glycyl-β-2-thienyl-L-alanine; m.p. 245-248°; specific rotation $[\alpha]^{25}_{D}$ +40.0° (20 mg. in 2 ml. of water).

Anal. Calc'd for $C_9H_{12}N_2O_3S$: N, 12.27. Found: N, 12.05.

Microbiological assay. The procedure was identical with that previously reported[3] for *E. coli* 9723. Under these conditions glycyl-β-2-thienyl-L-alanine completely inhibited growth at a level of one microgram in 5 ml. of medium; the D isomer showed no toxicity up to 100 micrograms per 5 ml.

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The Rearrangement of 2,3,5,6-Tetraphenylindenone Oxide

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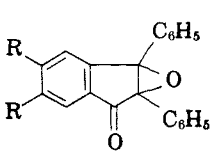
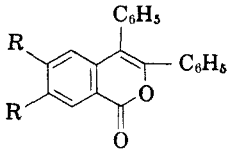
The acid-catalyzed isomerization of substituted indenone oxide systems (I) has been studied by several groups of workers.[1-4] 2,3-Diphenylindenone oxide (Ia) was reported[1-4] to yield the lactone IIa; however the tetraphenyl compound Ib was reported[3] to yield the red cyclobutanone III, m.p. 219–220°, which could be converted to the colorless lactone IIb, m.p. 230°, by treatment with a variety of reagents. A previous attempt to isolate a cyclobutanone derivative, analogous to III, from the oxide Ia was unsuccessful.[4] As part of a study[5] of isomerizations of α,β-epoxycycloalkanones which result in ring contraction we were led to reinvestigate the behavior of the aforementioned indenone oxides.

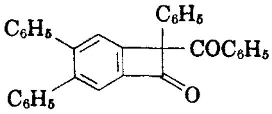
Reaction of the diphenylindenone oxide Ia with a mixture of acetic and sulfuric acids, as previously described,[1-4] produced the lactone IIa. The composition and spectra (Table I) of our product are consistent with the structure previously proposed. Saponification of IIa with ethanolic potassium hydroxide produced the keto acid IVa[1,2] which was reconverted to IIa by treatment with a boiling solution of *p*-toluenesulfonic acid in benzene. The same isomerization product IIa was formed in yields ranging from 60–81% when the oxide Ia was treated with boron trifluoride etherate in either benzene or ether with various reaction times (10–30 minutes). Thus, the isomerization of the oxide Ia in either hydroxylic or non-hydroxylic solvents appears to produce the lactone IIa rather than a cyclobutanone derivative.



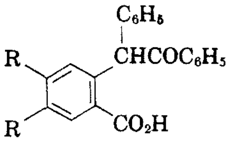
Ia, R=H
b, R=C6H5



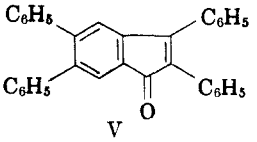
IIa, R=H
b, R=C6H5



III



IVa, R=H
b, R=C6H5



V

The tetraphenylindenone oxide Ib was prepared by the epoxidation of a solution of the unsaturated ketone V in acetone with alkaline hydrogen peroxide. The unsaturated ketone V was obtained by the thermal rearrangement of 2-bromo-3,3,5,6-tetraphenylindanone as described earlier;[6] in our hands this procedure was definitely superior to an alternate preparative method for V which involved the rearrangement and dehydrogenation of 3,4,5,6-tetraphenylindanone in the presence of sulfur.[7] Recrystallization of either of the products from ethanol afforded two red, crystalline products, m.p. 163–165° and 177–178.5°, rather than the single product, m.p. 166°, previously reported.[7] Both of the products had the composition expected of the ketone V and the infrared and ultraviolet spectra (Table I) of the two samples were identical. Treatment of each of the samples with alkaline hydrogen peroxide yielded the same oxide Ib. We therefore concluded that the two samples represent different crystalline modifications of V.

Samples of the oxide Ib were treated with boron trifluoride in ether, with boron trifluoride etherate in benzene, with a mixture of acetic and sulfuric acids, and with a solution of hydrogen bromide in acetic acid. The last two procedures were reported[3] to convert the oxide Ib to the diketone III. The infrared spectra of the crude, red or orange crystalline products, all of which melted within the range 211–225°, isolated in each case were all essentially identical. Repeated recrystallization of the products from a benzene–hexane or a benzene–ethanol

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mixture afforded light orange prisms, m.p. 226.5–229°. The infrared spectra of purified material established that the structure of the crude products was not altered by this purification. The infrared spectrum of this product (Table I) is consistent with the lactone structure IIb but not with the diketone structure III previously proposed. The product was saponified to the keto acid IVb and subsequently converted to the lactone IIb by the procedure employed with the lactone IIa. This procedure was previously reported[3] to convert the diketone III to the lactone IIb.

