[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, CROWN ZELLERBACH CORPORATION]

Conidendrin. I. Its Isomerization and Demethylation[1]

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Improved methods for isomerizing conidendrin (I) to its beta form have been devised. Demethylation of conidendrin has given two crystalline isomers, designated α- and β-norconidendrin (III). Conidendrin and α-norconidendrin have the same structural configuration, while the beta compounds are sterically identical. Formation of the beta series is explained by an inversion at the carbon atom adjacent to the carbonyl group. Derivatives of the norconidendrins are reported.

Conidendrin, (I) known for about 50 years, has been found in substantial amounts in sulfite waste liquor from the pulping of western hemlock[2] from which it can be easily removed by precipitation with organic liquids.[3] This paper reports a study of its conversion to a steric isomer which we designate β-conidendrin, and the demethylation of conidendrin and its beta form.

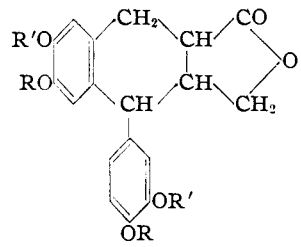
Holmberg[4] early noted that conidendrin could be changed to what appeared to be a diastereoisomer by the action of heat or alcoholic sodium ethoxide. During the latter treatment part of the product separated as an insoluble sodium salt, a part remained in solution. Either, on working up, gave the isomer, β-conidendrin. Holmberg[5] found that the new compound had the same empirical structure as conidendrin but on methylating it he obtained a substance having a melting point and optical rotation differing from that produced by methylation of conidendrin itself. The former compound he called β-dimethylconidendrin and the latter α-dimethylconidendrin (II).

We have found that Holmberg's preparation of β-conidendrin can be materially improved and simplified by the use of methanolic sodium methoxide whereby the precipitation of the product during the reaction is avoided. The same conversion was found to be effected by the action of organic amines or ammonia and the last reagent proved to be the most satisfactory. The conditions used were such that any amide formed by opening the lactone ring was converted again to the lactone by loss of ammonia. The β-conidendrin formed by these new procedures has been shown to be identical with Holmberg's product prepared by the action of heat or sodium ethoxide. Our product has also been characterized by the preparation of a crystalline diacetate (IV) and ditosylate (V).

The first attempt to demethylate conidendrin was by Fisher, *et al.*,[6] who obtained an amorphous mixture of products.

Recently Erdtman and Lindberg[7] treated conidendrin with pyridine hydrochloride and obtained a crystalline, demethylated product (III), β-norconidendrin, which they proved by methylation to have the same configuration as Holmberg's[5] β-dimethylconidendrin.

Prior to Erdtman's publication we had been investigating the demethylation of conidendrin. During the course of these studies, we found that two crystalline demethylated conidendrins (III) can be produced. One of these was identical with Erdtman's β-norconidendrin and the other we designated α-norconidendrin. They differ by the same alteration in configuration which exists between conidendrin and its beta isomer.



I, R = H; R′ = CH_3
II, R = R′ = CH_3
III, R = R′ = H
IV, R = $COCH_3$; R′ = CH_3
V, R = $OSO_2C_6H_4CH_3$; R′ = CH_3
VI, R = R′ = $COCH_3$
VII, R = R′ = COC_6H_5

Fig. 1

α-Norconidendrin (III) has been produced using a mixture of hydriodic and acetic acids. Many other demethylating agents including hydrochloric acid, aluminum chloride, aluminum bromide, sodium hydroxide and boron trifluoride were tried without success. Methylation of α-norconidendrin produced a tetramethyl derivative (II) which was found to be identical with the methylated derivative of conidendrin (Holmberg's α-dimethylconidendrin[5]). A tetraacetate of α-norconidendrin (VI) was prepared but attempts to crystallize it did not succeed. As a crystalline derivative, the tetrabenzoate has been produced (VII).

Our procedure for preparing β-norconidendrin is somewhat simpler than Erdtman's[7] and gives substantially the same yield. Methylation of our product also gave Holmberg's[5] β-tetramethylconidendrin. The tetraacetate was also prepared.

In addition, β-norconidendrin was prepared by demethylating β-conidendrin with hydriodic acid. This definitely proved that α- and β-norconidendrin differ by the same structural change that exists between conidendrin and its beta isomer.

