was dissolved in 300 ml. of chloroform and the solution was washed successively with a saturated sodium bicarbonate solution, water, 1 *N* hydrochloric acid, and finally 3 times with water. The chloroform solution was concentrated to dryness and the residue was recrystallized from 100 ml. of ethyl acetate. The recovery was 16.8 g., m.p. 113–123°, of N-(N-phthaloyl-β-alanyl)-S-benzyl-β-aminoethanethiol.

Anal. Calcd. for $C_{20}H_{20}N_2O_3S$: C, 65.19; H, 5.47; N, 7.61. Found: C, 65.14; H, 5.72; N, 7.78.

N-(β-Alanyl)-S-benzyl-β-aminoethanethiol Hydrochloride (VIIa).—A mixture of 7.37 g. (0.02 mole) of N-(N-phthaloyl-β-alanyl)-S-benzyl-β-aminoethanethiol and 1.18 g. (0.02 mole, 1.15 ml.) of 85% hydrazine hydrate in 50 ml. of ethanol was heated at the reflux temperature. Complete solution was obtained rapidly and after about 15 minutes a precipitate began to separate. Heating was continued a total of 1 hour. The reaction mixture was concentrated to dryness and 150 ml. of water and 50 ml. of 1 *N* hydrochloric acid were added. To ensure complete dissolution of the acid soluble components, the mixture was warmed to about 50° and then cooled to room temperature. The undissolved solid was removed and the filtrate was concentrated under reduced pressure. The residue (5.8 g.), m.p. 130–150°, was recrystallized 3 times from alcohol–ether to yield 4.0 g. of N-(β-alanyl)-S-benzyl-β-aminoethanethiol hydrochloride, m.p. 164.5–166.5°.

S-Benzylpantetheine (VIII).—A solution of 30% sodium hydroxide was added to a solution of 8.8 g. (0.032 mole) of N-(β-alanyl)-S-benzyl-β-aminoethanethiol hydrochloride in 80 ml. of ice and water until the free amine separated. The oil was extracted into several 50-ml. portions of chloroform. The combined chloroform extracts were washed with two portions of water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residual oil was dissolved in 30 ml. of methanol and 4.2 g. (0.032 mole) of (−)-pantolactone was added. The solution was refluxed for 1 hour and the solvent was removed under reduced pressure. The viscous oil remaining was dissolved in about 200 ml. of chloroform and extracted with 25 ml. of 0.5 *N* hydrochloric acid followed by three 25-ml. portions of water. The chloroform solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure; 11 g. of S-benzylpantetheine was obtained, $[\alpha]^{24}D$ +20° (*c* 1.7 in methanol).

Anal. Calcd. for $C_{18}H_{28}N_2O_4S$: C, 58.67; H, 7.64; N, 7.60. Found: C, 58.71; H, 7.52; N, 7.89.

Pantetheine (IX).—To 5.4 g. (0.0147 mole) of S-benzylpantetheine in a flask cooled in a mixture of Dry Ice and alcohol was added 150 ml. of liquid anhydrous ammonia. The cooling bath was removed and 1.37 g. (0.0596 mole) of sodium was added in small portions with stirring. At the end of the addition a permanent blue color was obtained. About 10 g. of ammonium sulfate was added and stirring was continued while the ammonia evaporated. The residue was dissolved in ice-water and the mixture was extracted with three 70-ml. portions of 1-butanol. The combined 1-butanol extracts were washed with three 50-ml. portions of water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to yield 4.2 g. of pantetheine. Enzymatic assay indicated that the product was 80 to 90% pure.

S-Acetylpantetheine (X).—Pantetheine (10 g., 0.036 mole) was dissolved in 60 ml. of water and to this solution was added 20 ml. (0.28 mole) of freshly distilled thiolacetic acid. The mixture was allowed to stir overnight at room temperature. The reaction mixture, which had become homogeneous, was concentrated under reduced pressure. The yield of S-acetylpantetheine, a pale yellow viscous oil, was quantitative.

Anal. Calcd. for $C_{13}H_{24}N_2O_5S$: C, 48.73; H, 7.55; N, 8.75; acetyl, 13.43. Found: C, 48.39; H, 7.40; N, 8.18; acetyl, 13.59.

RAHWAY, N. J.