TABLE I

PROPERTIES OF THE INDENONES AND THEIR DERIVATIVES

Compound	M.p., °C.	Infrared Absorption	Ultraviolet Maxima
Ia	140–141°(dec.)[a]	1725 cm.$^{-1}$ (C=O)[b]	220 mμ (ε 26,100) 258 mμ (ε 8,200)
Ib	195–196°(dec.)[c]	1715 cm.$^{-1}$ (C=O)[d]	256 mμ (ε 31,600)
IIa	171–172°[e]	1740 cm.$^{-1}$[b] (C=O) [1705 cm.$^{-1}$[d]] (C=O) 1620 cm.$^{-1}$ (C=C)[b,d]	229 mμ (ε 28,700) 296 mμ (ε 17,000)
IIb	226.5–229°[f]	1730 cm.$^{-1}$ (C=O)[g] 1615 cm. (C=C)	272 mμ (ε 32,000) [inflection at 286 mμ (ε 30,600)]
IVa	149.5–151°(dec.)[h]	2900 cm.$^{-1}$(broad) (associated O—H)[d] 1710 cm.$^{-1}$(shoulder) (C=O of carboxyl group) 1675 (C=O of conjugated ketone)	
IVb	218–221°(dec.)[i]	3000 cm.$^{-1}$(broad) (associated O—H)[g] 1720 cm.$^{-1}$(shoulder) (C=O of carboxyl group) 1680 cm.$^{-1}$(C=O of conjugated ketone)	
V	163–165°[j] 177–178.5°[j]	1710 cm.$^{-1}$(C=O)[g] 1610 cm.$^{-1}$ (C=C)	281 mμ (ε 51,900) 457 mμ (ε 1,400)

[a] Lit.[1] 141° (dec.). [b] Determined in carbon tetrachloride solution. [c] Lit.[3] 199–200°(dec.). [d] Determined in chloroform solution. [e] Lit. 168–169°,[2] 170–172°,[4] *Anal.* Calc'd for $C_{21}H_{14}O_2$: C, 84.55; H, 4.73. Found: C, 84.77; H, 4.73. [f] Lit.[3] 230°, *Anal.* Calc'd for $C_{33}H_{22}O_2$: C, 87.92; H, 4.92; M.W. 450. Found: C, 88.05; H, 5.15; M.W. 416 (Rast). [g] Determined as a suspension in a potassium bromide pellet. [h] Lit. 138–142°,[2] 142°,[1] *Anal.* Calc'd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.82; H, 5.10. The keto acid was purified by recrystallization from aqueous ethanol. [i] Lit.[3] 244°. The decomposition point of the acid was dependent on the rate at which the sample was heated. Since attempts to purify the keto acid resulted in erratic melting point behavior, the keto acid was cyclized without further purification. [j] Lit.[7] 166°.

Comparison of infrared spectra and a mixture melting-point determination both indicate that the isomerization product obtained from the oxide Ib and the lactone IIb prepared from IVb are identical. We are therefore led to the conclusion that the acid-catalyzed isomerization of the oxide Ib yields the lactone IIb rather than the cyclobutanone III. The red product, previously isolated and assigned structure III, was apparently the lactone IIb which contained a small amount of a deeply colored impurity. This view is supported by the facts that the two compounds were reported[3] to have identical chemical properties and that the ketone III was reported[3] to be converted to the lactone IIb under very mild conditions in spite of the fact that the ketone III was stable to boiling acetic acid for long periods of time.

EXPERIMENTAL[8]

2,3,5,6-Tetraphenylindenone (V) *and 2,3,5,6-tetraphenylindenone oxide* (*Ib*). A 20-g. (0.039 mole) sample of 2-bromo-3,3,5,6-tetraphenylindanone was heated to 250° for 2.5 hours. The resulting red melt was dissolved in boiling ligroin and allowed to cool. The product separated as red prisms, m.p. 177–178°, yield 9.2 g. (55%). When the product was allowed to crystallize slowly from ethanol two different types of crystals separated. The indenone initially separated as red-orange prisms, m.p. 163–165°.

Anal. Calc'd for $C_{33}H_{22}O$: C, 91.21; H, 5.11. Found: C, 91.32; H, 5.26.

A solution of 0.50 g. (0.0012 mole) of the material in 25 ml. of acetone was stirred with 3 ml. of aqueous hydrogen peroxide and 1 ml. of 10% aqueous sodium hydroxide for 20 minutes, diluted with water, and filtered. The residual oxide Ib crystallized from acetone as light yellow needles, m.p. 195.5–196.5° (dec.), yield 0.321 g. (64%).

The second crystalline form of the indenone separated as wine-red prisms, m.p. 177–178.5°.

Anal. Calc'd for $C_{33}H_{22}O$: C, 91.21; H, 5.11. Found: C, 91.16; H, 5.29.

When the material was treated with alkaline hydrogen peroxide as described earlier, the oxide Ib, m.p. 195–196° (dec.), was isolated in 69% yield. A mixture melting-point determination established the identity of the two oxide samples.

