Lythraceae Alkaloids. II. Structural Studies on Decodine and Verticillatine[1]

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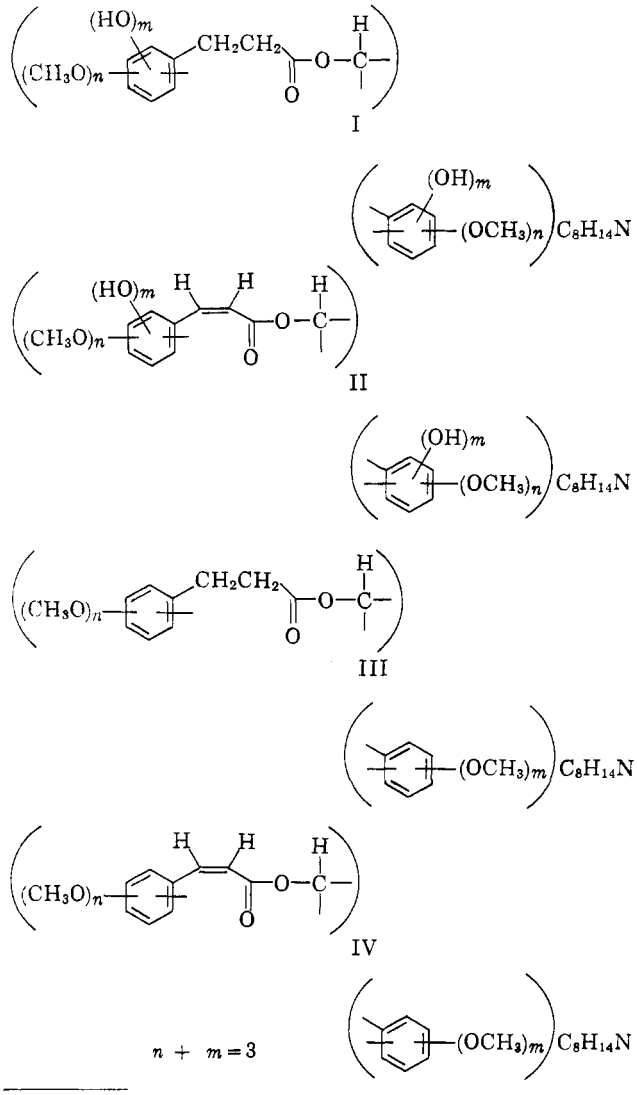
Chemical proof for the presence of a lactone in decodine (I) and verticillatine (II) is presented. Lithium aluminum hydride reduces the lactone ring to the corresponding diols. Sodium hydroxide cleaves the lactone ring in the decodine series to a hydroxy acid. N.m.r. evidence is presented to show that the ether oxygen of the lactone is equatorial in decodine and axial in verticillatine. Vigorous oxidation of dimethyldecodine (III) yielded hemipinic acid, succinic acid, and 4-methoxyisophthalic acid. The isolation of the isophthalic acid derivative requires that one of the aromatic rings be bridged across two *meta* positions by six or more carbon atoms.

In the first paper of this series we described the isolation and characterization of seven alkaloids from *Decodon verticillatus* (*L.*) *Ell.* and the assignment of part structures I and II to five of these bases.[2] In this paper we will present chemical evidence in support of these part structures for decodine (I) and verticillatine (II) and also provide information as to the exact nature of the substitution on the aromatic rings.

Previously we reported[2] that verticillatine could be hydrogenated to give a dihydroderivative, a compound that was very similar to but not identical with decodine.



On the basis of this close similarity we concluded that decodine and dihydroverticillatine have the same gross structure but differ only in configuration at one or more asymmetric centers. Therefore, it seemed profitable to study both of these bases concurrently as most of the chemical data obtained for one would be useful in deducing the structure of the other.