[CONTRIBUTION FROM WARNER-CHILCOTT RESEARCH LABORATORIES]

The Preparation of Some Nitrogenous Derivatives of Conidendrin

BY JOHN SWIDINSKY, FREEMAN H. MCMILLAN AND JOHN A. KING

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Ten amides have been prepared by the reaction of methylated *l*-conidendrin with a variety of amines and three of these amides have been reduced to the corresponding amines by lithium aluminum hydride. It has been observed that the lactone linkage in the dehydrogenated methylated conidendrin is very stable and non-reactive.

As a member of the group of lignans[1] which occur in woody tissue, *l*-conidendrin (I) has been known for many years. It was first isolated from sulfite waste liquor by Lindsey and Tollens[2] in 1892, and the proof of its skeletal and functional group structure was summarized by Haworth in the 1942 Tilden Lecture[3]; the stereochemistry of the hydroaromatic ring has not been established although it has been deduced (Haworth, ref. 3) that the molecule has the *trans* (1:2), *trans* (2:3) structure (using Haworth's numbering system, in which the aryl group is at position 1). Its isolation and identification a few years ago by Brauns[4] and Pearl[5] as a constituent to the extent of 0.6% of the weight of the wood charged of sulfite waste liquor of western hemlock have stimulated interest in the use of it[6] or its demethylated derivative[7,8] as antioxidants in edible oils and have led to the development of commerical processes for its isolation,[9,10] isomerization[11,12] and demethylation.[11,13]

The probable close structural relationship of conidendrin to podophyllotoxin and to α- and β-peltatin[14,15] and the recent observations concerning the high necrotizing activity for mouse sarcoma 37 of these latter substances[16,17] make a study of chemical

(1) The term lignan was proposed by Haworth some years ago to include the group of natural products characterized by the 2,3-dibenzylbutane skeleton (as such or cyclized). *Cf. Ann. Repts. on Progress of Chem.* (*Chem. Soc.*, **33**, 270 (1936)).

(2) J. B. Lindsey and B. Tollens, *Ann.*, **267**, 341 (1892).

(3) R. D. Haworth, *J. Chem. Soc.*, 448 (1942).

(4) F. E. Brauns, *J. Org. Chem.*, **10**, 216 (1945).

(5) I. A. Pearl, *ibid.*, **10**, 219 (1945).

(6) P. Swartling, *Proc. 12th Intern. Dairy Congr.* (*Stockholm*), **2**, 375 (1949); *C. A.*, **44**, 2664 (1950).

(7) G. S. Fisher, L. Kyame and W. G. Bickford, *J. Am. Oil Chemists' Soc.*, **24**, 340 (1947).

(8) R. N. Moore and W. G. Bickford, *ibid.*, **29**, 1 (1952).

(9) H. B. Lackey, W. W. Moyer and W. M. Hearon, *Tappi*, **32**, 469 (1949).

(10) H. B. Lackey (to Crown Zellerbach Corporation), U. S. Patent 2,577,470, December 4, 1951.

(11) W. M. Hearon, H. B. Lackey and W. W. Moyer, THIS JOURNAL, **73**, 4005 (1951).

(12) W. M. Hearon and V. V. Jones (to Crown Zellerbach Corporation), U. S. Patent 2,610,970, September 16, 1952.

(13) W. M. Hearon (to Crown Zellerbach Corporation), U. S. Patent 2,612,508, September 30, 1952.

(14) J. L. Hartwell and W. E. Detty, THIS JOURNAL, **72**, 246 (1950).

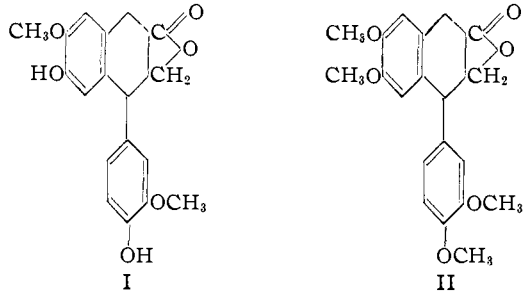
(15) J. L. Hartwell and A. W. Schrecker, Paper No. 5 presented before the Division of Medicinal Chemistry at the 117th Meeting of the American Chemical Society, Philadelphia, Pa., April 10, 1950.