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[8] All melting points are corrected. The infrared spectra were determined with a Baird double beam infrared recording spectrophotometer, model B, fitted with a sodium chloride prism. The ultraviolet spectra were determined in 95% ethanol with a Cary recording spectrophotometer, model 11 MS. The microanalyses were performed by Dr. S. M. Nagy and his associates.

Rearrangement of 2,3,5,6-tetraphenylindenone oxide (Ib). A solution of 394 mg. (0.00088 mole) of the oxide and 0.5 ml. (0.004 mole) of boron trifluoride ethereate in 20 ml. of benzene was allowed to stand at room temperature for 15 minutes. The reaction mixture was diluted with ether, washed with water, dried over magnesium sulfate, and concentrated. The product crystallized from a benzene–ethanol mixture as red-orange prisms, m.p. 220–225°, yield 133 mg. (34%). Two additional recrystallizations from a benzene–hexane mixture afforded the lactone IIb as light orange prisms, m.p. 226.5–229° Similar results were obtained when the isomerization was effected in an ethereal solution of boron trifluoride or by the procedures previously described.[3]

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Synthetic Schistosomicides. I. A Diphenylsulfide Analog of Miracil D

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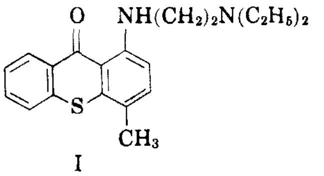
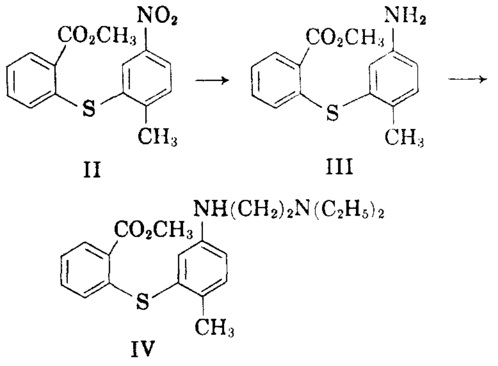
Received July 31, 1956

The development of Miracil D (I) in Germany during the recent war[4] represented a promising new lead in the field of schistosomiasis chemotherapy. The chemistry of Miracil D and some related compounds was published by Mauss in 1948,[5] while the biological and toxicological results were described in papers by Hawking,[6] Kikuth,[7] Vogel,[8] and Alves.[9] Further studies concerning related xanthenones and thiaxanthenones have been described in subsequent publications.[10–14]



I

In the course of studies directed toward the synthesis of compounds related to Miracil D, we have prepared methyl *o*-[5-(2-diethylaminoethylamino)-*o*-tolylmercapto]benzoate (IV), a diphenysulfide analog of Miracil D. The reaction sequence involved in its synthesis is indicated by formulas II through IV.



II III IV

Methyl *o*-(5-nitro-*o*-tolylmercapto)benzoate (II) was prepared by allowing the silver salt of methyl *o*-mercaptobenzoate to react with 2-iodo-4-nitrotoluene according to the method of Hammick,[12] or by the reaction of methyl *o*-chlorobenzoate with the silver salt of 5-nitro-*o*-toluenethiol. The latter mercaptan was synthesized by the following scheme: bis(5 - nitro - *o* - tolyl)disulfide was obtained by treating 5-nitro-*o*-toluenesulfonyl chloride with 50% hydriodic acid.[15] Reduction of the disulfide with potassium hydroxide and ethanol[16] yielded 5-nitro-*o*-toluenethiol, m.p. 52–53°, whose silver salt was readily prepared using ammoniacal silver nitrate in ethanol. Attempts to reduce the disulfide with a mixture of sodium hydroxide, ethanol, and sodium sulfide[17] yielded only an unworkable gum.

Reduction of the nitro ester (II) with Raney nickel and hydrogen gave 89% of methyl *o*-(5-amino-*o*-tolylmercapto)benzoate (III), which upon heating at 150–160° with freshly distilled 2-diethylaminoethyl chloride yielded methyl *o*-[5-(2-diethylaminoethylamino) - *o* - tolylmercapto]benzoate (IV). The ultraviolet absorption spectra of the ester IV in ethanol showed a band at 324 mμ (ε 8,000) and a band at 257 mμ (ε 22,000), with evidence of a stronger band at lower wave length. The infrared spectrum, run as a liquid film on a Beckman IR-2T Spectrophotometer, showed a band at 5.85 μ which is typical for a conjugated ester carbonyl, a week band at 2.94 μ which arises from an –NH– stretching vibration, and other prominent bands at 3.37, 6.26, 6.69, 6.87, 7.00, 7.76, 7.88, 8.02, 8.74, 9.04, 9.44, 9.67, 12.24, and 13.42 μ.

The Miracil D analog IV was essentially inactive

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[1] Work done at James Millikin University.

[2] Bureau of Standards, Washington, D. C.

[3] Phillips Petroleum Company, Bartlesville, Oklahoma.

[4] Office of the Publication Board, Department of Commerce, Washington, D. C., Report No. 981.

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