The Alkaloids of the *Amaryllidaceae*. XIV.[1] Hofmann Degradation of Albomaculine

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The Hofmann degradation of albomaculine is shown to give 3,4-dimethoxy-5-hydroxy-3′-vinylbiphenyl (II, R = OH; R′ = CH=CH$_2$) directly. The conversion of the biphenyl (II, R = OH; R′ = CH=CH$_2$) to 3,4,5-trimethoxy-3′-biphenylcarboxylic acid (II, R = OMe, R′ = CO$_2$H) and the synthesis of the latter are described. The results are interpreted as providing evidence for the structure of albomaculine (I, R = OMe).

Our recent interest[3] in the aromatic oxygenation patterns of trioxyaryl *Amaryllidaceae* alkaloids of the hemiacetal and lactone series[4] led us to carry out chemical studies[5] concurrently with proton magnetic resonance (p.m.r.) spectral investigations. The results of the chemical investigation with the lactone alkaloid, albomaculine (I, R = OMe), are reported in this paper.

The choice of this comparatively rare *Amaryllidaceae* alkaloid rather than the more readily accessable lactone or hemiacetal bases of this family was determined by several considerations. Important among these was the fact that at the time of our investigation the structure proposed[4,6] for albomaculine rested on a knowledge of the functional groups present, and on infrared and ultraviolet spectral data, which had permitted the assignment of the three methoxyl groups to the aromatic ring and indicated the presence of an aryl conjugated lactone. Based on these preliminary findings, Wildman and co-workers[6] suggested the tentative structure I (R = OMe)[7] on the assumption that albomaculine possessed the same ring system as homolycorine (I, R = H).

Our primary goals, therefore, were to obtain evidence both for the presence of the homolycorine-type ring system and for the position of the aromatic oxygen functions in albomaculine. It seemed that these aims might be achieved by an appropriate stepwise degradation of albomaculine to a substituted biphenyl[8] whose structure would be amenable to a ready synthesis.

Separation of the crude alkaloid extract obtained from *Haemanthus albomaculatus*[9] and chromatography of the fraction of mixed bases having chloroform-soluble hydrochlorides afforded the lactone alkaloids, albomaculine (I, R = OMe) and homolycorine (I, R = H). In addition, a nonlactonic base was obtained which was identified as 7-O-ethyllycorenine from its p.m.r. spectrum and by its conversion to lycorenine in dilute hydrochloric acid.[10]

The conversion of albomaculine methiodide to the corresponding methohydroxide was achieved in the usual way with silver oxide. The methohydroxide decomposed slowly at 160–170° to afford (after several days) a colorless oil in low yield.[11] The infrared spectrum of the Hofmann product showed hydroxyl and aromatic absorption bands but no bands attributable to a carbonyl group. Its ultraviolet spectrum was suggestive of a biphenyl system, and the characteristic bathochromic shift of the spectrum in alkali was indicative of the presence of a phenolic hydroxyl. The phenolic character of the Hofmann product was confirmed by the preparation of a methyl ether and an acetate. Elemental analysis of these derivatives pointed to a $C_{16}H_{16}O_3$ formula.[12] This molecular formula for the product was very surprising indeed and indicated that some profound changes must have taken place in the reaction. An inspection of the p.m.r. spectrum of the methyl ether proved very informative.

The spectrum showed three- and six-proton singlets at 3.93 and 3.95 p.p.m., respectively, attributable to three aromatic methoxyl groups, and a two-proton singlet at 6.87 p.p.m., ascribable to aromatic protons adjacent to an oxygen function.[13] In addition, the characteristic 12-line ABX pattern of a vinyl group[14] was present in the olefinic region of the spectrum. A complex series of peaks in the aromatic region accounted for the remaining four hydrogens. The foregoing features of the spectrum indicate a trimethoxybiphenyl structure in which the symmetrical distribution of the three methoxyls on one ring is defined by the magnetic equivalence of the two aromatic hydrogens at 6.87 p.p.m. The complex nature of signals from the remaining aromatic protons restricts the location of the vinyl group to the 2′- or 3′-positions.[15] The position of the vinyl function would be predicted to occur at the 3′-position on the basis of the structure for albo-

(1) Part XIII: R. C. Clark, K. Pachler, and F. L. Warren, *J. Chem. Soc.*, in press.

