Potential Anticancer Agents.[1] LIX. The Thiourethan Neighboring Group. III. Synthesis of *cis*-2-Mercaptocyclopentanol *via* the Benzoylthiourethan Neighboring Group

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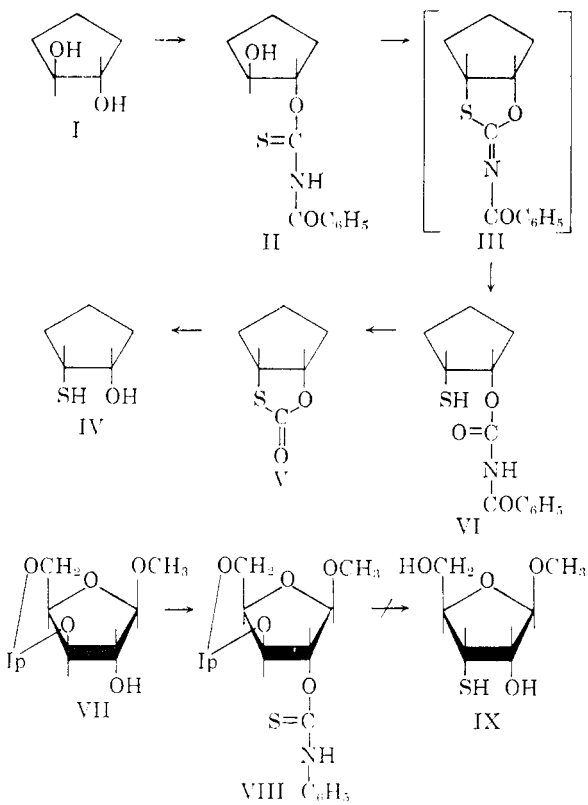
A previous paper in this series[2] reported the synthesis of *cis*-2-mercaptocyclopentanol (IV) from *trans*-1,2-cyclopentanediol (I) using the thiourethan neighboring group. The synthesis of IV was carried out as a model for the preparation of the glycoside (IX) of 3-mercaptoribose and, ultimately, for the preparation of nucleosides containing the 3-mercaptoribose moiety. The previously cited paper[2] also recorded the preparation of *trans*-2-(benzoylthiocarbamoyloxy)cyclopentanol (II); this manuscript reports an alternative synthesis of IV from II.

The reaction of the benzoylthiourethan (II) with thionyl chloride afforded the mercaptan (VI) as the directly isolated product in 30% yield. It is interesting that the intermediate acylated imine (III) hydrolyzed during the reaction workup, whereas in the analogous phenylthiourethan case,[2] the corresponding anil was stable to the same reaction work-up conditions and was the directly isolated reaction product. Attempts to remove the benzoylurethan group of VI by methanolysis or with lithium aluminum hydride were unsuccessful. The treatment of VI with 6*N* hydrochloric acid, however, gave a 70% yield of the thiolcarbonate (V)[2] and the conversion of V to IV with methanolic sodium methoxide utilized the procedure previously developed for the preparation of IV.[2] The over-all yield of IV from II was 13%.

The applications of either the phenylthiourethan or the benzoylthiourethan neighboring group to the synthesis of the glycoside (IX) were unsuccessful. The xyloside (VII)[3] was properly blocked for the attempted synthesis of IX and its reaction with phenyl isocyanate afforded the crystalline phenylthiourethan (VIII). All attempts to remove the isopropylidene blocking group, either with methanolic hydrogen chloride or with aqueous acetic acid,



however, led to the generation of hydrogen sulfide and the production of an unpalatable mixture of products. A number of attempts to prepare the benzoylthiourethan of VII gave, at best, intractable mixtures of starting material with possibly some product.