To show further the relation between α- and β-norconidendrin the former was converted to the latter by heating with alcoholic ammonia. In all our experiments to convert the alpha to the beta form, either with conidendrin or the norconidendrins, the equilibrium appeared to be well on the beta side. This observation differed from that of

(1) Presented before the Division of Sugar Chemistry at the 116th Meeting of the American Chemical Society, Atlantic City, N. J.

(2) I. A. Pearl, *J. Org. Chem.*, **10**, 219 (1945).

(3) H. B. Lackey, W. W. Moyer and W. M. Hearon, *Tappi*, **32**, No. 10, 469 (1949).

(4) B. Holmberg, *Ber.*, **54**, 2389 (1921).

(5) B. Holmberg and M. Sjoberg, *ibid.*, **54**, 2406 (1921).

(6) C. H. Fisher, L. Kyame and W. G. Bickford, *J. Am. Oil Chem. Soc.*, **24**, No. 10, 340 (1947).

(7) H. Erdtman and B. Lindberg, *Acta Chem. Scand.*, **3**, 982 (1949).

Holmberg[8] who found that dimethylconidendrin, properly catalyzed, produced an equilibrium of the alpha and beta forms when approached from either direction and that the equilibrium mixture contained approximately equal quantities of each form.

A possible explanation for the structural change which takes place in the conversion from the alpha to the beta form has been postulated by Emde,[9] who suggested that an inversion occurs at the carbon atom adjacent to the carbonyl group of the lactone ring. This appears to be a most reasonable explanation since this conversion is promoted by reagents which might produce enolization of the carbonyl group This hypothesis is supported by three pieces of evidence: First, the gradual precipitation of the sodium salt of β-conidendrin in Holmberg's preparation[4] would indicate that enolization takes place. Second, it has been found by us that no isomerization occurs if the lactone ring is open. Last, the tendency to form a lactone ring in the case of β-conidendrin is considerably greater than for α-conidendrin indicating that the configuration of the alicyclic ring has been changed to allow less strain in the lactone ring. This would require an inversion at either of the asymmetric carbon atoms making up the lactone ring. If this hypothesis is correct, the change from alpha to beta form represents an epimerization of non-carbohydrate material.

Experimental

β-Conidendrin (I). A. **Using Sodium Methoxide.**—A 10-g. portion of conidendrin was refluxed on a steam-bath with 650 ml. of methanol until complete solution occurred. To this was added a solution of 2.0 g. of sodium in 50 ml. of methanol. The refluxing was continued for another 45 minutes, after which 1200 ml. of warm water and 50 ml. of concentrated hydrochloric acid were added to the clear solution. After standing for six hours, the liquid deposited 9.0 g. of white β-conidendrin monohydrate (86% of theory) which was removed by filtration, washed with water and dried in air at room temperature; m.p. 208–210°[10] with earlier shrinking. The product, on heating an hour at 100°, lost its water of hydration which was not regained in air. The anhydrous material still melted at 208–210° but with no previous change. A mixed m.p. with Holmberg's product from the action of sodium ethoxide on conidendrin showed no depression; $[\alpha]^{25}D$ +32.5° (*c* 3.00, acetone); Holmberg[4] gave m.p. 210–211° $[\alpha]D$ +31.3° (*c* 3.00, acetone).

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.4; H, 5.63; OCH_3 17.4; mol. wt. 356. Found: C, 67.3; H, 5.96; OCH_3, 17.6; mol. wt., (Rast camphor method), 357.

The β-conidendrin was insoluble in water but soluble in aqueous alkali, warm carbonate, and many of the common organic solvents. In ethanol, it gave a green color with ferric chloride. It reduced hot Tollens reagent slowly, but did not affect Fehling solution. Its solution in cold concentrated sulfuric acid was yellow.

B. **Using Ammonia.**—A mixture of 10 g. of conidendrin, 100 ml. of ethanol and 7 ml. of concentrated ammonium hydroxide was heated in a glass-lined bomb at 180° for 1.5 hours. The resulting solution deposited 7.3 g. of β-conidendrin monohydrate (70%) melting at 208–210° with earlier shrinking.