(16) J. L. Hartwell, THIS JOURNAL, **69**, 2918 (1947).

(17) J. L. Hartwell and W. E. Detty, *ibid.*, **70**, 28 (1948).

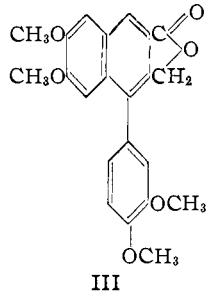
transformation products of conidendrin of considerable interest. The present paper reports a short series of nitrogenous derivatives of this substance.

Because Hearon and co-workers[11] reported that ammonia or primary amines convert conidendrin to a stereoisomer called by them β-conidendrin and identified with a substance isolated by Holmberg[18] by treatment of conidendrin with alcoholic sodium ethoxide, it appeared to us desirable to eliminate stereochemical considerations by working with a completely aromatized compound. For protection of the phenolic hydroxyl groups conidendrin was converted to its dimethyl ether (II) by the procedure of Holmberg and Sjöberg.[19] II has been dehydrogenated to the completely aromatic naphthalene derivative (III) by both selenium and lead tetraacetate[20]; with the former, however, the yield was quite poor, and the latter reagent, while giving a 70% yield of product, has certain objections if appreciable-sized amounts are employed. Recourse was had to the use of chloranil[21] for this de-



I

II



III

hydrogenation, which was carried out, giving an excellent yield of dehydromethylconidendrin (III). In contrast to I, which was reported by Holmberg[18] to yield an amide of the hydroxyacid when a suspension of it was shaken with concentrated ammonia, III underwent no reaction under these conditions; neither did it react with *n*-propylamine in chloroform solution at room temperature, nor with morpholine at the reflux temperature of the latter. Since Bistrzycki and Schmutz[22] had found phthalide to react with the strongly basic ethylenediamine, III was refluxed with this amine in ethanol–chloroform; the only product was a higher-melting polymorphic form of III, which an experiment showed could be obtained from III and the solvent alone upon prolonged refluxing. III and *n*-butylamine similarly yielded the same substance. As a matter of fact, subsequent preparations of III from II frequently led to the higher melting form during simple recrystallization.

Since III did not react with amines directly, it was hoped that the acid chloride or ester prepared from the hydroxy acid corresponding to the lactone III would prove suitable for this purpose. Whereas the hydroxy acids corresponding to both I[18] and II[19] could be isolated and easily converted back to I and II, that corresponding to III tended to reform the lactone so readily that it could not even be isolated from its solution in alcoholic 1 *N* potassium hydroxide. Saturated aliphatic γ-lactones are converted into ethyl esters of γ-hydroxy acids by treatment with thionyl chloride in benzene, followed by decomposition with alcohol[23]; III, however, was recovered unchanged after four hours refluxing with thionyl chloride in benzene or xylene; after two hours heating at 70° with PCl_5 in xylene[24] the material was largely unchanged, but did yield a small amount of dichloroester. In an attempt to prepare the ethyl ester of the hydroxy acid by treatment of the silver salt of the hydroxy acid (precipitated by adding aqueous silver nitrate solution to an aqueous solution of the potassium salt of the hydroxy acid) with ethyl iodide in toluene suspension, there was ready formation of silver iodide, but the only organic reaction product isolable was III; either the lactone linkage reformed during the metathesis or the ester formed very readily lost a molecule of ethanol to give the lactone.

In view of the difficulties encountered in obtaining derivatives of dehydromethylconidendrin (III) it was decided to study the reaction of methylconidendrin (II) with amines, despite possible stereochemical complications, since Holmberg's abovementioned conversion of I to an amide indicated that the less rigid hydroaromatic system was more amenable to reaction of the lactone. Under appropriate conditions, either standing for a number of days at room temperature or refluxing for a day or two in a solvent, II underwent reaction with ammonia and amines to give the amides (IV) listed in Table I. In most cases the unreacted II was recovered unchanged, although in three cases the reactions with diethanolamine, diethylamine and piperidine there was recovered the "β-dimethyl lactone" described by Holmberg and Sjöberg[19] as obtained by treating their "α-dimethyl lactone" or, as we call it, methylconidendrin, with sodium ethoxide; it should be noted here that with diethylamine the β-lactone was the only product; no amide was isolated. Since the inversion could also be effected by autoclaving II at 200° in ethanol with sulfuric acid catalyst it is considered probable that the α- and β-methylconidendrins are diastereomers differing only in the configuration of the carbon adjacent to the carbonyl group. Since Haworth's conclusions[3] that the carboxyl and hydroxymethyl

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

(19) B. Holmberg and M. Sjöberg, *ibid.*, **54**, 2406 (1921).

