evaporated to dryness to give 1.5 g. of DL-α-methylhomoserine; m.p. 214–215.5° (sealed tube); reported[6] m.p. 228°.

Anal. Calcd. for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.29; H, 8.24; N, 10.50.

4-Benzyloxy-4-methyl-2-pentanone (Ib). This ketone was prepared according to the procedure described by Hoffman[7] in which 135 g. (1.38 moles) of mesityl oxide and 146 g. (1.35 moles) of benzyl alcohol were cooled to −30° during the addition of 7.0 g. (0.07 mole) of concd. sulfuric acid. The resulting solution was maintained at this temperature for 2 weeks and then neutralized with sodium carbonate. The dark brown reaction mixture was steam distilled until 1.2 l. of distillate was collected. The organic layer in the distillate contained the unchanged benzyl alcohol and mesityl oxide. The organic layer in the distilling flask was separated, the aqueous phase extracted with three 100-ml. portions of benzene, and the combined benzene and organic layer dried over calcium chloride for 24 hr. The benzene was removed under reduced pressure and the residue fractionated through a 30 × 1.8 cm. Vigreux column. The fraction boiling at 93°/0.05 mm., weighed 58.0 g.; n_D^{25} 1.5000.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.69; H, 9.33.

Semicarbazone. m.p. 136.5–137.5°; reported[7] m.p. 138–139°.

DL-*5-(2-Benzyloxy-2-methylpropyl)-5-methylhydantoin* (IIb). The hydantoin was prepared from Ib by the same method used for the preparation of DL-5-(2-benzyloxyethyl)-5-methylhydantoin; it was recrystallized from 50% ethanol; yield 85%; m.p. 180–181.5°.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.33; H, 7.27; N, 10.18.

DL-*O-Benzyl-4-hydroxy-2-methylleucine* (IIIb). DL-5-(2-(Benzyloxy-2-methylpropyl)-5-methylhydantoin, 41.5 g. (0.15 mole), was hydrolyzed in base by the same procedure as that used for the hydrolysis of DL-5-(2-benzyloxyethyl)-5-methylhydantoin (IIa). The water insoluble amino acid was isolated by acidification of the basic reaction mixture with sulfuric acid which precipitated most of the amino acid along with the barium sulfate. The precipitate was collected by suction filtration and was washed with 300 ml. of hot 10% sulfuric acid and then an equal volume of hot water. The filtrate from the reaction mixture and the washings were combined and the *p*H adjusted to 5 with 28% aqueous ammonia to precipitate the crude amino acid. Recrystallization of the product from 50% ethanol gave a 75% yield of pure amino acid; m.p. 239.5–240.5° (sealed tube).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.99; H, 8.14; N, 5.54.

DL-*4-Hydroxy-2-methylleucine, lactone, hydrochloride* (V). In a Parr hydrogenation bottle containing 4.5 ml. of hydrochloric acid in 100 ml. of absolute alcohol was placed 12.6 g. (0.05 mole) of DL-*O*-benzyl-4-hydroxy-2-methylleucine and 2 g. of 15% palladium-charcoal catalyst. The reaction mixture was shaken under 60 p.s.i. of hydrogen until the calculated amount of hydrogen had been absorbed. The reaction mixture was then filtered free of catalyst and evaporated to dryness. The product was redissolved in 15 ml. of hot absolute ethanol and ether added to the cloud point. The lactone crystallized on cooling to give 8 g. of crude product; m.p. 195–200°. Recrystallization from absolute ethanol afforded 6.5 g. of pure lactone; m.p. 190–191°. The infrared spectrum showed no absorption in the 2.5–3.0 μ range (—OH^-) λ_{max}^{Nujol} 3.28 μ (w.) (—NH); a series of weak bands in the 3.6–4.2 range (—NH_3^+); 5.69 μ (s.) (C=O); 9.03 μ (s.) (≡C—O—C).

Anal. Calcd. for $C_7H_{14}ClNO_2$: C, 46.80; H, 7.85; Cl, 19.74; N, 7.80. Found: C, 46.90; H, 7.87; Cl, 19.36; N, 7.62.