β-Dimethylconidendrin (II).—Following the procedure of Holmberg,[5] 9.7 g. of β-conidendrin (made by ammonia method), 11 g. of sodium hydroxide and 18 ml. of dimethyl sulfate gave, from alcohol, 9.0 g. (89% of theory) β-dimethylconidendrin melting at 154–155° after sintering at 140°; $[\alpha]^{25}D$ 0.0 (*c* 4.00, acetone). Holmberg[5,8] reported a melting point of 141–142° and 156–157° depending on the crystalline form and $[\alpha]D$ 0.0 (*c* 3.00, acetone). β-Dimethylconidendrin made by methylating the product from the action of sodium ethoxide on conidendrin (Holmberg's method[4]) melted at 155–156° and showed no depression when admixed with the product above.

β-Conidendrin Diacetate (IV).—β-Conidendrin (2.0 g.) (by ammonia method) with dry pyridine (20 ml.) and acetic anhydride (10 ml.) gave 2.5 g. crude, and 2.0 g., pure (from alcohol) diacetate melting at 205–207°; $[\alpha]^{25}D$ +25 (*c* 2.00, acetone).

Anal. Calcd. for $C_{24}H_{24}O_8$: C, 65.4; H, 5.49. Found: C, 65.4; H, 5.45.

β-Conidendrin Ditosylate (V).—β-Conidendrin (2.09 g.) (by ammonia procedure) and *p*-toluenesulfonyl chloride (4.0 g.) in dry pyridine (20 ml.) gave, from 1:1 aqueous pyridine, 3.2 g. or 86% of theory of white crystals melting at 166.5–167°; $[\alpha]^{25}D$ +13 (*c* 4.00, acetone).

Anal. Calcd. for $C_{34}H_{32}O_{10}S_2$: C, 61.4; H, 4.85; S, 9.64. Found: C, 61.5; H, 4.76; S, 9.50.

α-Norconidendrin (III).—A mixture of 5 g. of finely divided conidendrin, 25 ml. of 57% hydriodic acid, 25 ml. of glacial acetic acid and 0.5 g. of red phosphorus was gently refluxed 30 minutes under an air condenser through which methyl iodide was allowed to escape. The temperature of the mixture rose to 118° in 10 minutes and remained there during the rest of the refluxing period. The mixture was then transferred to a distilling flask and 60 g. of distillate removed by heating on a steam-bath under pressure from an aspirator. The sirupy residue was taken up in 100 ml. of hot water, filtered hot from phosphorus and allowed to cool. The nearly colorless precipitate was filtered off, washed with water and dried in air at room temperature giving 3.9 g. or 76% of theory of α-norconidendrin dihydrate melting at 102–103°. Heating the product at 100° for one hour produced the anhydrous material m.p. 165–166° which, however, regained two molecules of water by standing in air; $[\alpha]^{25}D$ −75° (*c* 4.00, acetone).

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.9; H, 4.91; OCH_3, 0.0. Found: C, 66.0; H, 4.91; OCH_3, 0.09. Calcd. for $C_{18}H_{16}O_6 \cdot 2H_2O$: C, 59.3; H, 5.53. Found: C, 59.1; H, 5.32.

The compound was soluble in hot water, cold aqueous alkali or carbonate, and most of the usual organic solvents. It reduced Fehling solution in the hot, and gave an immediate black precipitate of silver with Tollens reagent. An aqueous solution of α-norconidendrin gave a dark green color with ferric chloride which turned to a deep red on the addition of sodium carbonate. α-Norconidendrin dissolved quickly in aqueous sodium hydroxide to give a yellow solution turning almost at once to green, then blue. Warming changed this to black, then brown, and finally to red. A solution of the substance in aqueous sodium carbonate was yellow turning to deep red on heating.

α-Tetramethylnorconidendrin (II).—α-Norconidendrin dihydrate, dimethyl sulfate and alkali in the usual manner gave a 95% yield of tan colored crystals. Three recrystallizations from hot ethanol lowered the yield to 47% but gave white crystals melting at 177–178°. α-Dimethylconidendrin made by direct methylation of conidendrin[5] melted at 179–180° and did not depress the melting point of the methylated α-norconidendrin.

α-Norconidendrin Tetraacetate (IV).—A suspension of 5 g. of α-norconidendrin in 25 ml. of acetic anhydride treated with two drops of concentrated sulfuric acid, gave a white amorphous product, 6.4 g. or 85% of theory; $[\alpha]^{25}D$ −57.5° (*c* 4.00, acetone). The material was soluble in many common organic solvents but could not be crystallized from any.