The corresponding dimethyl ethers of these two bases, dimethyldecodine (III) and dimethylverticillatine (IV) were used as starting points in the degradation studies, as possible side reactions which might occur *via* the phenolic hydroxyl groups were blocked. Dimethyldecodine can be prepared conveniently by treatment of decodine with sodium hydroxide and dimethyl sulfate or with diazomethane and methanol. It was found that treatment with ethereal diazomethane yielded only the monomethyldecodine as shown by its conversion to a monoacetate with acetic anhydride and by its conversion to dimethyldecodine with dimethyl sulfate. Djerassi and co-workers were unable to prepare the methyl ether of pilocereine with ethereal diazomethane but were successful using diazomethane in methanol.[3] These workers ascribed this lack of reactivity to steric hindrance of the hydroxyl group in pilocereine. This would suggest that one of the phenol groups of decodine is hindered also. Verticillatine could be converted to dimethylverticillatine with diazomethane in methanol. The maxima at 293 mμ assigned to the *cis*-cinnamic ester function in verticillatine shifted to 280 mμ in dimethylverticillatine suggesting something other than simple methylation took place. However an infrared carbonyl band at 1700 cm.$^{-1}$ and the presence of the pair of doublets in the n.m.r. centered at 3.13 and 4.12 τ (J 12.7 c.p.s.) assigned to the vinyl hydrogens and a doublet at 5.70 τ (J 10.7 c.p.s.) tentatively assigned to a proton on a carbon atom between a nitrogen and a phenyl ring[2] are consistent with simple methylation of the phenolic hydroxyl groups. Hydrogenation of dimethylverticillatine resulted in uptake of one molar equivalent of hydrogen to yield dihydrodimethylverticillatine, a base which is isomeric with dimethyldecodine. The infrared spectrum of dihydrodimethylverticillatine was almost identical with that of dimethyldecodine and the ultraviolet spectra of the two bases were identical.

Chemical evidence for the presence of a lactone ring in decodine and verticillatine was obtained by lithium aluminum hydride and sodium hydroxide cleavage of the dimethyl derivatives of these two bases. These reactions are outlined in the part structures on Charts I and II. Lithium aluminum hydride reduction of

(1) Supported by a Frederick Gardner Cottrell grant from the Research Corporation and by a grant (MY-4748) from the U. S. Public Health Service. Presented in part at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 13-O of the abstracts.

(2) J. P. Ferris, *J. Org. Chem.*, **27**, 2985 (1962).

(3) C. Djerassi, S. K. Figdor, J. M. Bobbitt, and F. K. Markley, *J. Am. Chem. Soc.*, **78**, 3861 (1956).

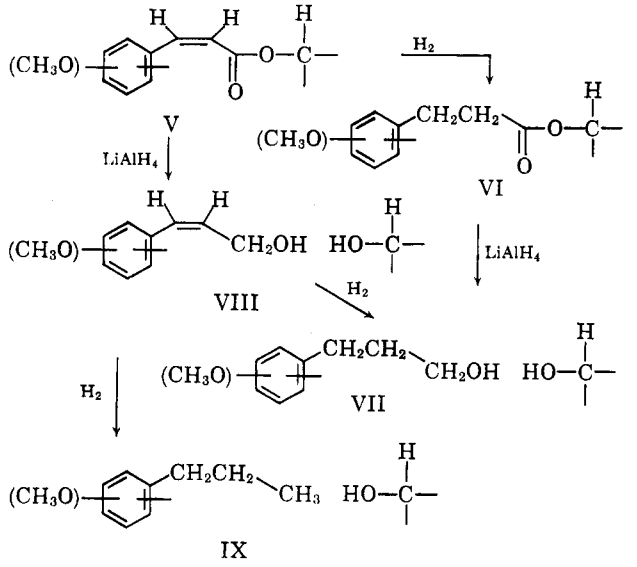


Chart I

Reactions of the unsaturated lactone ring of dimethylverticillatine.

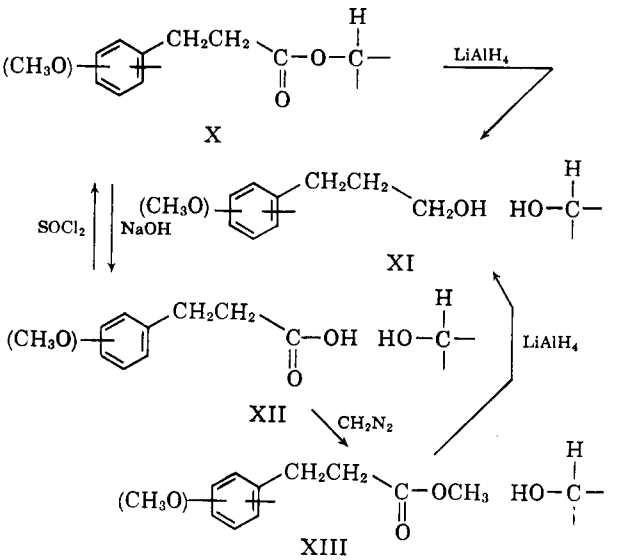
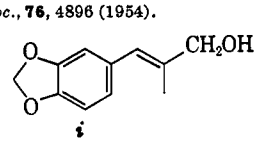


Chart II

Reactions of the lactone ring of dimethyldecodine.