DL-*4-Hydroxy-2-methylleucine* (IVb). In order to avoid the cyclization which occurs during hydrogenolysis of the *O*-benzyl derivative in acid, the reduction was performed in an alkaline medium by a method previously described by Hartung.[8]

Accordingly, 2.5 g. (0.01 mole) of finely powdered DL-*O*-benzyl-4-hydroxy-2-methylleucine was suspended in a solution of 10 ml. of concd. ammonia solution and 100 ml. of water and one gram of a 15% palladium-charcoal catalyst was added. After the required amount of hydrogen was absorbed, the solution was filtered free of catalyst and the filtrate evaporated to dryness under reduced pressure. The product was redissolved in water and again evaporated to dryness to remove the last traces of ammonia. Needles were obtained from 90% ethanol; yield 1.1 g.; m.p. 218–219° (sealed tube); λ_{max}^{Nujol} 2.76 μ, 3.11 μ, 3.20 μ (—OH, —NH); 6.27–6.39 μ (CO_2^-); 8.43 μ, 8.78 μ [$(CH_3)_2$ C<, ≡C—OH].

Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.23; H, 9.34; N, 8.62.

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Potential Anticancer Agents.[1] LII. *meso*-1,4-Bis(1-aziridinyl)-2,3-butanediol

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A recent note[2] from these laboratories described the synthesis of several monofunctional aziridines related to Tetramin (I) as possible anticancer agents. They were all inactive when tested on the mouse tumors Sarcoma 180, Adenocarcinoma 755, and Leukemia L-1210. In some related work, a difunctional alkylating agent, *meso*-1,4-bis(1-aziridinyl)-2,3-butanediol (IV) was prepared by the reaction of *meso*-1,2:3,4-diepoxybutane (II)[3] with ethylenimine.[4] This diaziridine (IV) showed considerable antitumor activity when tested in mice; accordingly, efforts were made to prepare a number of analogs.

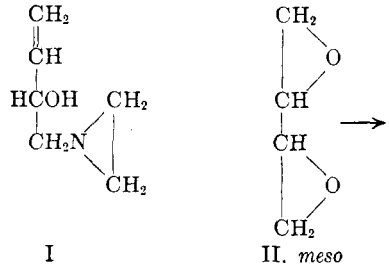
(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1557 (1961).

(2) E. J. Reist, I. G. Junga, and B. R. Baker, Paper XXXVII of this series, *J. Org. Chem.*, **25**, 1673 (1960).

(3) Farchan Research Laboratories, 28915 Anderson Rd., Wickliffe, Ohio.

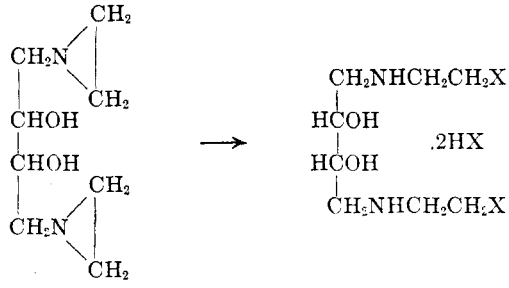
(4) L. Vargha, L. Toldy, and E. Kasztreiner, *Acta Chim. Acad. Sci. Hung.*, **19**, 295 (1959).

While this work was in progress, a report by Vargha *et al.*,[4] appeared describing the preparation of IV. Their preparation, however, contained polymer which they were unable to remove. This tendency towards polymer formation is a noteworthy property of the diaziridines of the type illustrated by IV. Thus, the preparation of IV in these laboratories using water, ethanol, benzene, ether, or pentane as diluents for the ethylenimine-epoxide reaction, or the reaction in the absence of diluent as carried out by Vargha, *et al.*,[4] gave varying amounts of polymer. The use of 2-methoxyethanol as a diluent and the presence of a small quantity of sodium hydroxide, however, gave a 38% yield of the diaziridine (IV) which contained only a trace of polymer. These small amounts of polymer were easily removed by recrystallization from 2-methoxyethanol. The diaziridine (IV) was characterized by reaction with hydrochloric and hydrobromic acids to give the crystalline dichloroethylamine dihydrochloride (VI) and dibromoethylamine dihydrobromide (VII), respectively, derivatives which were also reported by Vargha *et al.*[4]