(2) Work taken in part from a thesis submitted by T. P. Toube in partial fulfillment of the M.S. degree, University of Natal, 1961.

(3) (a) P. W. Jeffs and W. A. Hawksworth, *Tetrahedron Letters*, 273 (1963); (b) W. A. Hawksworth, P. W. Jeffs, B. K. Tidd, and T. P. Toube, *J. Chem. Soc.*, 1991 (1965).

(4) For a review of these alkaloids, see W. C. Wildman in "The Alkaloids," Vol. VI, Academic Press Inc., New York, N. Y., 1960.

(5) Unfortunately, the alkaloid albomaculine is known to occur only in the plant *Haemanthus albomaculatus* and since our departure from South Africa we have been unable to obtain further supplies of this rare botanical. This has prevented us from carrying out a more thorough investigation of the Hofmann reaction.

(6) C. K. Briggs, P. F. Highet, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 2899 (1956).

(7) In proposing this structure, the authors made the reservation that the aromatic methoxyls could be located at the alternative 9-, 10-, 11-position (*cf.* footnote 14 in ref. 6).

(8) For an example of the degradation of a hemiacetal alkaloid of this ring system to a substituted biphenyl, see H. Kondo and T. Ikeda, *Ber.*, **73**, 867 (1940).

(9) Collected in March 1961 from Isipingo Beach, Natal, South Africa. We are indebted to Mrs. M. E. von Klemperer and Mrs. E. Hughes for assistance in collecting the plant material.

(10) This compound is presumed to be an artifact produced from lycorenine in the isolation procedure. (See Experimental Section.)

(11) In a subsequent experiment the yield was raised to 30% by increasing the reaction temperature to 200°. Since this exceeds the theoretical yield of 25% on the basis of the mechanism proposed, *vide infra*, we feel that this is best explained by assuming the presence of an external base (see Experimental Section).

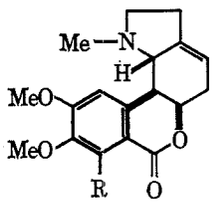
(12) The sensitivity of the Hofmann product to air oxidation precluded the obtention of reliable elemental analytical results. However, several determinations did show the absence of nitrogen in this compound.

(13) J. B. Bredenberg and J. N. Shoolery, *Tetrahedron Letters*, 285 (1961); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p. 63.

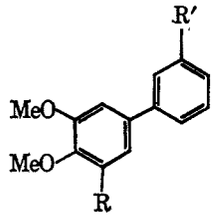
(14) W. Brugel, T. Ankel, and F. Kruckeberg, *Z. Electrochem.*, **64**, 1121 (1960).

(15) If the vinyl group had been located at the 4′-position, the four protons on ring B (ring bearing the vinyl group) would have given rise to a recognizable A_2B_2 pattern.

maculine proposed previously. To verify this, the methyl ether of the Hofmann product was oxidized with permanganate to a biphenylcarboxylic acid, m.p. 161–163°. The structure of this acid (II, R = OMe; R′ = CO_2H) was established by an unambiguous synthesis *via* an Ullmann coupling of 1-iodo-3,4,5-trimethoxybenzene[16] and methyl *m*-iodobenzoate. This synthesis constitutes proof of the structure of the Hofmann methyl ether as II (R = OMe; R′ = $CH{=}CH_2$) and provides the first chemical evidence for the orientation of the aromatic methoxyls in albomaculine (I, R = OMe).[17] It remained to de-