dimethyldecodine (X) and dihydrodimethylverticillatine (VI) proceeded without loss of carbon to yield diols XI and VII, respectively, a result which confirms the presence of a lactone ring in these bases. The n.m.r. spectra of the diacetates of the diols were very similar and in agreement with structure X. For example diacetylhexahydrodimethylverticillatine (VII—diacetate) exhibited a broad one-hydrogen signal at 4.82 τ assigned to the proton attached to the same carbon as the secondary acetate group and a triplet centered at 5.90 τ (J 6.6 c.p.s.) assigned to a methylene flanked by an acetate group and another methylene grouping. Lithium aluminum hydride reduction of dimethylverticillatine (V) yielded a diol (VIII) with the double bond still intact as shown by an ultraviolet maxima at 257 mμ and an inflection at 282 mμ (log ϵ 4.10 and 3.60, respectively).[4] Again the n.m.r. spectra of this derivative confirmed the assigned structure with a doublet at 3.58 τ (J 11.4 c.p.s.) and a broad multiplet of *ca.* five peaks centered at 4.36 τ assigned to the vinyl hydrogens and a doublet at 5.78 τ (J 6.8 c.p.s.) which shifts in the diacetate to 5.15 τ (J 6.4 c.p.s. each peak is partially split into two maxima, J 1.4 c.p.s.) assigned to the methylene flanked by the double bond and the hydroxyl group. The signal centered at 5.70 τ in dimethylverticillatine and diacetylverticillatine[2] was not observed in either of the above diol (VIII) or its diacetate indicating that this signal is not due to the double bond alone but also requires the presence of the lactone ring. This is consistent with the previous structural assignment.[2] Hydrogenation of diol VIII in acid solution resulted in the hydrogenolysis of the vinylic benzyl alcohol to yield IX. N.m.r. revealed the presence of the C-methyl group by a triplet at 9.05 τ and this was confirmed by Kuhn–Roth analysis.

(4) The *trans*-cinnamyl alcohol structure *i* has maxima at 261 and 282 mμ (log ϵ 4.05 and 3.92, respectively); *cf.* A. W. Schrechter and J. L. Hartwell, *J. Am. Chem. Soc.*, **76**, 4896 (1954).



i

Additional evidence for the lactone group was obtained by vigorous hydrolysis of dimethyldecodine (X) to yield a hydroxy acid (XII). The lactone ring could be reclosed using thionyl chloride giving an 18% yield of dimethyldecodine. Use of dicyclohexylcarbodimide in an attempt to get a better yield of dimethyldecodine resulted in products which appeared to be acylureas. The hydroxy acid (XII) was readily converted to a hydroxy ester (XIII) with diazomethane and the hydroxy ester could be converted to a monoacetate. Lithium aluminum hydride reduction of the hydroxy ester yielded the same diol (XI) as was formed from the reaction of dimethyldecodine with lithium aluminum hydride thereby proving that no rearrangement took place during the vigorous hydrolysis of dimethyldecodine.

One important difference between the decodine series and the verticillatine series is the chemical shift for the acetates of the secondary alcohol formed on cleavage of the lactone ring. The proton attached to the same carbon atom as the secondary acetate group exhibits a greater chemical shift (from tetramethylsilane) in the verticillatine series than in the decodine series. The same is true for the methyl group of the acetate (see Table I). It has been observed that a proton attached to the same carbon atom as an axial acetate exhibits a greater chemical shift than does the cor-

TABLE I

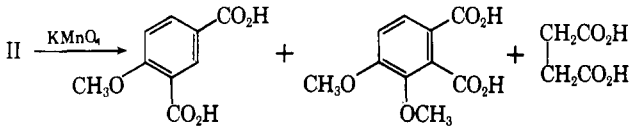
CHEMICAL SHIFT (C.P.S.) FOR THE ACETATES OF THE SECONDARY ALCOHOL

	O ‖ *H*-COCR	O ‖ COC*H*$_3$	Acetate conformation
Acetoxy ester (XIII—Acetate)	289	103	Equatorial
Diacetyltetrahydrodimethyldecodine	290	103	Equatorial
Diacetyltetrahydrodimethylverticillatine	305	115	Axial
Diacetylhexahydrodimethylverticillatine	310	116	Axial

(5) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider *ibid.*, **80**, 6098 (1958).

responding equatorial acetate.[5] The same observation was made for the chemical shift of the methyl group of the acetate. This evidence confirms the fact that decodine and verticillatine differ in stereochemistry at the carbon atom bearing the ether oxygen of the lactone ring[2] and suggests that this oxygen group is equatorial in decodine and its derivatives and axial in verticillatine and its derivatives.