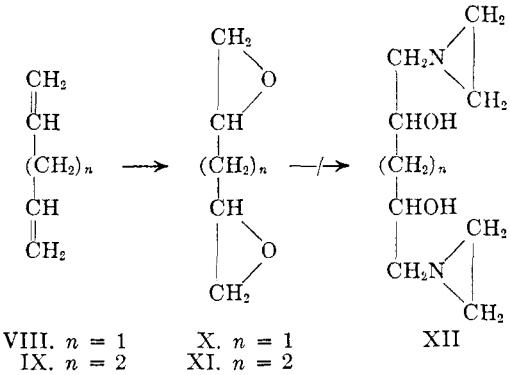
I

II. *meso*
III. racemic



IV. *meso*
V. racemic

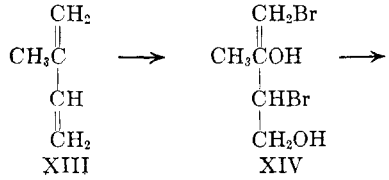
VI. X = Cl
VII. X = Br



VIII. $n = 1$
IX. $n = 2$

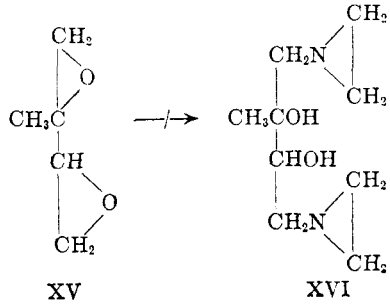
X. $n = 1$
XI. $n = 2$

XII



XIII

XIV



XV

XVI

This procedure, which was successful for the preparation of the crystalline *meso*-1,4-bis(1-aziridinyl)-2,3-butanediol (IV), was unsuccessful when the reaction products were noncrystalline. Thus, the reaction of ethylenimine with DL-1,2:3,4-diepoxybutane (III),[5] 1,2:4,5-diepoxypentane (X), 1,2:5,6-diepoxyhexane (XI),[6] and 1,2:3,4-diepoxy-2-methylbutane (XV) gave, in every case, sirups that had infrared spectra reasonably compatible with the spectra of the desired products. All efforts at purification, however, resulted in the formation of intractable polymers. Attempts to characterize the reaction products—while they were still tractable—by opening the aziridine rings with hydrochloric acid or hydrobromic acid were also unsuccessful. Again intractable polymers resulted.

The starting diepoxides when not commercially available were made from the corresponding diolefins. Thus, 1,2:4,5-diepoxypentane (X) and 1,2:5,6-diepoxyhexane (XI) were prepared by the epoxidation of the pentadiene or hexadiene (VIII or IX, respectively) with trifluoroperoxyacetic acid in the manner described by Emmons and Pagano.[6]

The preparation of 1,2:3,4-diepoxy-2-methylbutane (XV) was accomplished *via* the dibromohydrin (XIV). This dibromohydrin (XIV) was synthesized from isoprene (XIII) and two moles of *N*-bromosuccinimide by a procedure similar to that used for the preparation of the monobromohydrin of isoprene.[2,7] Petrov[7] reported that a crystalline dibromohydrin was obtained as a by-product in low yield when isoprene was allowed to react with one mole equivalent of *N*-bromoacetamide. He assigned the structure 1,3-dibromo-2,4-dihydroxy-2-methylbutane (XIV) to this solid. In our hands, the use of two mole equivalents of *N*-bromosuccinimide gave a 66% yield of a crude crystalline

(5) Peninsular ChemResearch, Inc., P.O. Box 3597, Gainesville, Fla.

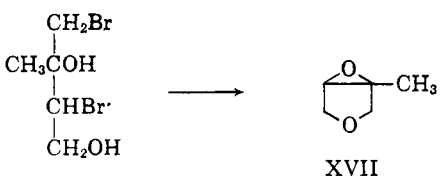
(6) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

(7) A. A. Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **13**, 481 (1943).

product. Recrystallization from ether-petroleum ether gave approximately equal amounts of crystalline and sirupy dibromohydrins (XIV). Since neither of these bromohydrins consumed periodate, the structures are compatible with XIV; hence neither of them can be the 1,4-dibromo-2,3-dihydroxy-2-butane which would be the product expected from normal Markownikoff addition to the double bonds.

The isomeric 2,4 - dibromo - 3,4 - dihydroxy-2-methylbutane would not be expected as the product, since the initial attack on isoprene is at the C_1—C_2 double bond with hydroxyl eventually adding to the tertiary carbon, as is characteristic of isobutylene.