EXPERIMENTAL[4]

cis-2-(Benzoylcarbamoyloxy)cyclopentanethiol (VI). To 20 ml. of thionyl chloride which had been cooled to 0° was added 4 g. of *trans*-2-(benzoylthiocarbamoyloxy)cyclopentanol (II)[2] with stirring. The yellow solution was kept at 3–5° for 2 days, then poured into a stirred suspension of 50 g. of sodium bicarbonate in 400 ml. of water. After the addition was complete, the mixture was stirred for 1 hr., then extracted with three 100-ml. portions of dichloromethane The combined dichloromethane extracts were washed with 50 ml. of 5% aqueous sodium bicarbonate and 50 ml. of water, then dried over magnesium sulfate and evaporated to dryness *in vacuo*. The residue weighed 3.2 g. and gave a positive nitroprusside test for a thiol.

The residue was dissolved in 10 ml. of methanol and 75 ml. of water was added. The solution was heated at reflux for 10 min., then decanted from an insoluble yellow oil. The supernatant liquid was cooled to give 0.28 g. of the thiol (VI). The insoluble oil was retreated with methanol-water two more times to give an additional 0.90 g. for a total yield of 1.18 g. (30%) of the thiol (VI), m.p. 131–132°; $\lambda_{max(\mu)}^{Nujol}$ 3.10 (NH); 3.92 (SH); 5.72 (C=O).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.8; H, 5.70; N, 5.28; S, 12.1. Found: C, 58.9; H, 5.73; N, 5.10; S, 12.1.

cis-2-Mercaptocyclopentanol (IV). A solution of 1.33 g. of *cis*-2-(benzoylcarbamoyloxy)cyclopentanethiol (VI) in 14 ml. of 6*N* hydrochloric acid was heated at reflux for 2 hr. At the end of the reflux period the reaction was extracted

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(2) L. Goodman, A. Benitez, C. D. Anderson, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 6582 (1958).

(3) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Am. Chem. Soc.*, 77, 7 (1955).

(4) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Boiling points are also uncorrected.

with two 10-ml. portions of dichloromethane. The combined dichloromethane layers were washed with 20 ml. of 5% aqueous sodium bicarbonate and 10 ml. of water, then dried over magnesium sulfate, and evaporated to dryness *in vacuo* to give 0.5 g. of a sirup which had an infrared spectrum very similar to that of an authentic sample of tetrahydro-3aH-cyclopenta-1,3-oxathiolan-2-one (V).[2]

Treatment of crude V with methanolic sodium methoxide in the manner described previously[2] gave 0.25 g. (43% based on VI) of *cis*-2-mercaptocyclopentanol (IV), b.p. 75–85° (6–7 mm.), that had an infrared spectrum in complete agreement with that of an authentic sample.[2]

The distilled IV gave an 87% yield of a crystalline bisurethan, m.p 173–174°; there was no melting point depression when mixed with the authentic bisurethan of III.[2]

Methyl 2-O-(phenylthiocarbamoyl)-3,5-O-isopropylidene-β-D-xylofuranoside (VIII).[5] A solution of 2.7 g. of methyl 3,5-*O*-isopropylidene-β-D-xylofuranoside (VII)[3] in 27 ml. of toluene and 13.2 ml. of 1*N* methanolic sodium methoxide was evaporated to dryness *in vacuo*. The residue was dissolved in 27 ml. of hot toluene and re-evaporated to dryness *in vacuo*. The residual sodium salt was dissolved in 27 ml. of toluene at 80° and 1.73 ml. of phenyl isothiocyanate was added. Rapid precipitation of a gelatinous sodium salt took place before all the thiocyanate could be added. The thick gel was thinned by the addition of 27 ml. more of toluene and the mixture was heated in a bath at 85° for 15 min. while protected from moisture. After the addition of 1.7 ml. of acetic acid and 50 ml. of water, the mixture was shaken until the solids dissolved. The separated toluene layer was washed with water, then evaporated to dryness *in vacuo* to give 3.7 g. of an oil which contained unreacted phenyl isothiocyanate. The oil darkened on standing but crystallized after 8 days. The waxy solid was dissolved in 25 ml. of warm benzene, then diluted with 75 ml. of hexane. The solution was clarified with Norit, then diluted with an additional 25 ml. of hexane

The solution was stored at 3° overnight to afford, after filtering and washing with 15% benzene in hexane, 2.0 g. (45%) of product, m.p. 92–96°.