The chemical evidence presented so far provides confirmation for the part structures postulated initially for decodine and verticillatine on the basis of spectral evidence.[2] Part structures I and II were extended by studying the vigorous permanganate oxidation of dimethyldecodine. It is possible to isolate three acids from this oxidation by fractional sublimation. The first to sublime is succinic acid which, after one resublimation, was identical in all respects with an authentic sample. The other two acids sublimed at a higher temperature and formed two fairly distinct bands of crystals. The lower band of crystals, which predominated when larger amounts of permanganate were used, was rinsed with chloroform and resublimed and identified as 4-methoxyisophthalic acid. The identity of this novel degradation product was proved by the identity of its melting point, infrared spectrum, and ultraviolet spectrum with that of an authentic sample. In one reaction this lower band of sublimate was treated directly with diazomethane and on sublimation dimethyl 4-methoxyisophthalate was obtained. Its identity was proved by comparison of melting point and infrared spectrum with an authentic sample. The upper band of crystals from the sublimation were rinsed with ether and then heated to 160° for five minutes and then resublimed to yield hemipinic anhydride as shown by the identity of its melting point and infrared spectrum with that of an authentic sample.



The isolation of the isophthalic acid derivative from these oxidations requires that the aromatic ring be joined to a carbocyclic ring in two *meta* positions, a structural unit that is unique in alkaloid chemistry so far as we have been able to determine.[6,7] Prelog and co-workers[8] have shown that a carbocyclic ring spanning the two *meta* positions of an aromatic ring must have at least six members, if the aromatic character of the ring is to be maintained, which together with the three aromatic carbon atoms requires a minimum ring size of nine members. Hemipinic acid is a commonly observed permanganate oxidation product especially in tetrahydroisoquinoline alkaloids, *e.g.*, capaurine.[9] It is not known which aromatic ring in structure III gives rise to the 4-methoxyisophthalic acid and which to the hemipinic acid. The fact that the ultraviolet spectra of the dihydroverticillatine series of compounds is identical with that of the decodine series leaves no doubt that the same aromatic ring systems are present in both.

So far attempted degradation reactions in the vicinity of the nitrogen atom have been unsuccessful. Attempted oxidation of the amine in dimethyldecodine to the lactam using potassium permanganate[10] or chromic anhydride in pyridine,[10] yielded recovered starting material. It was possible to prepare the *N*-oxide of dimethyldecodine very readily but upon pyrolysis of this *N*-oxide the only product that could be characterized was dimethyldecodine. None of the noncrystalline portions of the reaction mixture gave a positive test for hydroxylamines,[11] suggesting that it was impossible for the *N*-oxide to be eliminated in the usual manner either due to absence of *beta* hydrogens or to an inability to form the proposed cyclic transition state.[12] Attempted rearrangement of this *N*-oxide with potassium chromate and potassium dichromate gave only recovered starting material.[13] Other attempts to degrade these alkaloids in the vicinity of the nitrogen atom are now in progress.

Experimental[14]

Monomethyldecodine.—A suspension of 100 mg. of decodine (I) in ethereal diazomethane gradually dissolved on standing at room temperature overnight. The solution was then concentrated to dryness and after crystallization from methanol yielded 73 mg. of product, m.p. 225–227°. Recrystallization from methanol yielded an analytical sample, m.p. 227–228°, $[\alpha]$ −132°, (*c* 1.18), λ_{max} 286 mμ (ϵ 4850), λ_{min} 257 mμ, (ϵ 748), ν_{max} 3450, 1725 cm.$^{-1}$. The sample was dried at 170° for 1 min. before analysis.

Anal. Calcd. for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; 2-OCH_3, 14.18. Found: C, 71.63; H, 7.39; OCH_3, 13.92.

Dimethyldecodine (III). (a) *Via* **Monomethyldecodine and Dimethyl Sulfate.**—To a vigorously stirred suspension of 48 mg. of monomethyldecodine in 1 ml. of water containing 0.1 g. of sodium hydroxide was added 0.2 ml. of dimethyl sulfate. An additional 0.1 g. of sodium hydroxide and 0.1 ml. of dimethyl sulfate was added after 20 min. and the mixture was stirred overnight. The product was extracted into chloroform and was crystallized from methanol to yield 41 mg., m.p. 204.5–205.5°. An analytical sample was prepared by recrystallization from methanol, m.p. 206–207°, $[\alpha]$ −90° (*c* 1.24), λ_{max} 285 mμ, (ϵ 4980), λ_{min} 258 mμ, (ϵ 836), ν_{max} 1724 cm.$^{-1}$ pK_a' 7.5. The ultraviolet spectrum was unchanged in 0.1 *N* sodium hydroxide in methanol and 1 *N* hydrochloric acid in methanol.

Anal. Calcd. for $C_{27}H_{33}NO_5$: C, 71.81; H, 7.37; N, 3.20; 3-OCH_3, 20.62; mol. wt., 451.54. Found: C, 71.80; H, 7.27; N, 3.35; OCH_3, 19.90; mol. wt. (by titration), 457.

