 1.5264, for a total yield of 65%. A residue of 0.77 g. remained in the distillation flask. In the infrared, fraction 2 had λ_{max}^{film} (μ) 5.76 (C=O), 9.06 and 9.27 (C–O–C), and no absorption near 3.0 μ.

Anal. Calcd. for $C_5H_8O_2S$: C, 50.0; H, 5.59; S, 22.2. Found (fraction 2): C, 49.9; H, 5.70; S, 22.4.

An attempt was made to prepare IX by the sodium methoxide transesterification of diethyl carbonate with *cis*-2-mercaptocyclopentanol (X) (see below). A product (in about 50% yield) which distilled at 68–73° (0.5 mm.) and whose refractive index was $n^{20}D$ 1.5150 was collected. Its infrared spectrum showed it to be mainly IX but it was contaminated with an impurity such that the carbon and hydrogen analyses were high and the sulfur analysis low as compared with the theoretical values for IX.

***cis*-2-Mercaptocyclopentanol (X). (A) From Thiolcarbonate IX.**—To 0.88 g. (6.10 mmoles) of cold (0°) tetrahydro-3aH-cyclopenta-1,3-oxathiolan-2-one (IX) was added a cold solution of 0.36 g. (6.66 mmoles) of sodium methoxide in 6 ml. of reagent methanol. The mixture was stored at 0° for 77 hours and then evaporated *in vacuo*. To the residue was added a solution of 0.45 g. of glacial acetic acid in 3 ml. of water and the aqueous solution was extracted with 30 ml. of methylene chloride. The methylene chloride extract was washed with seven 10-ml. portions of water and dried over magnesium sulfate. After filtration and evaporation of the filtrate *in vacuo*, there remained 0.41 g. (57%), $n^{20}D$ 1.5329, of residue whose spectrum agreed well with that of authentic mercaptoalcohol X. The residue was characterized by preparation of the 2,4-dinitrophenyl sulfide derivative (see below) which had m.p. 112.7–113.3° and did not depress the melting point of the derivative of X prepared by the alternative procedure (see section B).

When 10.0 g. of anil VIII was converted to X without purification of the intermediate IX, the following fractions were collected: (1) 1.16 g., b.p. 70–71° (8 mm.), $n^{20}D$ 1.5231; (2) 1.48 g., b.p. 71° (8 mm.); and (3) 0.73 g., collected at 1 mm., $n^{20}D$ 1.5268. A flask residue of 1.19 g. remained. The yield based on fractions 1 to 3 was 63% and all fractions had infrared spectra in agreement with the mercaptoalcohol X prepared by an alternative synthesis (section B).

The anil VIII (3.0 g., 13.7 mmoles) was heated at reflux with a solution of 0.82 g. (15.2 mmoles) of sodium methoxide in 30 ml. of reagent methanol for 7 hours. The reaction mixture was evaporated *in vacuo*, the residue treated with a solution of 0.91 g. of glacial acetic acid in 25 ml. of water and the resulting solid after thorough washing and drying weighed 2.95 g. and had an infrared spectrum identical with that of the starting anil VIII.

(B) **From *cis*-2-(Acetylthio)-cyclopentyl Acetate (XIII).**—A solution of 35.2 g. (0.174 mole) of *cis*-2-(acetylthio)-cyclopentyl acetate (XIII) ($n^{20}D$ 1.4910–1.4915), 1.23 g. (6.47 mmoles) of *p*-toluenesulfonic acid (monohydrate) and 185 ml. of absolute methanol was heated under reflux for 6 hours. Hydrogen sulfide was liberated during the reaction as detected with lead acetate paper. After the solution had stood at room temperature for 15 hours, methyl acetate and a small portion of the methanol (b.p. 53–64°) were removed by slow distillation through a 1 × 50 cm. column packed with glass helices. The solution remaining was neutralized with an excess (2 g.) of sodium bicarbonate and evaporated at 30° and water aspirator pressure. Methylene chloride (50 ml.) was added to the residue and the mixture was filtered. The residue was washed with methylene chloride (50 ml.) and the combined methylene chloride solutions were evaporated at 30° and water aspirator pressure. The liquid residue was distilled at reduced pressure and the following fractions were collected:

Fraction	Weight, g.	$n^{20}D$	B.p., °C. (7 mm.)
1	0.50	1.5223	72.5
2	4.74	1.5228	72.5
3	4.85	1.5227	72.5
4	1.35	1.5226	72.5
5	1.47	1.5224	Material distilled at 3 mm.
Flask residue	4.12		

Fractions 1 to 5 (12.91 g.) gave a yield of 62.8%. In the infrared, fractions 1 to 5 had λ_{max}^{film} (μ) 2.91 (OH), 3.90 (SH), 9.20, 9.70 and 9.90 (C–O).

Anal. Calcd. for $C_5H_{10}OS$: C, 50.8; H, 8.53; S, 27.1. Found (fraction 5): C, 50.7; H, 8.64; S, 25.8, 26.1.

The diacetate XIII (10.0 g., 0.049 mole) in 25 ml. of reagent methanol was heated with 70 ml. of aqueous 2 *N* sodium hydroxide under reflux for 2 hours in a bath at 80–90°. The methanol was distilled; the aqueous residue was adjusted to *p*H 5 with 1 *N* hydrochloric acid and extracted with four 20-ml. portions of methylene chloride. The combined extracts were washed with water (25 ml.), dried over magnesium sulfate and filtered. The filtrate was distilled through a short Vigreux column, first at atmospheric pressure to remove methylene chloride and finally at reduced pressure to yield: (1) 1.73 g., b.p. 54° (3 mm.), $n^{20}D$ 1.5220; (2) 0.93 g., b.p. 54° (3 mm.), $n^{20}D$ 1.5228; (3) 0.17 g., collected at 1 mm., $n^{20}D$ 1.5225; (4) 0.47 g., collected at 1 mm., $n^{20}D$ 1.5314. A flask residue of 1.39 g. remained. The yield based on fractions 1 to 4 was 57%. The infrared spectra of the fractions were identical with that of the material from the acid-catalyzed transesterification of XIII.

When 6.31 g. (0.031 mole) of *cis*-2-(acetylthio)-cyclopentyl acetate (XIII) was allowed to react with 3.37 g. (0.062 mole) of sodium methoxide in 25 ml. of methanol for 22 hours at room temperature, 1.27 g. (34.5%) of X was collected at 76° (10 mm.) after a work-up similar to that described above.

***cis*-2-(2,4-Dinitrophenylthio)-cyclopentanol.**—A mixture of 0.41 g. (17.1 mmoles) of sodium hydride, 2.0 g. (16.9 mmoles) of *cis*-2-mercaptocyclopentanol (X) and 15 ml. of dry toluene was stirred under nitrogen at 90° until hydrogen was no longer evolved (2 hours). The mixture was cooled to 0° and a solution of 3.43 g. (16.9 mmoles) of 1-chloro-

2,4-dinitrobenzene in 10 ml. of dry toluene was added dropwise with stirring. The mixture was heated, with stirring, at 90° for 3 hours and, after 18 hours at room temperature, it was filtered and the residue washed with 5 ml. of toluene. The combined filtrate washings were washed with 25 ml. of water, dried over magnesium sulfate and filtered. The filtrate was evaporated to dryness *in vacuo;* the residue (4.67 g.) crystallized slowly. After one recrystallization from 95% ethanol the solid (3.08 g., 64%) had m.p. 37–95°. A second recrystallization from carbon tetrachloride gave 1.64 g. (34%), m.p. 95–97°, and a third recrystallization from carbon tetrachloride gave 1.35 g. (28%), m.p. 112–113°. The mixed melting point with *trans*-2-(2,4-dinitrophenylthio)-cyclopentanol (*cf.* below) was 96–109°. In the infrared it had λ_{max}^{KBr} (μ) 2.87–2.95 (OH), 6.62, 7.48 (NO_2), 9.24 (C–O), 12.01 (trisubstituted phenyl).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$: C, 46.5; H, 4.25. Found: C, 46.4; H, 4.20.