Treatment of the crystalline dibromohydrin (XIV) with aqueous potassium hydroxide gave the desired epoxide (XV) in 22% yield. A less likely, though possible structure for XV would be the furan epoxide (XVII). Structure XV is more



XIV XVII

compatible than XVII with the observed CH vibrations at 3.29 (weak), 3.37 (strong), 3.42 (medium), and 3.50 μ (very weak), since tetrahydrofuran has CH vibrations of equal intensity at 3.42 and 3.50 μ, while *meso*-1,2:3,4-diepoxybutane (II) has its CH vibrations at 3.27 (medium), 3.34 (strong), 3.43 (medium), and 3.50 μ (very weak); the strong CH_2 vibration of tetrahydrofuran at 3.52 μ compared to the very weak vibration of XV at 3.50 μ is particularly noteworthy.

The diaziridine (IV) showed appreciable inhibition against Sarcoma 180 and Leukemia L-1210 with borderline activity against Adenocarcinoma 755. The chloroethyl and bromoethyl derivatives (VI and VII) were both inactive against Sarcoma 180 and active against Leukemia L-1210. The chloroethyl derivative was also active against Adenocarcinoma 755.[8,9]

EXPERIMENTAL[10]

meso-1,4-Bis(1-aziridinyl)-2,3-butanediol (IV). To a stirred solution of 12.0 g. (0.14 mole) of *meso*-1,2:3,4-diepoxybutane (II)[3] and 40 ml. of 2-methoxyethanol which had been cooled to 15° with an ice bath was added 0.1 g. of sodium hydroxide, then 24.0 g. (0.56 mole) of ethylenimine. The reaction temperature was maintained at 23–26° by a large water bath for 7 hr. by which time heat evolution had subsided. The mixture was stirred at room temperature for a total of 20 hr., then was concentrated to 35 ml. on a rotary evaporator at 20–25 mm. (bath 45°). The concentrated mixture was cooled to 5°, then filtered to give 9.0 g. (38%) of the product (IV), m.p. 169–171°; this sample had an infrared spectrum essentially identical with that of the analytical sample. Recrystallization of a sample from 2-methoxyethanol gave white crystals, m.p. 170–171°, that had an infrared spectrum identical with that of the analytical sample.

The insolubility of the polymer from IV in hot 2-methoxyethanol served as a sensitive test for the presence of polymer, as did the infrared spectrum. The melting point of IV was unaffected by relatively large amounts (10–15%) of polymer and was not a useful criterion of purity; combustion analyses obviously cannot detect polymer.

Recrystallization of a previous run from benzene gave the analytical sample, m.p. 168–170°; $\lambda_{max(\mu)}^{Nujol}$ 3.20 (OH), 7.95 (C—N), 9.26 (C—OH).

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.8; H, 9.32; N, 16.3. Found: C, 55.9; H, 9.44; N, 16.5.

Vargha, *et al.*,[4] reported m.p. 168–170°.

1,4-Bis(2-chloroethylamino)-1,4-dideoxyerythritol dihydrochloride (VI). *meso*-1,4-Bis(1-aziridinyl)-2,3-butanediol (IV) (5.0 g.) was added slowly with stirring to 50 ml. of concd. hydrochloric acid which had been cooled to 0° in an ice bath. The reaction was stirred at 0° for 30 min., then the small amount of insoluble material (about 50 mg.) was removed by filtration and the filtrate was concentrated to dryness *in vacuo* to yield 10.6 g. of a solid. Recrystallization from 150 ml. of 95% ethanol gave 7.34 g. (82%) of product, m.p. 229–231°, which had an infrared spectrum identical with that of the analytical sample.

Recrystallization of a previous run from 95% ethanol gave the analytical sample, m.p. 228–230°; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (OH), 3.98, 4.10, 6.24 ($NH_2^{\oplus}$), 9.16, 9.32 (C—OH).

Anal. Calcd. for $C_8H_{18}Cl_2N_2O_2 \cdot 2HCl$: C, 30.2; H, 6.29; Cl, 44.7; N, 8.81. Found: C, 30.5; H, 6.35; Cl, 44.4; N, 9.12.

Vargha *et al.*,[4] reported m.p. 240–242°.