(b) *Via* **Decodine and Dimethyl Sulfate.**—To 5 ml. of a solution of 158 mg. of decodine (I) and 0.4 g. of sodium hydroxide was added 0.2 ml. of dimethyl sulfate. The mixture was stirred for 2 hr. and then an additional 0.2 ml. of dimethyl sulfate was added. At the end of 4 hr. the mixture was extracted with chloroform and was crystallized from methanol to yield 134 mg. of dimethyldecodine, m.p. 203.5–205°.

(c) *Via* **Decodine and Diazomethane.**—To a solution of 48 mg. of decodine (I) in 5 ml. of methanol was added 5 ml. of ethereal diazomethane and the mixture was allowed to stand overnight at 0°. Crystallization of the product from methanol yielded 45 mg. of dimethyldecodine, m.p. 203.5–205°.

(6) This degradation product was also isolated from the permanganate oxidation of tiliacarine but one carboxyl group resulted from the cleavage of a hydroxylated aromatic ring. K. W. J. Rao and L. R. Row, *Chem. Ind.* (London), 407 (1960).

(7) We have also obtained 4-methoxyisophthalic acid from the permanganate oxidation of methyldecinine[2] along with succinic acid and 4,5-dimethoxyphthalic acid.

(8) V. Prelog, K. Wiesner, W. Ingold, and O. Hafliger, *Helv. Chim. Acta*, **31**, 1325 (1948).

(9) R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67**, 95 (1945).

(10) R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 2689 (1956).

(11) G. A. Snow, *ibid.*, 2588 (1954).

(12) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 362 (1960).

(13) P. J. Scheuer, W. I. Komoto, and K. Ohinata, *J. Am. Chem. Soc.*, **75**, 3029 (1953).

(14) All physical constants were determined as described previously.[2] Thin-layer chromatography plates, prepared according to directions supplied by Brinkman Instruments, Great Neck, N. Y., utilized silica gel as the stationary phase and methanol as the solvent. Melting points taken with a hot stage microscope are designated by "block."

Acetylmonomethyldecodine.—A solution of 44 mg. of monomethyldecodine in 0.5 ml. of acetic anhydride and 0.5 ml. of pyridine was allowed to stand at room temperature overnight and was then concentrated to dryness by heating under reduced pressure. The residue was taken up in water and extracted into chloroform. Crystallization from methanol yielded 44 mg. of product, m.p. 195–197°. Recrystallization from methanol afforded an analytical sample, m.p. 195.5–196.5°; $[\alpha]$ −132° (*c* 0.65), λ_{max} 281 mμ, (ϵ 2470), λ_{min} 262 mμ, (ϵ 1260), ν_{max} 1762, 1715 cm.$^{-1}$. The sample was dried at 77° *in vacuo* before analysis.

Anal. Calcd. for $C_{28}H_{33}NO_6$: C, 70.12; H, 6.94; N, 2.92. Found: C, 70.31; H, 6.95; N, 3.10.

Hydroxy Acid (XII).—To a solution of 700 mg. of dimethyldecodine (X) in 20 ml. of methanol was added 600 mg. of sodium hydroxide and 10 ml. of water and the resulting mixture was refluxed for 43 hr. The condenser was then removed and the methanol distilled. An additional 20 ml. of water was added and the solution was washed with chloroform. The aqueous layer was acidified with hydrochloric acid to pH 6 and the resulting precipitate was extracted into chloroform to yield 659 mg. of amorphous acid. Titration of 100 mg. of this acid with 0.1 *N* hydrochloric acid gave a neut. equiv. of 610 (theory for $C_{27}H_{35}NO_6 \cdot H_2O \cdot CHCl_3$ 607.6) pK_a' 5.0. A sample for analysis was prepared by elution from grade 5 alumina with methanol and drying at 77° *in vacuo*, m.p. 165–215°, $[\alpha]$ +114° (*c* 0.57), λ_{max} 282 mμ (ϵ 4250), λ_{min} 257 mμ (ϵ 1020), ν_{max}, 1540 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{35}NO_6 \cdot H_2O$; C, 66.51; H, 7.65. Found: C, 65.78; H, 7.44.

Hydroxy Ester (XIII).—Hydroxy Acid XII (132 mg.) was suspended in a solution of diazomethane in ether and it gradually dissolved with gas evolution. The solution was allowed to stand overnight and was then washed with dilute sodium bicarbonate solution and concentrated to yield 94 mg. of product. An analytical sample was prepared by elution from grade 3 alumina with benzene to yield a colorless gum, $[\alpha]$ −54° (*c* 0.83), λ_{max} 282 mμ (ϵ 4,420), λ_{min} 257 mμ, (ϵ 1110), ν_{max} 1722 cm.$^{-1}$; pK_a' 8.6.