The *trans*-2-(2,4-dinitrophenylthio)-cyclopentanol was prepared, using the same quantities and procedure as described above for the *cis*-compound; 5.58 g. of product was isolated. This was recrystallized from carbon tetrachloride, yielding 2.62 g. (54%), m.p. 116–117°. Further recrystallization did not raise the melting point. In the infrared it had λ_{max}^{KBr} (μ) 2.83–2.95 (OH), 6.65, 7.46 (NO_2), 9.15 (C–O), 12.01 (trisubstituted phenyl).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$: C, 46.5; H, 4.25. Found: C, 46.4; H, 4.34.

Bis-phenylurethan of *cis*-2-Mercaptocyclopentanol (X).—A mixture of 1.18 g. (10 mmoles) of *cis*-2-mercaptocyclopentanol (X), 3.57 g. (30 mmoles) of phenyl isocyanate and 15 ml. of reagent benzene was heated under reflux, with exclusion of moisture, for 20 hours. The precipitate (2.45 g.), m.p. 171–176°, was filtered and was recrystallized once from chloroform and once from methanol to give a product of analytical purity, m.p. 170–171°. In the infrared it had λ_{max}^{KBr} (μ) 3.02, 6.46 (NH), 5.86 (O-urethan C=O), 6.05 (S-urethan C=O), 7.59 (C–N), 8.06, 8.15 (C–O–C), 13.19 and 14.40 (monosubstituted phenyl).

Anal. Calcd. for $C_{19}H_{20}N_2O_3S$: C, 64.0; H, 5.66; S, 8.99. Found: C, 64.1; H, 5.74; S, 8.94, 8.85.

Another crop of the bis-urethan, 0.45 g., was recovered from the filtrate to give a total yield of 81%.

The bis-phenylurethan of *trans*-2-mercaptocyclopentanol[9] was prepared using 2.2 moles of phenyl isocyanate per mole of mercaptoalcohol. The product had m.p. 173–174° (Harding and Owen[17] reported the m.p. as 162°). The mixed melting range of the *cis*- and *trans*-bis-urethan was 149–161°.

Anal. Calcd. for $C_{19}H_{20}N_2O_3S$: C, 64.0; H, 5.66. Found: C, 64.2; H, 5.81.

The infrared spectrum agreed well with the *cis*-bis-urethan spectrum, but as major differences it lacked a band at 9.05 μ present in the *cis* compound, had a more intense S-urethan C=O at 6.00 μ, and had a monosubstituted phenyl band at 13.26 μ compared with a band at 13.19 μ for the *cis* compound.

When equimolar amounts of *cis*-2-mercaptocyclopentanol (X) and phenyl isocyanate were used, the major product was the S-phenylurethan as shown by the strong S-urethan carbonyl at 6.08 μ and the weak O-urethan carbonyl at 5.90 μ in the infrared spectrum.

Disulfide of *cis*-2-(*n*-Butylcarbamoyloxy)-cyclopentanethiol (XI).—A mixture of 0.99 g. (6.87 mmoles) of thiolcarbonate IX (impure, $n^{20}D$ 1.5032–1.5150), 1.0 g. (13.7 mmoles) of *n*-butylamine and 12 ml. of methanol was refluxed for 6 hours and the mixture was evaporated *in vacuo*. The residue was dissolved in 15 ml. of methylene chloride and the solution was washed with four 7-ml. portions of 1 *N* hydrochloric acid and four 10-ml. portions of water, then dried over magnesium sulfate. After filtration, the solution was evaporated *in vacuo* and the residue was recrystallized from Skellysolve B; yield 0.10 g., m.p. 165–166°. A second recrystallization from 100 ml. of Skellysolve B gave 0.07 g., m.p. 166–167°; λ_{max}^{KBr} (μ) 2.95, 6.50 (NH), 5.88 (urethan C=O), 7.85 (C–O–C). There was no SH absorption near 3.9 μ.