(20) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935).

(21) (a) R. T. Arnold and C. J. Collins, THIS JOURNAL, **61**, 1407 (1939); (b) R. T. Arnold, C. J. Collins and W. Zenk, *ibid.*, **62**, 983 (1940); (c) B. M. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945); (d) H. M. Crawford and H. B. Nelson, THIS JOURNAL, **68**, 134 (1946).

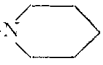
(22) A. Bistrzycki and W. Schmutz, *Ann.*, **415**, 1 (1918).

(23) P. Barbier and R. Locquin, *Bull. soc. chim.*, **13**, 223 (1913) [*J. Chem. Soc.*, **104**, I, 336 (1913)].

(24) Phthalide at 100–150° with PCl_5 was reported by E. Vongerichten, *Ber.*, **13**, 417 (1880), to give 1,1,3,3-tetrachlorophthalan.

TABLE I

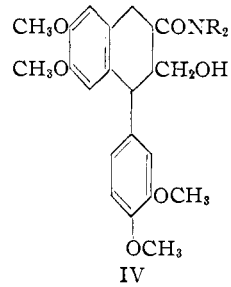
METHYLCONIDENDRIN AMIDES, R'CONR$_2$

-NR$_2$	M.p., °C.	$[\alpha]^{25}D$ 1% in $CHCl_3$	Preparative method and time	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
-NH_2	189–191	....	A, 2 wk.	96	$C_{22}H_{27}NO_6$	65.84	65.70	6.78	6.58	3.49	3.37
-$N(CH_3)_2$	232–233	+39°	B, 2 wk.	84	$C_{24}H_{31}NO_6$	67.11	66.73	7.28	7.13		
-NHC_3H_7-*n*	183–186	+62	C, 48 hr.	84	$C_{25}H_{33}NO_6$	67.70	67.92	7.50	7.63	3.16	3.24
-NHC_3H_7-*i*	199–201	+48	C, 48 hr.	7	$C_{25}H_{33}NO_6$	67.70	67.30	7.50	7.63	3.16	3.34
-$NHC_{12}H_{25}$-*n*	158	+50	C, 48 hr.	78	$C_{34}H_{51}NO_6$	71.67	71.71	9.02	9.25	2.46	2.57
-$N(CH_2CH_2OH)_2$	176–177	−143	C, 24 hr.	32	$C_{26}H_{35}NO_8$	63.63	63.50	7.40	7.34	2.86	2.98
	204–205	+38	C, 8 hr.	45	$C_{27}H_{35}NO_6$	69.15	69.25	7.52	7.69	2.99	2.71
	221–222	+50	C, 8 hr.	74	$C_{26}H_{33}NO_7$	66.18	65.95	7.05	6.70	2.97	3.11
-$NHCH_2CH_2NH_2 \cdot H_2O$	182–183	....	D	42	$C_{24}H_{32}N_2O_8 \cdot H_2O$	62.32	62.11	7.41	7.20	6.07	6.33
-NHC_6H_5	119–121	+22	E	63	$C_{28}H_{31}NO_5$	70.42	70.35	6.54	6.53		