Anal. Calcd. for $C_{26}H_{24}O_{10}$: C, 62.9; H, 4.87. Found: C, 61.9; H, 4.89.

Acetylation of 1.9 g. of α-norconidendrin with 12 ml. of acetic anhydride and 24 ml. of dry pyridine gave 2.4 g. (84% of theory) of white, amorphous acetate, to all appearances identical to that made using acetic anhydride and sulfuric acid, but it could not be crystallized either.

α-Norconidendrin Tetrabenzoate (VII).—A mixture of 5 g. of α-norconidendrin, 25 ml. of benzoyl chloride and 40 ml. of dry pyridine was left at room temperature for 16 hours. The mixture was taken up in diethyl ether and washed successively with dilute hydrochloric acid, water, di-

(8) B. Holmberg, *Ann. Acad. Sci. Fennicae*, **29A**, No. 6, 3 (1927).

(9) H. Emde and H. Schartner, *Naturwissenschaften*, **22**, 743 (1934).

(10) Mixtures of conidendrin and beta conidendrin melted between 210 and 250° instead of below 210° as might be expected.

lute sodium carbonate and water. The ether was dried over sodium sulfate and evaporated to a sirup which was stirred on a steam-bath with 200 ml. of ethanol whereby a voluminous white, crystalline precipitate formed; weight 7.7 g. or 68% of theory; m.p. 176–177°. Recrystallization from 2:1 ethanol–acetone gave 7.0 g. (62%) melting at 179–180°; $[\alpha]^{25}D$ −75° (*c* 2.00, acetone).

Anal. Calcd. for $C_{46}H_{32}O_{10}$: C, 74.2; H, 4.33. Found: C, 74.4; H, 4.41.

β-Norconidendrin (III). A. From Conidendrin.[7]—A mixture of 10 g. of conidendrin and 9 g. of pyridine hydrochloride was heated in a 200-ml. round-bottomed flask with an air condenser to 155° until a yellow solution resulted. The temperature was then raised to 180° and kept there for one hour. The clear melt was dissolved in 250 ml. of hot water and then held at 50° for three hours during which crystallization rapidly took place. After standing 16 hours at room temperature, the mixture was filtered giving 7.6 g. (82% theory) of nearly white β-norconidendrin melting at 251–252°; $[\alpha]^{25}D$ +15° (*c* 5.00, acetone).

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.9; H, 4.91; OCH_3, 0.0. Found: C, 66.0; H, 5.01; OCH_3, 0.08.

The product was soluble in hot water, cold aqueous alkali or carbonate, and in most of the common organic solvents It reduced hot Fehling solution and gave an immediate black precipitate of silver with Tollens reagent. An aqueous solution of β-norconidendrin gave a light green color with ferric chloride which turned to deep red with sodium carbonate. β-Norconidendrin dissolved quickly in aqueous sodium hydroxide to give a yellow solution which on heating turned successively green, blue, black, brown and red. A solution of the substance in aqueous sodium carbonate was yellow turning to orange on heating.

B. **From β-Conidendrin.**—A mixture of 5 g. of β-conidendrin (ammonia method), 25 ml. of 57% hydriodic acid and 25 ml. of glacial acetic acid was refluxed for 30 minutes. The excess acids were removed on the steam-bath under pressure from an aspirator. The resulting sirup was dissolved in 125 ml. of hot water which deposited 2.8 g. (61% yield) of a mixture of white and brown crystals after standing four hours at 40° and 16 hours at room temperature. Recrystallization from 40 ml. of hot water containing 0.5 g. of sodium bisulfite gave 1.9 g. (41% yield) of white crystals melting at 245–247°. A mixture with the product from conidendrin and pyridine hydrochloride melted at the same temperature. A mixture with conidendrin melted below 225°.

C. **From α-Norconidendrin and Ammonia.**—A solution of 10 g. of α-norconidendrin in 100 ml. of ethanol and 6 ml. of concentrated ammonium hydroxide was sealed in a glass-lined bomb in which the air had been displaced by nitrogen. The bomb was heated in a constant-temperature bath at 145° for one hour. The contents of the bomb were then diluted with 700 ml. of hot water containing 7 ml. of concentrated hydrochloric acid. The solution was boiled to remove alcohol, then cooled at 0° for 18 hours. The clear supernatant liquid was decanted from the tar which had settled out and left at room temperature for 24 hours during which time 1.7 g. (17% yield) white crystals came out, melting at 249–250°. A mixed melting point with β-norconidendrin made from conidendrin and pyridine hydrochloride showed no depression.