Anal. Calcd. for $C_{20}H_{36}N_2O_4S_2$: C, 55.5; H, 8.39; N, 6.48; S, 14.8. Found: C, 55.9; H, 8.54; N, 7.13; S, 14.7, 15.0.

(17) J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1528 (1954).

1-Cyclopentenyl Acetate.—To 72.0 g. (0.856 mole) of cyclopentanone, which contained 1.71 g. (0.899 mmole) of partially dissolved *p*-toluenesulfonic acid monohydrate, was added 120.0 g. (1.199 moles) of isopropenyl acetate. The solution was heated for 6 hours at a bath temperature of 100–110°, during which time 37.8 g. (76% of theory) of acetone was collected. After addition of 75 ml. of methylene chloride, the brown reaction mixture was washed once with a solution of 6 g. of sodium bicarbonate in 100 ml. of distilled water and a second time with 100 ml. of cold water. The methylene chloride solution was dried over anhydrous magnesium sulfate and filtered. The solvent was removed from the filtrate by distillation at atmospheric pressure and then the following fractions were collected at reduced pressure using a short Vigreux column

Fraction	Weight, g.	$n^{20}D$	B.p., °C. (69 mm.)
1	7.13	1.4417	81–83
2	9.29	1.4448	83–85
3	55.86	1.4500	85–87.5
4	0.92	1.4510	87.5
5	13.39	1.4493	84–87
6	2.40	1.4505	Flashed over at 2 mm.

The yield, based on fractions 2 to 6, was 76%. Fraction 5 was submitted as the analytical sample. In the infrared it had λ_{max}^{film} (μ) 3.25, 10.41 (CH from —C=CH), 5.68 (vinyl ester C=O), 5.96 (C=C), 7.25 (CH_3), 8.15–8.40 (C–O–C).

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 7.99. Found: C, 65.3, 65.5; H, 8.03, 8.01.

***cis*-2-(Acetylthio)-cyclopentyl Acetate (XIII).**—A solution of 9.91 g. (78.6 mmoles) of 1-cyclopentenyl acetate (XII) (previously exposed to sunlight for 3 days) and 11.26 g. (0.148 mole) of redistilled thiolacetic acid was heated on the steam-bath for 3 hours and then allowed to stand at room temperature for 15 hours. The reaction mixture was distilled at reduced pressure and the following fractions were collected after removal of the excess thiolacetic acid.

Fraction	Weight, g.	$n^{20}D$	B.p., °C. (0.5 mm.)
1	1.85	1.4930	80–85
2	2.14	1.4917	85–86
3	3.27	1.4911	86
4	2.67	1.4911	86
5	2.16	1.4911	86

The yield of the light yellow distillate was 76%. Fraction 4 was used as the analytical sample. In the infrared it had λ_{max}^{film} (μ) 5.75 (O-acetate C=O), 5.93 (S-acetate C=O), 7.29 (O-acetate CH_3), 7.38 (S-acetate CH_3), 8.15 and 9.80 (ester C–O–C).

Anal. Calcd. for $C_9H_{14}O_3S$: C, 53.4; H, 6.98. Found: C, 53.4; H, 7.12.

In another experiment, 1-cyclopentenyl acetate (XII), which had not been previously exposed to sunlight, was heated with thiolacetic acid for 3 hours and then allowed to stand at room temperature for 43 hours. The total yield of product XIII, $n^{22}D$ 1.4911–1.4925, collected by distillation was 91%.

Reaction of Thiourethan VII with Tosyl Chloride in Pyridine.—To a cooled and stirred solution of 6.07 g. (25.6 mmoles) of VII in 25 ml. of dried pyridine was added slowly 9.77 g. (51.2 mmoles) of *p*-toluenesulfonyl chloride. Precipitation of pyridine salts began almost immediately. The mixture was stirred at room temperature for 28 hours protected from moisture, then water (10 ml.) was added with cooling. The resulting mixture was poured into 40 ml. of water and extracted with three 35-ml. portions of chloroform. The aqueous layer analyzed for 43.2 meq. of chloride ion and 6.81 meq. of acid.