Anal. Calcd. for $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90; mol. wt., 483.6. Found: C, 69.25; H, 7.98; N, 3.18; mol. wt. (by titration), 479.

Acetoxy Ester.—A solution of 136 mg. of hydroxy ester XIII, 1 ml. of pyridine, and 1 ml. of acetic anhydride was allowed to stand at room temperature overnight and was then concentrated to dryness using aspirator vacuum. The residue was taken up in ether and the ether solution was extracted with dilute hydrochloric acid. The acid solution was made basic with sodium carbonate and was then extracted with ether to yield 132 mg. of gum. An analytical sample was prepared by elution from grade 3 alumina with benzene $[\alpha]$ −32°, (*c* 2.51), λ_{max} 281 mμ (ϵ 4760), λ_{min} 254 mμ (ϵ 926), ν_{max} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{39}NO_7$: C, 68.55; H, 7.48; acetyl (as the acetate ester), 8.19. Found: C, 68.71; H, 7.68; acetyl (by hydrolysis), 6.75.

Preparation of Dimethyldecodine from Hydroxy Acid.—A solution of 100 mg. of hydroxy acid XII in 20 ml. of chloroform and 1 ml. of thionyl chloride was refluxed for 15 hr. The pale yellow solution was concentrated to dryness, taken up in chloroform and dilute sodium carbonate solution, and then extracted with ether to yield 36 mg. of crude product. Elution of this material from grade 3 alumina with benzene and then ether yielded 17 mg. (18%) of dimethyldecodine after crystallization from ether, m.p. 198–200°. The melting point of this material was not depressed on mixture with an authentic sample of dimethyldecodine and the infrared spectrum (potassium bromide) of this material was identical with that of dimethyldecodine.

To show that the low yield of dimethyldecodine was not due to the presence of dimethyldecodine in the starting material another 100 mg. sample of hydroxy acid from the same batch as was used above was dissolved in 10 ml. of dilute hydrochloric acid and 10 ml. of chloroform was added. The water layer was then made basic by addition of sodium carbonate and it was then extracted with ether as above. Concentration of the ether solution to dryness yielded only 3 mg. of a yellow gum which would not crystallize.

Attempts to close the lactone ring by using dicyclohexylcarbodiimide in chloroform solution[15] or in refluxing pyridine,[16] resulted in the formation of an amorphous product which was characterized by its infrared maxima in potassium bromide at 1700 and 1650 cm.$^{-1}$.

Tetrahydrodimethyldecodine (XI). (a) By the Reduction of Dimethyldecodine with Lithium Aluminum Hydride.—To a solution of 200 mg. of dimethyldecodine in 25 ml. of ether was added 400 mg. of lithium aluminum hydride and the mixture was stirred at room temperature for 18 hr. The hydride was decomposed by slow addition of water to the solution and the precipitate was then filtered and washed thoroughly with chloroform. The combined organic washings were rinsed with water, dried with sodium sulfate, and concentrated to yield 185 mg. of a white froth. Numerous attempts to crystallize this material were unsuccessful. An analytical sample was prepared by eluting the compound from activity 3 alumina with 10% ether in benzene and then drying at room temperature *in vacuo*, m.p. about 70°, $[\alpha]$ −28° (*c*, 1.08) λ_{max} 282 mμ (ϵ 4680), λ_{min} 257 mμ (ϵ 1110).

Anal. Calcd. for $C_{27}H_{37}NO_5 \cdot H_2O$: C, 68.47; H, 8.30; 3 active hydrogens, 0.64. Found: C, 68.84; H, 8.28; active hydrogen, 0.64.

(b) By the Reduction of Hydroxy Ester XIII with Lithium Aluminum Hydride.—To a solution of 100 mg. of hydroxy ester (XIII) in ether was added 200 mg. of lithium aluminum hydride and the mixture was stirred at room temperature for 18 hr. The reaction was worked up exactly as in (a) to yield 87 mg. of tetrahydrodimethyldecodine the infrared and n.m.r. spectra of which were identical in all respects with that prepared by procedure a.