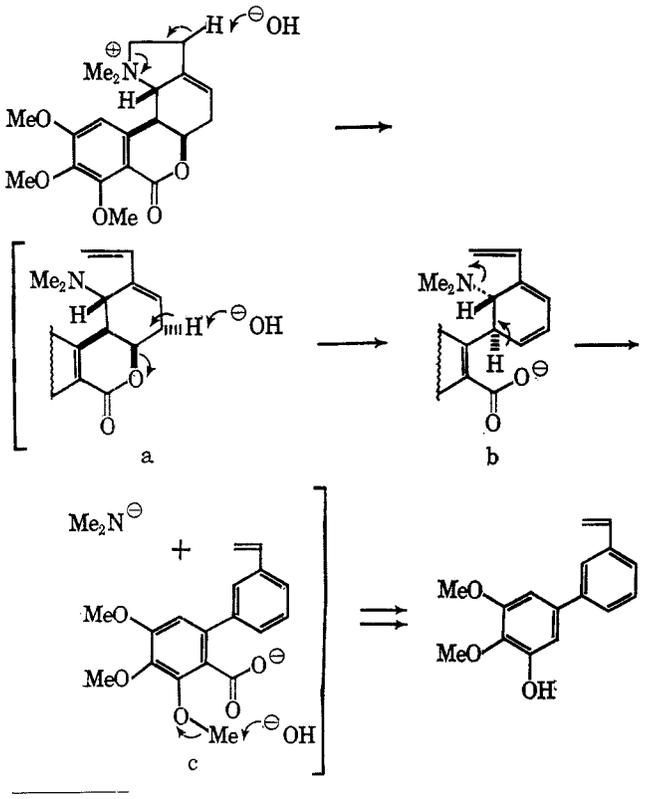


I



II

termine which of the three ring-A methoxyls had become demethylated in the course of the Hofmann degradation. The Hofmann product itself gives an azo dye on coupling with a diazonium salt, which suggests structure II (R = OH; R′ = $CH{=}CH_2$) rather than the alternative 4-hydroxy-3,5-dimethoxybiphenyl system. This was readily confirmed by the p.m.r. spectrum of the acetyl derivative in which the ring-A protons are nonequivalent, a result which is compatible only with the unsymmetrical substitution pattern of ring A as shown in structure II (R = OAc; R′ = $CH{=}CH_2$). A possible mechanism for the reaction is suggested below.



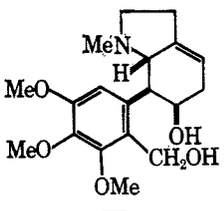
a b c

(16) C. Graebe and M. Suter, *Ann.*, **340**, 222 (1905).

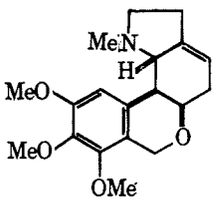
(17) Since this manuscript was prepared, a recent paper describing the Hofmann degradation and structure proof of the hemiacetal base, nerinine, has appeared: S. Ozeki, *J. Pharm. Soc. Japan.*, **85**, 206 (1965). In view of the demonstrated relationship between nerinine and albomaculine [H.-G. Boit and H. Emke, *Chem. Ber.*, **90**, 57 (1957)], this work constitutes an independent structure proof for albomaculine.

The appearance of the vinyl group in the product suggests that the first stage proceeds in the normal manner to afford the intermediate a. Abstraction of the appropriate *trans* C-4 allylic hydrogen by base with concomitant elimination of the lactone ring as a carboxylate anion may then proceed to generate the dihydrobenzene b.[18] The aromatization of ring C can now provide the necessary driving force for the elimination of the dimethylamino anion by a weaker base.[19] The appearance of the phenolic hydroxyl at the 3′-position in the product makes it impossible to say categorically whether it is the C-8 or the C-10 methoxyl in albomaculine which is selectively demethylated. However, we feel that the steric compression around the C-8 methoxyl makes it a more logical choice for demethylation under the particular experimental conditions encountered in this reaction.[20]

Finally, an unexceptional thermal decarboxylation of the intermediate phenolic acid would lead to the observed Hofmann product. The mechanistic aspects of the selective demethylation are being investigated presently with model compounds.