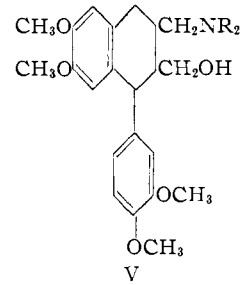
groups in *l*-conidendrin are *trans* appear to be valid, having been recently further strengthened by the lithium aluminum hydride reduction of α-methylconidendrin to the glycol, (+)-isolariciresinol dimethyl ether, by Haworth and Wilson,[25] this would indicate that the conversion of one form to the other occurs with transformation of the latent carboxyl group from the *trans* to the *cis* configuration relative to the latent hydroxymethyl group. This is in contradistinction to the opinion of White[26] who concluded that the differences in the infrared spectra of α- and β-conidendrin indicated that there must be some marked difference between them. Spearin,[27] on the other hand, made the same measurements and failed to arrive at the same conclusions. While the curves presented by the above-mentioned authors are hardly identical, it is apparent that each contains the expected hydroxyl band around 3.0 μ and the lactone carbonyl band at about 5.8 μ. In a recent paper, Schrecker and Hartwell[28] discuss the infrared spectra of two pairs of diastereoisomers in the desoxypodophyllotoxin series and clearly show that isomerization of the lactone ring from *trans* to *cis* results in a shift of the carbonyl band to a longer wave length. In the light of this fact, any apparent difference of interpretation by White and Spearin becomes resolved, and both would be in agreement with Haworth.

A final attempt to prepare amides corresponding to III was by the chloranil dehydrogenation of the amides corresponding to II; in the unsubstituted amide, the only product isolated from the reaction mixture was III itself; presumably, as with the ethyl ester described above, the tendency toward lactone formation was sufficiently great, after the nucleus had been aromatized, that a molecule of ammonia was intramolecularly eliminated. In the case of the morpholide and piperidide corresponding to II, the heterocyclic amine portion of the molecule was attacked preferentially to the carbocyclic nucleus by the chloranil, with resultant formation of methylconidendrin.

It was possible, however, to reduce the amides (IV) prepared from II to the corresponding amines (V) by means of lithium aluminum hydride, which has been previously used[29] for similar conversions.



IV



V

Biological Activity.—Tests at the Sloan–Kettering Institute for Cancer Research under the direction of Dr. C. Chester Stock showed that, despite preliminary promising data, none of these compounds had any definite activity against Sarcoma 180.

Experimental[30,31]

Dehydromethylconidendrin (III).—A solution of methylconidendrin (II) (m.p. 179°, prepared in 95% yield by the procedure of Holmberg and Sjöberg[19]) (38.4 g., 0.10 mole) and chloranil (49.1 g., 0.20 mole) in xylene (200 ml.) was refluxed ten hours, at which time chloranil was shown to be absent by failure of the solution to give a red color when one drop was boiled with 10% sodium hydroxide.[21c] The solution was allowed to cool to room temperature and the precipitated solid (26.3 g.) was removed by filtration; after recrystallization from 9:1 ethanol–chloroform (vol./vol.) it melted at 216–217°, in agreement with the literature.[32] Removal of the xylene from the filtrate, followed by mixing thoroughly with methanol and filtering, gave 10.2 g. of unchanged (m.p. 170–173°) methylconidendrin; thus, in the dehydrogenation reaction, although the conversion was only 68%, the yield on consumed starting material was 93%.

After the higher-melting form, m.p. 227–228°, had been obtained in this Laboratory, this form usually resulted from its preparation or recovery.

Anal. Calcd. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.32; H, 5.21.

(25) R. D. Haworth and L. Wilson, *J. Chem. Soc.*, 71 (1950); the reverse transformation, the oxidation of (+)-isolariciresinol dimethyl ether to *l*-conidendrin dimethyl ether, thereby first relating the two substances stereochemically, had been previously reported by Haworth in *J. Chem. Soc.*, 384 (1937).

(26) J. U. White, *Anal. Chem.*, **22**, 768 (1950).

(27) W. E. Spearin, *J. Org. Chem.*, **15**, 984 (1950).

(28) A. W. Schrecker and J. L. Hartwell, THIS JOURNAL, **75**, 5916 (1953).

(29) J. Ehrlich, *ibid.*, **70**, 2286 (1948); R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948); A. Uffer and E. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

(30) Melting points are uncorrected.

(31) Microanalyses were carried out under the direction of Dr. F. A. Buhler.

(32) R. D. Haworth and T. Richardson, *J. Chem. Soc.*, 633 (1935).

The true polymorphism of the two forms was demonstrated by their interconversion, on seeding a solution of each with the other.