(c) By the Action of Diborane on Dimethyldecodine.—Diborane (0.56 g.) was prepared by the reaction of sodium borohydride and boron trifluoride as described by Brown and Subba Rao[17] and bubbled into a solution of 90 mg. of dimethyldecodine in 75 ml. of tetrahydrofuran. The addition of the diborane to this mixture took place over 0.5 hr. and the mixture was allowed to stand at room temperature for an additional hour. The excess diborane was decomposed cautiously with water, the solution was concentrated to dryness and was taken up in chloroform and washed with water. The infrared spectrum of the crude product indicated it to be a mixture of dimethyldecodine and tetrahydrodimethyldecodine by the presence of a weak band at 1720 cm.$^{-1}$. Elution from activity 3 alumina with 10% ether in benzene yielded 25 mg. of dimethyldecodine, m.p. 201–205° undepressed when mixed with an authentic sample. Elution with ether yielded 37 mg. of tetrahydrodimethyldecodine which had an infrared spectrum that was identical with that of samples prepared by procedures a and b.

Diacetyltetrahydrodimethyldecodine.—A solution of 185 mg. of tetrahydrodimethyldecodine (XI) dissolved in 1 ml. of acetic anhydride and 1 ml. of pyridine was allowed to stand overnight at room temperature. After concentrating the solution to dryness the residue was taken up in ether, extracted with dilute hydrochloric acid, the acid solution was then made basic and then the bases were released from the hydrochlorides and extracted with ether. After washing the ether solution with water it was dried and concentrated to yield 173 mg. of noncrystalline gum. An analytical sample was prepared by chromatography on activity 3 alumina and elution with benzene and 10% ether in benzene $[\alpha]$ −24° (*c*, 0.96) λ_{max} 282 mμ (ϵ 4680), λ_{min} 257 mμ (ϵ 1255).

Anal. Calcd. for $C_{31}H_{41}NO_7$: C, 68.99; H, 7.66; 2-acetyl, 15.95. Found: C, 68.38; H, 7.57; acetyl, 16.36.

Dimethyldecodine *N*-Oxide.—To 45 mg. of dimethyldecodine was added 0.5 ml. of cold peracetic acid and the mixture was allowed to stand at room temperature overnight. The mixture was then poured into water, made basic with potassium hydroxide, and extracted in chloroform. Concentration of the chloroform to dryness yielded a colorless gum which crystallized on trituration with ether to yield 55 mg., m.p. 196–198°. An analytical sample was prepared by crystallization as large rhombs from methanol–ether which, when dried at 117° *in vacuo*, had the following constants; m.p. 200–202°, $[\alpha]$ −58° (*c*, 1.2), λ_{max} 284 mμ (ϵ 4910), λ_{min} 257 mμ (ϵ 1000), ν_{max} 3540, 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{33}NO_6 \cdot CH_3OH$: C, 67.31; H, 7.46. Found: C, 67.03; H, 7.65.

(15) J. C. Sheehan and G. F. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(16) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(17) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6428 (1959).

Reduction of Dimethyldecodine *N*-Oxide.—To a solution of 20 mg. of dimethyldecodine *N*-oxide in acetic acid was added a small amount of zinc dust and the mixture was allowed to remain at room temperature overnight. It was then diluted with water, neutralized with sodium carbonate, and extracted into chloroform. Concentration of the chloroform to dryness yielded 20 mg. of dimethyldecodine, m.p. 201–202°. This material did not depress the melting point of an authentic sample of dimethyldecodine and the infrared spectrum (potassium bromide) of this material was identical with that of dimethyldecodine.

Pyrolysis of Dimethyldecodine *N*-Oxide.—(a) Heating at 200° and 0.05 mm. for 18 hr. resulted in extensive decomposition and the sublimation of a small amount of product which was identified as dimethyldecodine by its infrared spectrum.

(b) A chloroform solution of 50 mg. of the *N*-oxide was concentrated to an amorphous froth and was then pyrolyzed at 150–180° under nitrogen for 30 min. Chromatography of the reaction mixture on grade 5 alumina yielded 2 mg. of material which was probably dimethyldecodine (m.p. 193–200°) when eluted with 10% ether in benzene. Elution with methanol gave 11 mg. of material which was shown to be identical with starting *N*-oxide by its infrared spectrum. None of the fractions from the column gave a positive hydroxylamine test with triphenyltetrazolium chloride.[11]

Attempted Rearrangement of Dimethyldecodine *N*-Oxide.—Warming the *N*-oxide in the presence of potassium chromate or potassium dichromate yielded only starting material.[13] Treatment with potassium permanganate at room temperature for 18 hr. also resulted in the recovery of starting material.

Neutral Potassium Permanganate[10] and Dimethyldecodine.—To a solution of 45 mg. of dimethyldecodine in 5 ml. of acetone was added 11 mg. of potassium permanganate and the mixture was allowed to stand at room temperature for 3 hr. The permanaganate was decolorized with sulfur dioxide and was concentrated to dryness. The residue was taken up in chloroform and dilute sodium bicarbonate. Concentration of the chloroform layer to dryness and recrystallization from methanol yielded 31 mg. (69%) of dimethyldecodine, m.p. 206–207°. The infrared spectrum of the filtrate from these crystals indicated that it was mainly, if not all, dimethyldecodine. There was no evidence for the presence of lactam or hydroxyl groups.