The chloroform extracts were evaporated *in vacuo;* the residue was dissolved in 25 ml. of benzene, washed with four 10-ml. portions of water and evaporated *in vacuo*, finally at 33° and 0.2 mm., to leave 7.79 g. of crude product as a viscous, brown liquid. In the infrared it had λ_{max}^{film} (μ) 4.68, 4.74 (N=C=N), 5.90, 6.08, 6.69 and 7.15 (unassigned). By chromatography on Florisil of a portion of the residue there was isolated a small amount of a yellow oil which appeared to be relatively pure diphenylcarbodiimide.

It was hydrolyzed to carbanilide, m.p. and mixed 250–251°, with dilute aqueous hydrochloric acid.

A portion of the crude tosylation product was evaporatively distilled at a bath temperature of 120–130° and 0.22 mm. pressure. The distillate contained diphenylcarbodiimide and probably the thionourethan XIV, as shown by infrared absorption at 4.70 μ (N=C=N) and 7.16 μ (probably C=S), but no pure materials could be isolated.

From another reaction of thiourethan VII with tosyl chloride in pyridine the crude product was dissolved in ether and allowed to react with an ethereal picric acid solution. A small amount of picrate (about 5% yield) was isolated, m.p. 110–150°. Its infrared spectrum showed that it was largely anil VIII picrate.

Hydrolysis of the Thiourethan VII–Tosyl Chloride Reaction Product.—The crude product was obtained as above from 10.0 g. (42.3 mmoles) of VII, 12.60 g. (66.1 mmoles) of *p*-toluenesulfonyl chloride and 20 ml. of pyridine. It weighed 12.87 g. and showed no OH absorption at 2.98 μ but contained diphenylcarbodiimide as shown by absorption at 4.68 μ.

A stirred mixture of the crude residue (12.73 g.), 24.0 g. (0.60 mole) of sodium hydroxide and 50 ml. of water was refluxed under nitrogen for 24 hours. The dark reaction mixture gave a positive nitroprusside test for mercaptans. It was diluted with 200 ml. of water and the solution extracted with six 25-ml. portions of methylene chloride. The combined methylene chloride solutions were extracted with five 30-ml. portions of 2 *N* aqueous hydrochloric acid and the acid extracts were chilled and made strongly basic with 6 *N* sodium hydroxide. The resulting solution was extracted with four 25-ml. portions of methylene chloride and the methylene chloride extracts were dried over magnesium sulfate. After filtration, the extracts were evaporated *in vacuo*, leaving 4.48 g. of brown liquid. This was steam distilled and 100 ml. of distillate was collected. The distillate was extracted to obtain 2.33 g. (59%) of crude aniline which gave 1.71 g. of aniline after distillation. The nonsteam-distillable liquid residue, 2.17 g. (31%), was distilled and gave 1.49 g. of *cis*-2-anilinocyclopentanol (XVI), b.p. 88–92° (1–5 μ), $n^{20}D$ 1.5773; λ_{max}^{film} (μ) 2.95 (OH, NH), 6.65 (NH), 7.63 (C–N), 13.35, 14.45 (monosubstituted phenyl).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.5; H, 8.53. Found: C, 74.1; H, 8.44.

The picrate of XVI was prepared by mixing a solution of 0.20 g. of XVI in 10 ml. of ether with a solution of 0.27 g. of picric acid in 30 ml. of ether. The crude product, 0.31 g., m.p. 147–150°, was recrystallized twice from benzene, m.p. 144–147°; λ_{max}^{KBr} (μ) 3.00 (OH, NH), 6.40, 7.51 (NO_2), 6.69 (NH), 12.66 (trisubstituted phenyl), 13.42, 14.42 (monosubstituted phenyl).