Reaction of Dehydromethylconidendrin with PCl_5.—A mixture of dehydromethylconidendrin (1.90 g., 5 millimoles), phosphorus pentachloride (1.75 g., 6 millimoles) and xylene (30 ml.) was stirred for two hours at 70°, then cooled and filtered to give back 1.6 g. of unchanged dehydromethylconidendrin, m.p. 200–201°. Removal of the solvent from the filtrate followed by treatment of the residue with hot ethanol (to destroy any remaining PCl_5 and to convert any acid chloride to the ethyl ester) gave on cooling 170 mg. of material, m.p. 212–214°, which gave analytical data for a dichloroester.

Anal. Calcd. for $C_{24}H_{24}Cl_2O_6$: Cl, 14.82. Found: Cl, 14.78.

Preparation of Amides from Methylconidendrin and Ammonia. Method A.—A suspension of methylconidendrin (19.2 g., 0.05 mole) in concentrated aqueous ammonia (250 ml.) was stirred two weeks at room temperature. Filtration gave 19.3 g. (96% yield) of material, m.p. 183° dec., which after recrystallization from absolute ethanol had m.p. 189–191°.

Dimethylamine. Method B.—Methylconidendrin (19.2 g., 0.05 mole) was added to a solution of dimethylamine (11.3 g., 0.25 mole) in chloroform (250 ml.) and the mixture was allowed to stand two weeks. After removal of the solvent and trituration with ethanol there was obtained, in three crops, 18.0 g. (84% yield) of amide which melted, after recrystallization from absolute alcohol, at 232–233° dec.

Isopropylamine. Method C.—A mixture of methylconidendrin (19.2 g., 0.05 mole), isopropylamine (15.0 g., 0.25 mole) and chloroform (250 ml.) was refluxed eight hours. Concentration of the reaction mixture gave 13.1 g. (68%) of unchanged starting material in the first crop and 1.7 g. (7.6% yield) of product which, after recrystallization from 95% ethanol, melted at 199–201°.

Ethylenediamine. Method D.—A mixture of methylconidendrin (19.2 g., 0.05 mole) and ethylenediamine (7.5 g., 0.125 mole, 12 ml. of 70% aqueous solution) in chloroform (250 ml.) was refluxed 8 hours and then allowed to stand 17 days at room temperature. After removal of the solvent under vacuum the semi-crystalline residue was recrystallized from ethanol to give 9.6 g. (42% yield), m.p. 182–183° after recrystallization from aqueous alcohol.

Aniline. Method E.—A mixture of methylconidendrin (96 g., 0.25 mole) and aniline (116 g., 1.25 moles) in chloroform was refluxed 48 hours, the solvent was removed and the residue was heated six hours in an oil-bath at 190–200° and then subjected to steam distillation to remove unchanged aniline. Crystallization of the steam distillation residue from ethanol gave in two crops, 75.2 g. (63% yield) of product which melted at 119–121°, after recrystallization from methanol.

Inversion of Methylconidendrin to β-Methylconidendrin.—A mixture of methylconidendrin (7.7 g., 0.02 mole), absolute ethanol (2.5 ml.) and concentrated sulfuric acid (one drop) was heated in a glass-lined pressure vessel for four hours at 180–200°. The cooled reaction mixture was dissolved in chloroform, washed with 2% sodium bicarbonate solution, the solvent removed and the residue crystallized from 95% ethanol to give 4.3 g. of material, m.p. 128–133°. Another crystallization gave 2.6 g., m.p. 138–139°, reported[19] m.p. 142–143°.

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.77; H, 6.19.

Chloranil Dehydrogenation of β-Methylconidendrin.—A mixture of β-methylconidendrin, m.p. 138–139° (4.52 g., 0.0118 mole) and chloranil (4.91 g., 0.02 mole) in xylene (20 ml.) was refluxed 16 hours, at which time a negative test for chloranil was obtained. The material filtered from the cooled reaction mixture weighed 2.4 g. and after recrystallization from ethanol–chloroform melted at 229–231°, alone or mixed with dehydromethylconidendrin prepared from α-methylconidendrin.

Chloranil Dehydrogenation of Methylconidendrin Amide. A mixture of the amide (2.0 g., 0.005 mole), chloranil (2.45 g., 0.01 mole) and xylene (10 ml.) was refluxed 18 hours and the solvent was removed under vacuum. The alcohol-insoluble portion of the residue (1.2 g.), after recrystallization from alcohol, gave a negative test for nitrogen (sodium fusion), melted at 218–219° and did not depress the melting point of dehydromethylconidendrin.