1,4-Bis(2-bromoethyl)-1,4-dideoxyerythritol dihydrobromide (VII). *meso*-1,4-Bis(1-aziridinyl)-2,3-butanediol (IV) (3.0 g.) was added slowly with stirring to 85 ml. of 48% aqueous hydrobromic acid which had been previously cooled to 0° in an ice bath. The mixture was stirred at 0° for 30 min., then filtered to remove the small amount of insoluble material. The filtrate was concentrated to dryness *in vacuo* to give a white solid, which was triturated with absolute ethanol, then filtered to give 7.4 g. (86%) of crude product. This material was dissolved in 200 ml. of hot 2-methoxyethanol, cooled, then diluted with 670 ml. of dry ethyl ether. The mixture was cooled to 0°, then filtered to give 6.2 g. of white crystals, m.p. 211–215°, which had an infrared spectrum similar to that of the analytical sample.

The analytical sample from a previous run had m.p. 214–215°; $\lambda_{max(\mu)}^{Nujol}$ 2.97 (OH), 4.03, 4.16, 6.33 ($NH_2^{\oplus}$), 9.27, 9.50 (C—OH).

Anal. Calcd. for $C_8H_{18}Br_2N_2O_2 \cdot 2HBr$: C, 19.4, H, 4.04; Br, 64.5; N, 5.65. Found: C, 19.5; H, 4.25; Br, 64.3; N, 5.60.

Vargha *et al.*,[4] reported m.p. 225–227°.

1,2:4,5-Diepoxypentane (XII, n = 1) was prepared in 29% yield from 1,4-pentadiene (XI, n = 1) and trifluoroperoxyacetic acid by the procedure of Emmons and Pagano.[6] It had b.p. 63–67° (26 mm.); n_D^{20} 1.4314; $\lambda_{max(\mu)}^{film}$ 3.35 (epoxide CH), 7.92 (epoxide). The vapor phase chromatogram[11] showed less than 5% impurity.

Anal. Calcd. for $C_5H_8O_2$: C, 60.0; H, 8.05. Found: C, 59.7; H, 8.42.

Paul and Tchelitcheff[12] prepared this compound in 64% yield by the reaction of 1,4-pentadiene with perbenzoic acid. They reported b.p. 160° and n_D^{20} 1.4360.

(8) Vargha *et al.*,[4] reported that IV as well as the chloro and bromo derivatives (VI and VII, respectively) showed appreciable inhibition of growth of various transplanted tumors.

(9) These assays were run by Dr. J. Greenberg and staff in this department, the assays being done under contract to the Cancer Chemotherapy National Service Center.

(10) Melting points and boiling points are uncorrected.

(11) DC-710 column, 170°.

(12) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 896 (1948).

1,3-Dibromo-2,4-dihydroxy-2(or 3)-methylbutane (XIV). To a stirred solution of 20.0 g. (0.29 mole) of isoprene (XIII) in 250 ml. of water was added 106 g. (0.59 mole) of *N*-bromosuccinimide in portions over 2 hr., maintaining the temperature at 15–20° with the aid of an ice bath. After the addition was complete, the reaction mixture was allowed to stand at room temperature overnight, then was extracted with three 100-ml. portions of ether. The combined extracts were washed with 100 ml. of water, dried over magnesium sulfate, then evaporated to dryness *in vacuo* to give a sirup which crystallized on standing. This crude product was dissolved in 60 ml. of ether and diluted with 100 ml. of petroleum ether (b.p. 30–60°). The solution was concentrated *in vacuo* to approximately 40 ml. at 0°, at which point crystallization occurred to give 21.0 g. (27%) of crystalline dibromohydrin (XIV), m.p. 81–83°; $\lambda_{max(\mu)}^{Nujol}$ 3.0 (OH), 9.35, 9.78 (C—OH), no C=C at 6.1–6.2 or C=CH_2 at 10.1.

Anal. Calcd. for $C_5H_{10}Br_2O_2$: C, 22.9; H, 3.81; Br, 61.1. Found: C, 23.0; H, 3.94; Br, 61.1.

Evaporation of the mother liquors gave 30 g. (39%) of the stereoisomeric XIV as a sirup; $\lambda_{max(\mu)}^{film}$ 3.00 (OH), 9.35, 9.75 (C—OH).

Anal. Calcd. for $C_5H_{10}Br_2O_2$: C, 22.9; H, 3.81; Br, 61.1. Found: C, 23.7; H, 4.02; Br, 62.4.