A second recrystallization gave the analytical sample, m.p. 94–96° (resolidifies and remelts at 101–102°); $\lambda_{max(\mu)}^{Nujol}$ 6.19 (phenyl), 6.42 (NH of thiourethan), 6.65 (phenyl + C = S).

Anal. Calcd. for $C_{16}H_{21}NO_6S$: C, 56.7; H, 6.25; N, 4.13; S, 9.43. Found: C, 56.8; H, 6.08; N, 4.07; S, 9.06.

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(5) Prepared originally at Southern Research Institute by one of the authors (B. R. B.).

Synthesis of 2-Indenylacetic Acid

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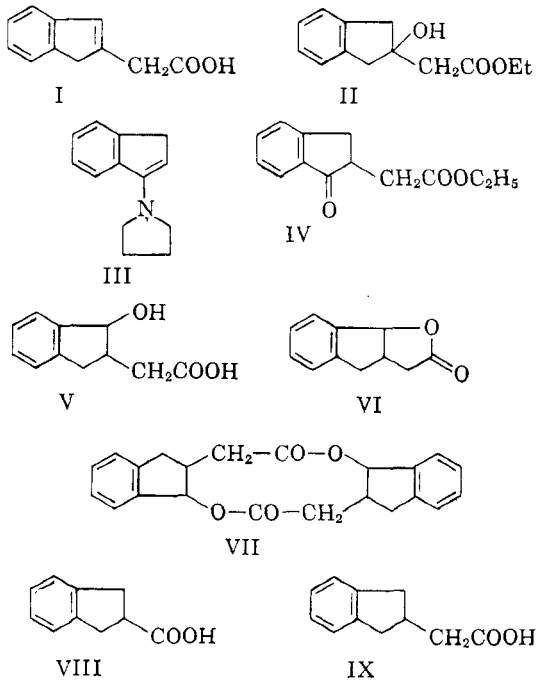
For some synthetic experiments, 2-indenylacetic acid (I) was required. Its formation as a by-product in the treatment of 1-hydroxy-2-indenylacetic acid with hydrobromic acid, has been claimed[1]; however, the reported melting point (150–160°) is not that of authentic (I). Very recently,[2] I has been obtained in 23% over-all yield, among other products in the Reformatsky reaction between 2-hydrindone and ethyl bromoacetate; the hydroxy ester (II) formed was dehydrated with formic acid and the unsaturated ester so obtained hydrolyzed to I. We report here on some alternative possibilities for the preparation of I.

When 2-hydrindone was heated with malonic acid, pyridine, and piperidine, only self-condensation took place.[3]

Condensation of the not very stable enamine (III) of 1-hydrindone with ethyl bromoacetate[4] resulted in an ester of the expected composition (IV), but only in 14% yield (calculated on 1-hydrindone).



A promising starting material appeared to be 1-hydroxy-2-hydrindylacetic acid (V) which is obtained[1] from ethyl acetoacetate and indene bromohydrin. However, V gave with hydrobromic acid or oxalic acid or under the conditions of reduction with hydriodic acid in glacial acetic acid, only the lactone (VI) which had been described before by Peacock and Menon[1] and was also formed when the methyl ester of V was treated with thionyl chloride or phosphorus oxychloride in pyridine. The lactone (VI) remained unchanged when heated with 85%

(1) D. H. Peacock and B. K. Menon, *J. Chem. Soc.*, 1296 (1934).

(2) H. Ahmed and N. Campbell, *J. Chem. Soc.*, 4115 (1960).

(3) Ch. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **115**, 143 (1919).

(4) According to the general method of G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).