III



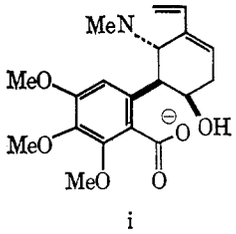
IV

The reduction of albomaculine to the known diol III[6] and the subsequent conversion of this diol by dilute acid to the cyclic ether, deoxynerinine (IV) parallel the reactions reported for homolycorine and are formulated accordingly.

Experimental Section[21]

The extraction procedure followed the general methods reported previously.[22] The crude mixture, 13.1 g., obtained by

(18) A referee has drawn our attention to the relative ease with which the lactone ring of albomaculine is opened by warm alkali. In view of this, the possibility exists that an intermediate such as i may be involved as a precursor to the dihydrobenzene b.



i

(19) The base involved in the abstraction of the benzylic hydrogen in this elimination step may be the conveniently situated carboxylate anion rather than an external hydroxide ion.

(20) The demethylation of β-dihydrothebainol methyl ether to β-dihydrothebainol under alkaline conditions [M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956)] provides an example of the possible selectivity of alkyl oxygen cleavage in phenol methyl ethers.

(21) Proton magnetic resonance spectra were taken in dilute deuteriochloroform solutions containing tetramethylsilane as an internal standard on a Varian A-60 spectrometer. Infrared spectra were obtained on a Perkin-Elmer 137B; ultraviolet spectra are of 95% ethanol solutions and were taken on a Perkin-Elmer 202 and Beckman DU spectrometers.

(22) See, D. F. C. Garbutt, P. W. Jeffs, and F. L. Warren, *J. Chem. Soc.*, 5010(1962).

the recovery of bases having chloroform-soluble hydrochlorides, was chromatographed over alumina to afford the following fractions: 2.6 g., 7-O-ethyllycorenine[22] (1.7 l. of benzene); 1.65 g., homolycorine (2.0 l. of benzene); and 4.1 g., albomaculine (4.2 l. of benzene containing 1% ethyl acetate).

7-O-Ethyllycorenine Picrate.—The crude material from the column was dissolved in ethanol and a solution of ethanolic picric acid was added. The picrate precipitated on scratching and was recrystallized twice from ethanol, m.p. 152°.

Anal. Calcd. for $C_{26}H_{30}N_4O_{11}$: C, 54.35; H, 5.26. Found: C, 54.68; H, 5.28.

7-O-Ethyllycorenine.—Attempts to crystallize the base failed and the crude material from the column fractions was purified *via* the picrate. The free base was obtained as a gum by passing a solution of the picrate in chloroform through a short column of alumina. The gum crystallized slowly from a concentrated ethereal solution as fine needles of 7-O-ethyllycorenine: m.p. 99–100°; $[\alpha]_D$ +204° (*c* 1.0, $CHCl_3$); infrared ($CHCl_3$) 6.18 (m) (aromatic ring), 9.50–9.70 (s) (cyclic ether) μ; p.m.r. three-proton triplet δ 1.28 (J = 7.0 c.p.s.), two-proton quartet δ 3.88 (J = 7.0 c.p.s.), three-proton singlets δ 2.09 (N-methyl hydrogens), 3.86, and 3.85 (aromatic methoxyls), one-proton multiplet δ 5.58 (C-4 hydrogen), one-proton singlet (fine splitting) δ 5.63 (C-7 hydrogen), one-proton singlets δ 6.78 and 6.87 (C-8 and C-11 hydrogens).

Anal. Calcd. for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88. Found: C, 69.60; H, 7.76.

