hexagonal, monomeric form) reacts with water in a violent manner, the polymeric forms react much more slowly with water, yielding suspensions and gels of varied polymeric composition.[2] Bearing in mind the presence of nucleosides in the nucleic acids, their behavior toward water is somewhat similar to that of the polymeric forms of "P_2O_5."

The *polymerized* acids are generally agreed to be tetra-basic per four phosphorus atoms.[22-25] That is, every phosphorus atom carries a primary titratable dissociation. As shown in Figs. 1 and 2, every phosphorus atom in the proposed formula is bound, in addition to the –O-nucleoside linkage, to a hydroxyl group, which would yield a primary dissociation.

Due to the heterogeneous nature of the degradation products, many titration results, reporting the existence of varying numbers of primary and secondary dissociations per four phosphorus atoms, represent meaningless averages.[26]

(22) J. M. Gulland, *J. Chem. Soc.*, 1722 (1938).
(23) F. W. Allen and J. J. Eiler, *J. Biol. Chem.*, **137**, 757 (1941)
(24) E. Hammarsten, *Biochem. Z.*, **144**, 383 (1924).
(25) Z. Makino, *Z. physiol. Chem.*, **236**, 201 (1935); **232**, 229 (1935).
(26) F. Schlenk, *Advances in Enzymol.*, **9**, 512 (1949).

The proposed formula permits any sequence and ratio of nucleosides and need not conform to the "tetranucleotide" concept, which has been challenged by Gulland, *et al.*,[27]

Astbury[11] offers data which indicates that ribose-nucleic acids and the desoxyribose varieties are very similar in structure. By replacing the uridine nucleoside in Fig. 1 by any nucleoside common to desoxyribose nucleic acids, the proposed structure is converted from the ribose to the desoxyribose types.

The recent work of Carter[28] points toward the establishment of C(5) as the site of the *one* phosphosugar ester link per nucleoside in thymus desoxyribonucleic acid. However, C(3) is still not excluded as a point of linkage and in some desoxyribose nucleic acids a portion of the nucleosides may be linked at C(5) while the others are at C(3).

Finally, the author wishes to express his appreciation to Drs. C. A. Knight and Frederick H. Carpenter for their criticism of this paper.

(27) J. M. Gulland, D. O. Jordan and C. J. Threlfall, *J. Chem. Soc.*, 1129 (1947).
(28) C. E. Carter, THIS JOURNAL, **73**, 1537 (1951).

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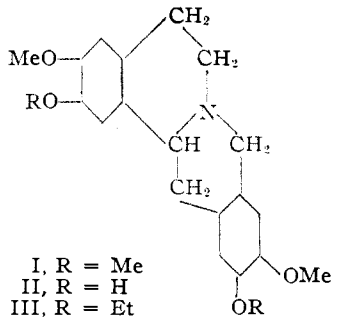
[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO. LTD.]

The Alkaloids of Fumariaceous Plants. XLVII. The Structure of Coreximine

BY RICHARD H. F. MANSKE AND WALTER R. ASHFORD

Coreximine has been shown to be 2,9-dimethoxy-3,8-dihydroxytetrahydroprotoberberine by a synthesis of its O,O-diethyl ether which was identical with the racemized diethyl ether of the natural alkaloid.

Coreximine has recently been shown to yield norcoralydine (I) on O-methylation with diazomethane.[1] Since it contains two hydroxyls, four structures are possible if vicinal hydroxyls are excluded. It was relatively easy to locate the position of the hydroxyl in the upper left hand



I, R = Me
II, R = H
III, R = Et

nucleus shown in the formula (I). Mild oxidation of the O,O-diethyl ether with permanganate yielded 1-keto-6-methoxy-7-ethoxytetrahydroisoquinoline. One of the hydroxyls in coreximine is therefore in the 7-position of the isoquinoline systems. Further oxidation however could yield only 4-methoxy-5-ethoxyphthalic acid regardless of the location of the original hydroxyls and this acid was the only one obtained experimentally.

(1) R. H. F. Manske, THIS JOURNAL, **72**, 4796 (1950).

There remained therefore only two possible structures for coreximine and it seemed most probable that ring closure of the benzylisoquinoline by condensation with a formaldehyde equivalent would only proceed if the hydroxyl were para to the position of attack. On this basis coreximine should be II and this supposition was confirmed by a synthesis of the compound III, which proved to be identical with a specimen of racemized coreximine O,O-diethyl ether.