Chloranil Dehydrogenation of Methylconidendrin Piperidide.—After a mixture of methylconidendrin piperidide (4.70 g., 0.01 mole), chloranil (4.91 g., 0.02 mole) and xylene (20 ml.) had been refluxed 8 hours (negative test for chloranil) the solvent was removed under vacuum, the residue was slurried with ethanol and filtered. The material (2.1 g.) after two recrystallizations from alcohol, melted at 179–180°, undepressed when mixed with methylconidendrin.

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.50; H, 6.44.

$LiAlH_4$ Reduction of Methylconidendrin Morpholide.—Powdered $LiAlH_4$ (1.14 g., 0.03 mole) was dissolved in tetrahydrofuran (500 ml., dried and then distilled over sodium) contained in a one-liter three-necked flask equipped with a stirrer and Soxhlet extraction apparatus and maintained an atmosphere of dry nitrogen. Methylconidendrin morpholide (9.43 g., 0.02 mole) had been placed in the extraction thimble prior to solution of the hydride so that as the tetrahydrofuran was refluxed it gradually dissolved the amide and washed it down into the reaction flask. After 20 hours refluxing the amide was all dissolved. Excess reagent and lithium complexes were decomposed by careful addition of cold, saturated aqueous ammonium chloride (5 ml.) and the resultant salts were removed by filtration. Removal of the solvent from the filtrate and crystallization of the residue from 25% ethanol gave 7.1 g. (77% yield) of amine which after recrystallization from methanol melted at 138–141°.

Anal. Calcd. for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 67.98; H, 7.52; N, 3.07.

Treatment of the base with dry HCl in ethanol–ether gave the hydrochloride, m.p. 239–241°, $[\alpha]^{25}D$ +10° (1% in H_2O).

Anal. Calcd. for $C_{26}H_{36}ClNO_6$: Cl, 7.18. Found: Cl, 7.13.

When the amine was treated with excess methyl iodide in boiling benzene for three hours an oily methiodide resulted. This was obtained as an amorphous solid which did not melt sharply.

$LiAlH_4$ Reduction of Methylconidendrin Piperidide.—By the technique described above methylconidendrin piperidide (18.6 g., 0.04 mole) gave 16.9 g. (92% yield) of amine, which after recrystallization from ethyl acetate melted at 148–150°.

Anal. Calcd. for $C_{27}H_{33}NO_5$: C, 71.18; H, 8.19; N, 3.07. Found: C, 70.93; H, 8.14; N, 3.18.

The hydrochloride, prepared as above, melted at 247–248°, $[\alpha]^{25}D$ +15° (1% in H_2O).

Anal. Calcd. for $C_{27}H_{35}ClNO_5$: Cl, 7.21. Found: Cl, 7.41.

Similarly, this amine gave an oily methiodide which could be lyophilized to an amorphous solid.

$LiAlH_4$ Reduction of Methylconidendrin *n*-Propylamide.—To a solution of $LiAlH_4$ (3.8 g., 0.10 mole) in tetrahydrofuran (250 ml.) there was added at reflux temperature a solution of methylconidendrin *n*-propylamide (22.2 g., 0.05 mole) in tetrahydrofuran (600 ml.). The mixture was refluxed for two hours, then cooled and decomposed with saturated ammonium chloride solution (15 ml.). This mixture was filtered and the solvent was evaporated from the filtrate under vacuum. This residue, which weighed 21 g., was crystallized from ethyl acetate giving 6 g. of starting amide (m.p. 182–184°). Evaporation of the mother liquor followed by successive crystallizations from moist ethyl acetate, carbon tetrachloride, methanol–Skelly B and isopropyl alcohol gave 7 g. of still impure amine. This was treated with dry HCl in ethanol–ether and the crude hydrochloride was recrystallized from ethanol (200 ml.). The product melted at 231–232°, $[\alpha]^{25}D$ +17° (1% in H_2O), and weighed 4.6 g.

Anal. Calcd. for $C_{25}H_{36}O_5NCl$: C, 64.42; H, 7.79; N, 3.01; Cl, 7.61. Found: C, 64.67; H, 7.78; N, 3.25; Cl, 7.80.

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