7-O-Ethyllycorenine Hydroperchlorate.—A solution of the base in methanol–ether was treated with a slight excess of perchloric acid. The hydroperchlorate crystallized from the solution on standing, and after recrystallization for methanol–ether, a pure sample, m.p. 183–185° dec., was obtained.

Anal. Calcd. for $C_{20}H_{28}ClNO_8$: C, 53.87; H, 6.32. Found: C, 54.10; H, 6.30.

Hydrolysis of 7-O-Ethyllycorenine.—A solution of 25 mg. of 7-O-ethyllycorenine was refluxed with 3 N hydrochloric acid for 6 hr. under a nitrogen atmosphere. After cooling, the solution was basified with sodium carbonate and extracted with chloroform, and the chloroform was recovered, affording the product as a gum. Purification of this material by thick layer chromatography, using silica gel and chloroform containing 10% methanol as a solvent, gave 8.3 mg. of lycorenine (identical in all respects with an authentic sample).

Albomaculine (I, R = OMe).—The combined benzene–ethyl acetate (99:1) eluate from the column gave 4.2 g. of semicrystalline material whose infrared spectrum was indistinguishable from the infrared spectrum of pure albomaculine. Crystallization of this material from ethyl acetate gave 3.4 g. of albomaculine: m.p. 178–179°; $[\alpha]^{16}_D$ +78° (*c* 1.0, chloroform); λ_{max} 224 mμ (log ϵ 4.45), 265 (4.04), 295 (sh) (3.43); infrared spectrum 5.80 (s) and 6.23 μ (m). These values are in good agreement with those reported for albomaculine. The melting points of the picrate and hydroperchlorate were also in good agreement with the literature values.

Albomaculine Methiodide. A.—Albomaculine was refluxed for 3 hr. in methanol containing methyl iodide. Removal of the solvent and crystallization from water or acetone gave prisms, m.p. 237–240° dec.

B.—Albomaculine (1.733 g.) was heated on a steam bath for 2 hr. with 44.40 ml. of 0.113 N sodium hydroxide (1 equiv.). A small quantity of undissolved fatty material was filtered off and the filtrate was evaporated to dryness, to leave 2.117 g. of a solid residue. Methyl iodide (5 ml.) and acetone (20 ml.) were added to the residue and the solution was refluxed for 2 hr. The solvent was removed and the solid residue was lixiviated with chloroform. Recovery of the chloroform gave a gum which crystallized from water as fine felt-like needles, m.p. 137–139°. The p.m.r. spectrum, three-proton singlets δ 2.94, 3.16 (N-methyl hydrogens), 3.90, 3.92, and 4.03 (aromatic methoxyls), one-proton multiplets δ 4.70 (5a-hydrogen) and 6.08 (4-hydrogen), and one-proton singlet δ 7.12 (11-hydrogen), of this compound in D_2O was identical in all respects with the spectrum of the methiodide, m.p. 237–240° dec., prepared in A. The conversion of the lower melting form to the higher melting form could be achieved by seeding an aqueous solution with the higher melting polymorph, or by crystallization from acetone. The analysis is reported for the higher melting form.

(23) The occurrence of this substance in the plant is extremely unlikely. We regard it as an artifact of lycorenine, produced during the addition of hydrochloric acid to the ethanolic extract of the total plant constituents.

Anal. Calcd. $C_{20}H_{26}INO_5$: C, 49.29; H, 5.38. Found: C, 49.25; H, 5.44.

Hofmann Degradation of Albomaculine.—An aqueous solution containing 3.4 g. of albomaculine methiodide was heated to *ca.* 60° and treated with an excess of silver oxide (*ca.* 1.7 g.). After a few minutes the solution was filtered. The filtrate was evaporated to dryness to give 1.72 g. of the crude methohydroxide.