The synthesis followed the well-known routes by which benzylisoquinolines may be obtained. The necessary β-dialkoxyphenethylamine is a well known compound[2] and was prepared by the details given by Fluchaire and Chambret[3] and the 3-ethoxy-4-methoxyphenylacetic acid[4] was prepared by a series of reactions detailed by Kindler and Peschke[5] for the dimethoxy analog. The combination of these two fragments to the necessary amide prior to ring closure was effected in quantitative yield by heating them in tetralin[6] and the subsequent reactions leading to 1-(3-ethoxy-4-methoxybenzyl) - 6 - methoxy - 7 - ethoxytetrahydroisoquinoline and the final ring closure with form-

(2) G. Barger, J. Eisenbrand, L. Eisenbrand and E. Schlittler, *Ber.*, **66**, 450 (1933).
(3) Fluchaire and F. Chambret, *Bull. soc. chim.*, **11**, 22 (1944).
(4) E. Späth and K. Tharrer, *Ber.*, **66**, 583 (1933).
(5) H. Kindler and W. Peschke, *Arch. Pharm.*, **271**, 431 (1933).
(6) B. I. O. S. No. 766, pl. 124.

aldehyde[7] proceeded with satisfactory or nearly quantitative yields.

Experimental

1-Keto-6-methoxy-7-ethoxytetrahydroisoquinoline.—The non-phenolic base resulting from the treatment of coreximine (0.3 g.) with an excess of diazoethane was dissolved in dilute hydrochloric acid, treated with aqueous sodium bicarbonate until the turbidity was just permanent and then treated in the cold with an aqueous solution of potassium permanganate (0.55 g.). When the oxidant had disappeared the heated mixture was filtered, cooled, and exhausted with ether. (The aqueous solution on further oxidation with permanganate yielded only 4-methoxy-5-ethoxyphthalic acid identified as its N-ethylimide, m.p. and mixed m.p. 205°.[8]) Even while the ether was distilling the *corydaldine* began to crystallize. When washed with a little ether it melted without further purification at 193° either alone or admixed with an authentic specimen.[9]

3-Methoxy-4-ethoxyphenethylamine.—3-Methoxy-4-ethoxyphenylacetonitrile[5] was reduced by the method of Fluchaire and Chambret.[3] For this purpose the nitrile (19.1 g.) in ethanol (160 cc.) containing sodium hydroxide (0.25 g.) was hydrogenated at 50 lb. pressure with Raney nickel (20 g.). Reduction was complete in 2.5 hr. The amine was isolated by conventional methods and distilled, b.p. 120–125° (1–2 mm.). The yield was quantitative. It formed a picrate which melted at 187° and was identical with that prepared by another route.[10]

3-Ethoxy-4-methoxy-mandelonitrile benzoate was prepared by stirring a mixture of 3-ethoxy-4-methoxybenzaldehyde (237 g.), benzoyl chloride (226 g.), ether (325 cc.) and potassium cyanide (113 g.) in water (325 cc.) at 5 to 15° for 2 hr.[5] The **benzoate** separated as a crystalline solid (260 g.) which when recrystallized from dilute methanol melted at 72°. *Anal.* Calcd. for $C_{18}H_{17}O_4N$: C, 69.45; H, 5.34. Found: C, 69.40, 69.24; H, 5.66, 5.62. A further small amount of it was obtained when the ether filtrate was again treated with benzoyl chloride (22 g.) and an equivalent amount of potassium cyanide.

3-Ethoxy-4-methoxyphenylacetic Acid.—A suspension of palladium-on-charcoal (10 g.) prepared from palladium chloride (1 g.) and nitric-acid washed charcoal (20 g.) in tetralin (100 cc.) was boiled until the water was entirely removed. A solution of the above benzoate (100 g.) in tetralin (400 cc.) was introduced and the mixture boiled under reflux in a carbon dioxide atmosphere for 2 hr. The catalyst was separated by decanting the cooled solution which was then washed with aqueous sodium carbonate to remove the benzoic acid. Three such runs were combined, the tetralin removed by distillation through a 24-inch Vigreux column, and the residue distilled *in vacuo*, b.p. 130–135° (1 mm.). The pale yellow oil thus obtained in 45% yield did not crystallize. It (47.5 g.) was directly hydrolyzed by boiling with potassium hydroxide (37 g.) in water (37 g.) and ethanol (150 cc.) until a test portion remained clear on the addition of water. The alcohol was then distilled off and the somewhat diluted residue extracted several times with ether. The addition of hydrochloric acid to the clear aqueous solution precipitated an oil which readily solidified; yield quantitative. A portion recrystallized from hot water and dried *in vacuo* melted at 69°.[4]

1-(3-Ethoxy-4-methoxybenzyl)-6-methoxy-7-ethoxy-3,4-dihydroisoquinoline.—The following is an adaptation of the procedure detailed in British Intelligence Objectives Subcommittee Reports (B.I.O.S.)[6] and is given in full because these reports are not always accessible. A mixture of 3-ethoxy-4-methoxyphenylacetic acid (2.0 g.) and β-3-methoxy-4-ethoxyphenethylamine (1.9 g.) in tetralin (10 cc.) was boiled slowly until it had lost half of the tetralin (30 min.). Most of the remainder was then removed *in vacuo*. The cooled residue was triturated with hexane (*ca.* 50 cc.) until it became crystalline. It was then separated by filtration and washed with hexane. The yield was quantitative. A specimen was recrystallized from a large volume of ether containing a little methanol and the **3-ethoxy-4-methoxyphenylacet-3-methoxy-4-ethoxyphenethylamide** thus obtained melted sharply at 95°. *Anal.* Calcd. for $C_{22}H_{29}O_5N$: C, 68.22; H, 7.49. Found: C, 68.03; H, 7.42.