Anal. Calcd. for $C_{17}H_{18}N_4O_8$: C, 50.2; H, 4.46. Found: C, 50.3, 50.5; H, 4.78, 4.66.

When the aqueous portion of the crude hydrolysate (after the methylene chloride extraction) was acidified with 6 *N* hydrochloric acid, hydrogen sulfide was evolved. The acidified solution was extracted with methylene chloride and the extracts were combined with the methylene chloride solution which had been extracted with 2 *N* hydrochloric acid in the separation of XVI and aniline (see above). These combined methylene chloride extracts were evaporated *in vacuo* to leave 3.66 g. of a dark, viscous residue whose infrared spectrum had λ_{max}^{film} (μ) 3.00 (NH, OH), 3.90 (SH), 6.66 (NH), 7.65 (C–N), 13.35, 14.45 (monosubstituted phenyl). No pure materials could be isolated from this mixture.

Hexahydro-3-phenyl-2H-cyclopenta[d]oxazol-2-one (XV).—A solution of 2.0 g. (11.3 mmoles) of crude *cis*-2-anilinocyclopentanol (XVI), 10 ml. of diethyl carbonate and 5 ml. of benzene was distilled until about 2 ml. of benzene was collected. Sodium methoxide (0.05 g.) was added and the reaction mixture was heated at a bath temperature of 130° for 11.5 hours. About 1.0 g. of ethanol was collected as a distillate during this period. Excess diethyl carbonate was removed by evaporation *in vacuo* and the residue was dissolved in 20 ml. of methylene chloride. The solution was washed with three 10-ml. portions of 1 *N* hydrochloric acid and three 15-ml. portions of water and was dried over magnesium sulfate. After filtration, the solution was evaporated to dryness *in vacuo*, leaving 1.88 g. (82%) of solid residue. The material was purified by dissolving 1.0 g. in 60 ml. of hot Skellysolve B and decanting the solution from a small amount of insoluble tar. The crystals which formed on cooling were recrystallized again from Skellysolve B with the aid of Norit, yielding 0.54 g. (44%), m.p. 57–58°. A final recrystallization from Skellysolve B raised the melting point to 58–59°; λ_{max}^{KBr} (μ) 5.77 (urethan C=O), 7.16 (C–N), 13.10, 14.42 (monosubstituted phenyl).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.45. Found: C, 70.9; H, 6.50.

Acknowledgments.—The authors are indebted to Dr. Peter Lim for infrared interpretations and to Mr. O. P. Crews, Jr., and his group for the large-scale preparation of intermediates.

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[CONTRIBUTION FROM THE PHYSIOLOGICAL CHEMISTRY BRANCH, DIRECTORATE OF MEDICAL RESEARCH, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

Stability of Pyridine-2-aldoxime Methiodide. I. Mechanism of Breakdown in Aqueous Alkaline Solution

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RECEIVED JULY 22, 1958

The mechanism of the deterioration of pyridine-2-aldoxime methiodide (2-PAM) in aqueous solutions of *p*H values ranging from 7 to 13 have been studied. At the indicated *p*H values, 2-PAM breaks down to N-methyl-α-pyridone. The following mechanism is suggested: (1) 2-PAM is dehydrated to 2-cyanopyridine methiodide, (2) 2-cyanopyridine methiodide is converted to 2-hydroxypyridine methiodide, (3) the latter rearranges to N-methyl-α-pyridone.

Pyridine-2-aldoxime methiodide (I), monoisonitrosoacetone and diacetylmonoxime have been reported to be effective in overcoming the toxic effects occurring in animals poisoned with inhibitors of the enzyme cholinesterase.[1–7] Of the three oximes, pyridine-2-aldoxime methiodide is the fastest known reactivator, *in vitro*, of cholinesterase inhibited by isopropyl methylphosphofluoridate.[2] An effective therapy for poisoning by anticholinesterase agents may be obtained by administering the oxime I in conjunction with the alkaloid atropine.[1,4,5,7] A knowledge of the behavior of dilute solutions of I is therefore desirable. This

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