The methohydroxide, 0.7 g., was heated at 165° and 0.01 mm. for several days until sublimation had ceased. The reaction product was lixiviated with benzene and the benzene extract was washed with three 5-ml. portions of 2 N hydrochloric acid. Concentration of the hydrochloric acid washings afforded 10 mg. of red gum which was not investigated. Removal of the benzene afforded 142 mg. of colorless oil II (R = OH; R′ = CH=CH_2)[24]: λ_{max} 222 mμ (log ϵ 4.52), 250 (4.41), or λ_{max} 241 mμ (log ϵ 4.49), 298 (3.67) in 0.1 N ethanolic sodium hydroxide; infrared ($CHCl_3$) 282 (hydroxyl), 6.30 (aromatic ring) μ.

A sample, distilled at 120° (0.05 mm.), showed the absence of nitrogen but gave inconsistent results for carbon and hydrogen on elemental analysis.[25]

It was, therefore, characterized as its O-acetate, prepared as follows. To a solution of 20 mg. of II (R = OH; R′ = CH=CH_2) in 5 ml. of pyridine was added 0.2 ml. of acetic anhydride and the solution was refluxed for 2 min. After 3 hr. the pyridine was removed to leave an oily residue. A chloroform solution of the residue was washed with dilute sodium carbonate and water. After drying, the solution over anhydrous sodium sulfate, the solvent was removed to leave the O-acetate II, (R = OAc; R′ = CH=CH_2) as a colorless oil: infrared ($CHCl_3$) 5.62 (s) (phenolic acetate), 6.32 (m) (aromatic ring) μ; p.m.r. three-proton singlets δ 2.34 (acetoxymethyl), 3.98, 3.92, and 3.95 (aromatic methoxyls), 12-line ABX pattern δ 5.18–5.97 (eight lines of AB part) and 6.62–7.08 (four lines of X part) (vinyl hydrogens), and one-proton singlets, δ 6.95 (broad) (C-6 hydrogen) and 7.04 (broad) (C-2 hydrogen).

A sample was distilled at 80° (0.25 mm.) for analysis.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.10. Found: C, 72.24; H, 6.20.

Methylation of the Phenol II (R = OH; R′ = CH=CH_2).—Phenol II (R = OH, 90 mg.) was dissolved in *ca.* 8 ml. of 33% sodium hydroxide solution. To this solution 0.5 ml. of dimethyl sulfate was added dropwise with vigorous stirring over a period of 3 hr. The alkaline solution was diluted with water and extracted with chloroform. Recovery of the chloroform left the methyl ether II (R = OMe; R′ = CH=CH_2) as a clear oil: λ_{max} 224 mμ (log ϵ 4.43), 254 (4.36); infrared ($CHCl_3$) 6.30 μ (aromatic ring); p.m.r. three-proton singlet, δ 3.43, six-proton singlet, δ 3.45 (aromatic methoxyls), 12-line ABX pattern, ν_A = 324 c.p.s., ν_B = 357 c.p.s., and ν_C = 412 c.p.s. (J_{AB} = 1.5 c.p.s., J_{AX} = 11 c.p.s., and J_{BX} = 17 c.p.s.) (vinyl hydrogens), and two-proton singlet δ 6.84 (C-2 and C-6 hydrogens).

The oil was distilled at 75° (0.2 mm.) for analysis.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71; OMe, 34.4. Found: C, 75.15; H, 7.12; OMe, 32.98.

Permanganate Oxidation of the Methyl Ether II (R = OMe; R′ = CH=CH_2).—To a cold solution of 70 mg. of the methyl ether II (R = OMe; R′ = CH=CH_2) in *ca.* 25 ml. of acetone was added 100 mg. of potassium permanganate during a 5-hr. period with stirring. The solution was maintained at 0° throughout the addition.

The manganese dioxide was filtered off, and the faintly pink solution was allowed to stand at room temperature for 12 hr. The solution was refiltered and the excess permanganate was reduced by passing sulfur dioxide. The solvent was removed by evaporation and the solid residue was heated with chloroform. Removal of the chloroform gave 12 mg. of product. The manganese dioxide which had been filtered off was treated with a saturated solution of sulfur dioxide and the solution was extracted with chloroform. Recovery of the chloroform afforded 54 mg. of oil which was combined with the 12 mg. obtained above.