Neither the crystalline dibromohydrin nor the mother liquors consumed any periodate over 20 hr. Petrov[7] has recorded m.p. 81–83° for the crystalline isomer of XIV.

On a large scale, 197 g. of isoprene (XIII) gave 199 g. (26%) of crystalline dibromohydrin (XIV), m.p. 80–84°.

1,2:3,4-Diepoxy-2-methylbutane (XV). A solution of 31.4 g. (0.52 mole) of potassium hydroxide in 17 ml. of water was added dropwise to a vigorously stirred suspension of 78.1 g. (0.3 mole) of crystalline 1,3-dibromo-2,4-dihydroxy-2(or 3)-methylbutane (XIV) in 200 ml. of ether. After the addition was complete (about 10 min.), the mixture was stirred for 1.5 hr., by which time solution of the dibromohydrin was complete. The ether layer was separated, then dried over potassium hydroxide and potassium carbonate. The filtered solution was concentrated to 80 ml. at 0° and 22 mm. The residue was distilled through a small Vigreux column to give 6.60 g. (22%) of the colorless diepoxide, b.p. 75–77° (70 mm.); n_D^{25} 1.4279; $\lambda_{max(\mu)}^{film}$ 3.29, 6.75 (epoxide CH), 8.01, 8.10 (C—O—C). This material was 96% pure as shown by vapor phase chromatography.[11]

Everett and Kon[13] obtained a 20% yield of diepoxide, b.p. 55° (20 mm.), when isoprene was allowed to react with perbenzoic acid at 0° for 14 days.

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(13) J. L. Everett and G. A. R. Kon, *J. Chem. Soc.*, 3131 (1950).

Friedelin and Related Compounds. IV.[1] A Convenient Isolation of Friedelin

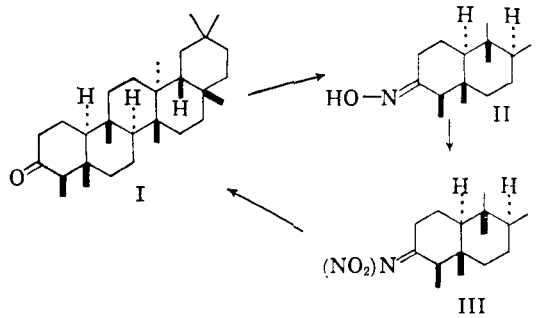
ROBERT STEVENSON

Received October 10, 1960

The isolation[2–4] of the pentacyclic triterpene ketone, friedelin (I), in appreciable quantities from cork suffers from the disadvantage of requiring extraction with large volumes of solvent in pilot-plant scale apparatus. A more convenient source, previously utilized,[1,5] is a resin known as "smoker wash solids" obtained as a by-product in the manufacture of corkboard by steam-baking. Friedelin is readily obtained in a crude state from this source by solvent extraction; purification by chromatographic or recrystallization procedures has proven troublesome, however, due to the presence of gelatinous contaminants.

In connection with other studies, friedelin oxime (II) was prepared as described by Drake and Shrader.[6] The realization that this derivative was sparingly soluble in the common organic solvents, notably chloroform in which most triterpenoid compounds are readily soluble, suggested a convenient purification procedure. Preliminary experiments showed that treatment of friedelin with hydroxylamine hydrochloride in aqueous pyridine yielded the oxime in high yield more conveniently. When applied to the neutral crude extract from the cork resin, this method afforded oxime of satisfactory purity after one crystallization from chloroform.

The regeneration of friedelin, in unspecified yield, from the oxime by hydrolysis with phosphoric acid in *n*-amyl alcohol, has previously been reported.[6] In seeking an alternative method, the action of nitrous acid was examined. The effective use of this reagent in hydrolyzing steroid oximes and semicarbazones has recently been demonstrated by Brooks *et al.*[7] who summarize much of the earlier work. Friedelin oxime, on treatment with this reagent, readily gave a product (III), $C_{30}H_{50}O_2N_2$, which in addition to having strong infrared absorption bands (in chloroform solution) at 6.42 and 7.63 μ, characteristic of the nitrimine (pernitroso) function, also had medium intensity bands at 6.16, 6.91, 7.22, and 9.35 μ. An authentic



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