β-Tetramethylnorconidendrin (II).—β-Norconidendrin (from conidendrin and pyridine hydrochloride) (1.0 g.) and dimethyl sulfate (3 ml.) gave, after recrystallization from ethanol, 0.3 g. (26% yield) of colorless crystals melting at 153–154°. A mixture of this product and β-dimethylconidendrin[5] melted at 154–155°.

β-Norconidendrin Tetraacetate (VI).—A suspension of 4 g. of β-norconidendrin (from conidendrin and pyridine hydrochloride) in 20 ml. of acetic anhydride treated with one drop of concentrated sulfuric acid gave 5.1 g. (84% yield) of colorless crystals melting at 175–178°. Recrystallization from hot ethanol gave 4.9 g. (81%) melting at 179–180°; $[\alpha]^{25}D$ +14° (*c* 4.00, acetone).

Anal. Calcd. for $C_{26}H_{24}O_{10}$: C, 62.9; H, 4.87. Found: C, 62.8; H, 4.94.

CAMAS, WASHINGTON RECEIVED FEBRUARY 26, 1951

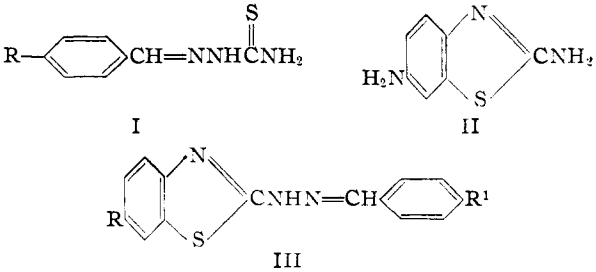
[CONTRIBUTION FROM THE SCHENLEY LABORATORIES, INC.]

Antituberculous Compounds. II. 2-Benzalhydrazinobenzothiazoles[1a]

BY LEON KATZ

A series of benzothiazole derivatives have been prepared for evaluation against *Mycobacterium tuberculosis*. These compounds were synthesized by replacement of the 2-chloro group in a benzothiazole (IV, VI, VIII and IX) by a hydrazino radical and subsequent condensation of the 2-hydrazinobenzothiazoles with aromatic aldehydes. Compounds 3 and 5 (Table I) were the most active.

Considerable interest has been aroused by the publication of Behnisch, Domagk, Mietzsch and Schmidt[1b] concerning the use of *p*-substituted benzaldehyde thiosemicarbazones, I,[2] in the treatment of tuberculosis. A good review of the work done by these investigators in correlating structure with activity appeared recently.[3] The important correlations were these: (1) *p*-substituted benzaldehydes gave rise to the most effective compounds, (2) S- or N-alkylation decreased the activity, and (3) reduction of the C=N bond did not result in loss of activity. These results have been confirmed in two independent laboratories.[4] A study was begun in this Laboratory with the aim of preparing effective compounds by modifying the structure of I.



I II

III

Freedlander and French[5] reported that 2,6-diaminobenzothiazole (II) which contains a cyclic thioureido group, was highly active *in vivo* against tuberculosis. If the 2-amino group were replaced

(1) (a) After this article had been submitted for publication a report by J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, THIS JOURNAL, **73**, 906 (1951), appeared, describing compounds 2, 4 and 5 (Table I). (b) G. Domagk, *et al.*, *Naturwissenschaften*, **33**, 315 (1946).

(2) R = CH_3CONH, Schenley "Tibione," Brand of Amithiozone.

(3) R. Behnisch, F. Mietzsch and H. Schmidt, *Am. Rev. Tuberc.*, **61**, 1 (1950). This article is a translation of an article published in *Angew. Chem.*, **60**, 113 (1948).

(4) E. Hoggarth, A. R. Martin, N. E. Storey and E. H. P. Young. *Brit. J. Pharmacol.*, **4**, 248 (1949); R. Donovick, F. Pansy, G. Stryker and J. Bernstein, *J. Bact.*, **59**, 667 (1950).

(5) B. L. Freedlander and F. A. French, *Proc. Soc. Exptl. Biol. Med.*, **66**, 362 (1947).