(24) In a subsequent experiment with 0.7 g. of the methohydroxide an improved yield of the product was obtained by increasing the reaction temperature to 195–200°. By this procedure *ca.* 250 mg. of product was obtained after 24 hr. Also, it is probable that an excess of base was present in this reaction, since no particular attempt was made to free the silver oxide from sodium hydroxide.

(25) The susceptibility of this phenolic compound to air oxidation on short exposure to the atmosphere probably accounts for the inconsistent analytical data.

The total product, 66 mg., was dissolved in aqueous sodium carbonate solution and extracted with chloroform. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The ether was dried over anhydrous sodium sulfate, and the ether was removed from the filtered solution to leave 32 mg. of crude acid. Crystallization of this material from ether–hexane gave the pure biphenylcarboxylic acid II (R = OMe; R′ = CO_2H), m.p. 161–163°, λ_{max} 217 mμ (log ε 4.53) and 265 (4.11).

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.70; H, 5.42.

Methylation of 6 mg. of the acid with ethereal diazomethane in the usual way afforded 5 mg. of the methyl ester II (R = OMe; R′ = CO_2Me), m.p. 138–139°.

Synthesis of 3,4,5-Trimethoxy-3′-biphenylcarboxylic Acid (II, R = OMe; R′ = CO_2H).—A mixture of 2 g. of 1-iodo-3,4,5-trimethoxybenzene[26] and 1 g. of methyl *m*-iodobenzoate was placed in a 15-in. Pyrex tube equipped with a glass stirring rod. The air was displaced from the tube by a stream of nitrogen and the tube and its contents were placed in a metal bath. The temperature of the bath was raised slowly to 170° while 2.5 g. of copper bronze was added with stirring over 30 min. The temperature was raised to 220° and the mass was stirred occasionally for a period of 3 hr. After cooling, the reaction product was extracted repeatedly with benzene, and the filtered benzene solution was concentrated. Chromatography over aluminum oxide in benzene–hexane (1:2) gave 340 mg. of crude ester II (R = OMe; R′ = CO_2Me), which crystallized from ether to afford pure methyl 3,4,5-trimethoxy-3′-biphenylcarboxylate: m.p. 138–139°; infrared (Nujol) 5.90 (s) (ester carbonyl) μ; p.m.r. three-proton singlet, δ 3.86, six-proton singlet, δ 3.91 (aromatic methoxyls), two-proton singlet, δ 6.77 (C-2 and C-6 hydrogens), and 18-line ABCD pattern, δ 7.41–8.23 (ring-B aromatic hydrogens).

The mixture melting point with the ester obtained from degradation of albomaculine and this sample showed no depression; the infrared spectra of the two samples were identical.

(26) This was prepared from gallic acid according to the procedure of Graebe and Suter.[16] The authors are indebted to Messrs. R. D. Haugwitz and W. Pearson, Indiana University, for their assistance with this preparation.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.32; H, 5.81.

Hydrolysis of Ester II (R = OMe, R′ = CO_2Me).—A methanolic solution of 15 mg. of the ester II (R = OMe) obtained by the Ullmann synthesis was refluxed with 2 ml. of 5 *N* potassium hydroxide for 3 hr. After cooling the solution, it was acidified with 2 *N* hydrochloric acid and then extracted with ether. Recovery of the product from ether afforded *ca.* 11 mg. of acidic material, which after two recrystallizations from ether gave 6 mg. of the pure acid II (R = OMe; R′ = CO_2Me), identical in every respect (infrared, mixture melting point) with that obtained from the Hofmann product.