The yield in the ring closure step is not increased when the intermediate amide is separately purified. The tetralin solution resulting from the amide step was heated to boiling on a steam-bath with benzene (20 cc.) and a solution of phosphorus oxychloride (4 g.) in benzene (10 cc.) added in the course of 15 min. Most of the benzene was then allowed to distil off during another 30 min. of heating and the somewhat cooled mixture decomposed with dilute (2%) hydrochloric acid. The aqueous separated layer was washed with several portions of ether, basified with excess ammonia, and the liberated base taken up in ether. The residue from the ether extract weighed about 3.0 g. (80% over-all yield) and solidified completely. A portion of the **dihydroisoquinoline** recrystallized from ether was obtained in fine colorless needles melting at 87°. *Anal.* Calcd. for $C_{22}H_{27}O_4N$: C, 71.54; H, 7.32. Found: C, 71.08, 71.09; H, 7.27, 7.37.

1-(3-Ethoxy-4-methoxybenzyl)-6-methoxy-7-ethoxytetrahydroisoquinoline.—The above dihydroisoquinoline (1.9 g.) was heated on a steam-bath for 8 hr. with tin (4 g.), hydrochloric acid (8 cc.) and methanol (10 cc.), then diluted with hot water (50 cc.) and the dissolved tin precipitated onto granulated zinc. The filtered solution was basified with excess ammonia and the liberated base taken up in ether. The colorless residue (1.4 g.) from the ether extract solidified slowly and when recrystallized from dry ether–hexane the **tetrahydroisoquinoline** was obtained in colorless fine plates which melted at 101°. *Anal.* Calcd. for $C_{22}H_{29}O_4N$: C, 71.16; H, 7.80. Found: C, 71.29; H, 7.80.

***dl*-Coreximine O,O-Diethyl Ether (III) (a).**—A solution of the above tetrahydroisoquinoline (1.2 g.) in 12% hydrochloric acid (10 cc.) was heated on the steam-bath for one hour during which time methylal (2 cc.) was added in small portions.[7] Some of the solvent was removed *in vacuo* and the residue solution diluted to 25 cc. A turbidity was dispelled by the dropwise addition of methanol and the sparingly soluble hydrochloride which then formed was separated by filtration. The *base* which was regenerated from this salt crystallized in sparingly soluble stout polyhedra as its ether solution was evaporated. When recrystallized from chloroform–methanol it melted sharply at 170° and when admixed in varying proportions with *dl*-coreximine O,O-diethyl ether obtained from coreximine the mixture melted at 169–170°. *Anal.* Calcd. for $C_{23}H_{29}O_4N$: C, 72.06; H, 7.57. Found: C, 72.02; H, 7.55.

The picrates crystallized from methanol–ether, from the two sources melted either alone or in admixture at 131°. *Anal.* Calcd. for $C_{29}H_{32}O_{11}N_4$: N, 9.15. Found: N, 9.06.

(b).—Coreximine O,O-diethyl ether[11] was oxidized in methanol solution with an excess of iodine in the presence of sodium acetate. The mixture was then reduced with zinc and hydrochloric acid until a colorless solution resulted. The base recovered by ether extraction of the basified solution crystallized as the solvent was being evaporated. When recrystallized once from chloroform–methanol it consisted of stout prisms melting at 169°.

1-(3-Ethoxy-4-methoxybenzyl)-2-methyl-6-methoxy-7-ethoxytetrahydroisoquinoline.—A solution of the dihydroisoquinoline (1.5 g.) in a little warm methanol was treated with ether (20 cc.) and methyl iodide (2 cc.). The pale yellow stout prisms (m.p. 200°) that separated in quantitative yield were dissolved in 50% acetic acid (50 cc.) and heated on a steam-bath for 5 hr. with an excess of granulated zinc and enough hydrochloric acid to cause evolution of hydrogen. The base, recovered from the colorless solution, was a clear resin which did not crystallize in contact with a number of solvents. **The hydrochloride** was obtained in stout colorless prisms, m.p. 178°, when crystallized by the addition of ether to a methanolic solution. *Anal.* Calcd. for $C_{23}H_{31}O_4N \cdot HCl$: C, 65.48; H, 7.59. Found: C, 65.41; H, 7.61.

The methiodide did not crystallize in contact with a number of solvents but when heated with aqueous potassium hydroxide readily yielded a crystalline **methine** which was sparingly soluble in ether and only moderately soluble in cold methanol from which it was crystallized, m.p. 144°. *Anal.* Calcd. for $C_{24}H_{33}O_4N$: N, 3.51. Found: N, 3.71.

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(8) All melting points are corrected.

(9) J. Gadamer, E. Späth and E. Mosetting, *Arch. Pharm.*, **265**, 683 (1927).

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