Deoxynerinine (IV).—The diol III (125 mg.) was heated at 90–100° for 3 hr. with 25 ml. of 5% sulfuric acid. After cooling and basifying the solution with 2 *N* ammonium hydroxide, the product was extracted with chloroform. Recovery of the chloroform gave 105 mg. of a colorless oil. Distillation of this material at 110° (0.1 mm.) gave pure deoxynerinine (IV) as an oil: $[\alpha]_D$ +83°; λ_{max}^{EtOH} 280 mμ (log ε 3.09); infrared ($CHCl_3$) 6.20, 6.26 (aromatic ring), 8.90 (s), 9.14 (s) (cyclic ether) μ; p.m.r. six-proton singlet, δ 3.90, three-proton singlets, δ 3.92 (aromatic methoxyls) and 2.03 (N-methyl hydrogens), one-proton multiplets, δ 3.90 (C-5a hydrogen) and 5.50 (C-4 olefinic hydrogen), one-proton doublets δ 4.95 (J = 17.5 c.p.s.) and 4.87 (J = 17.5 c.p.s. (C-7) methylene group), and one-proton singlet, δ 6.83 (hydrogen).

Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60. Found: C, 68.72; H, 7.83.

Deoxynerinine Perchlorate.—To an ether solution of 25 mg. of the ether III, was added 1 drop of 70% perchloric acid. Trituration of the gum with ether, containing a small amount of methanol, gave a solid which on crystallization from methanol–ether gave the pure hydroperchlorate, m.p. 244–245°.

Anal. Calcd. for $C_{19}H_{26}ClNO_8$: C, 52.84; H, 6.06. Found: C, 52.92; H, 6.36.

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Synthesis of Dicarboximidophosphonothioates

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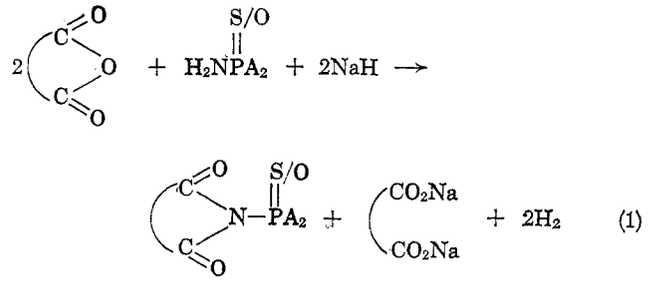
Dicarboximidophosphonothioates derived from a variety of five-membered ring dicarboximides and containing alkoxy, alkylamino, alkylthio, aryloxy, or alkyl groups attached to phosphorus have been prepared, principally by the novel reaction of cyclic anhydrides with phosphoramidothioates and sodium hydride. The reaction of phthalic anhydride with O,O-diethyl phosphoramidothioate and sodium hydride to form O,O-diethyl phthalimidophosphonothioate was shown to involve sodium O,O-diethyl phosphoramidothioate and disodium N-(diethoxyphosphinothioyl)phthalamate as intermediates.

Dicarboximidophosphonothioates, the N-phosphorothioyl derivatives of dicarboximides, have not been reported, and the related dicarboximidophosphonates have been described only recently and very briefly.[1] These compounds are not easily prepared by the usual methods,[2] but a wide variety of dicarboximidophosphonothioates and a few dicarboximidophosphonates have now been synthesized by the newly discovered reaction of cyclic dicarboxylic anhydrides with phosphorus amides and sodium hydride (reaction 1).



(1)

The obvious method for the preparation of dicarboximidophosphonothioates, the reaction of dicarboximide salts with phosphorus acid chlorides, can be realized, but usually only with fair yields and under exacting conditions. Thus, O,O-diethyl phthalimidophosphonothioate (I) was obtained in 50% yield from potassium phthalimide and O,O-diethyl phosphorochloridothioate (reaction 2) when the reaction was

(1) A. K. Tsolis, W. E. McEwen, and C. A. VanderWerf, *Tetrahedron Letters*, **No. 43**, 3217 (1964); A. K. Tsolis, Dissertation, University of Kansas, 1963.

(2) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 278–300.