Chromic Anhydride[10] and Dimethyldecodine.—A solution of 48 mg. of dimethyldecodine in 0.5 ml. of cold pyridine was added to 100 mg. of chromic anhydride in 0.5 ml. of cold pyridine and the mixture was allowed to warm to room temperature gradually over a period of 26 hr. A small amount of precipitate formed which was removed by centrifugation and the residue was washed several times with chloroform. The centrifugates were concentrated to dryness and chromatographed on grade 5 alumina. Elution with benzene and ether yielded 42 mg. (87%) of dimethyldecodine, m.p. 203–205°.

Attempted Reaction of Dimethyldecodine and Sodium Borohydride.—Attempted reduction of dimethyldecodine using sodium borohydride in ethanol, methanol, or diglyme solution gave starting material as the only product in about 50% recovery.

Attempted Reaction of Dimethyldecodine with Carbonyl Reagents. (a) **Hydroxylamine.**—Refluxing 48 mg. of dimethyldecodine for 2.5 hr. with 132 mg. of hydroxylamine hydrochloride in 5 ml. of pyridine led to recovery of 37 mg. of starting material.

(b) **2,4-Dinitrophenylhydrazine.**—To 50 mg. of dimethyldecodine in 2 ml. of ethanol was added 1.5 ml. 2,4-dinitrophenylhydrazine reagent[18] and the mixture was allowed to stand at room temperature for 24 hr. The mixture was then diluted to 20 ml. with water and extracted with ether to remove the yellow color. The acid solution remaining was made basic with sodium carbonate and extracted with chloroform. Crystallization of this extract from methanol gave 41 mg. of starting material.

Attempted Hydrogenation of Decodine and Dimethyldecodine.—Attempted hydrogenation of decodine using equal weights of decodine and platinum oxide at atmospheric pressure and room temperature in ethanol, 10% acetic acid in ethanol, and 0.1 *N* sulfuric acid resulted in no uptake of hydrogen and recovery of decodine in good yield. Attempted hydrogenation of dimethyldecodine using platinum oxide in glacial acetic acid and in 0.1 *N* sulfuric acid also was unsuccessful with no uptake of hydrogen and recovery of starting material.

(18) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 219.

Vigorous Oxidation with Potassium Permanganate. (a) **Dimethyldecodine.**—A solution of 400 mg. of dimethyldecodine in 15 ml. of dilute sulfuric acid was made basic by the addition of sodium carbonate and then 2.0 g. of potassium permanganate was added to the mixture over a period of 2 hr. About 0.5 g. of the permanganate was decolorized in 15 min. but the last portion was not decolorized until 15 hr. had elapsed. After 24 hr. of stirring at room temperature the mixture was centrifuged and decanted and the precipitated manganese dioxide was washed with sodium bicarbonate. The combined aqueous layers were acidified with sulfuric acid and extracted with ethyl acetate. Concentration of the ethyl acetate to dryness yielded 285 mg. of a white froth. This was transferred to a sublimation tube and heated at 100° and 0.1 mm. for 24 hr. A small amount of a crystalline solid sublimed.

The residue from this sublimation was sublimed at 130–150° and 0.05 mm. for 24 hr. to give two bands of crystalline sublimate along with some oil. The two bands were separated by breaking the tube between them and the upper band was washed with ether and transferred to another sublimation tube. It was heated at its melting point (about 160°) for 5 min. and was then sublimed at 90° and 0.05 mm. The crystalline product had a melting point of 158–160° (block) which was not depressed upon mixture with an authentic sample of hemipinic anhydride (lit.,[19] m.p. 167°). The infrared spectrum of this material was identical with that of an authentic sample of hemipinic anhydride.

(b) **Dimethyldecodine.**—Dimethyldecodine (430 mg.) was oxidized with 3.22 g. of potassium permanganate as described in procedure a to yield 220 mg. of acid extract. This was sublimed at 100° and 0.05 mm. The sublimate was washed with chloroform to yield succinic acid, m.p. 178–182°. The infrared spectrum of this material in potassium bromide was identical with that of an authentic sample.

The residue from the sublimation of succinic acid was sublimed at 150° and 0.05 mm. for 3 hr. to give two bands of crystals. The lower band was dissolved in methanol and diazomethane was added to it. The solvent was distilled and the residue sublimed at 0.025 mm. and 100° to yield clusters of needles, m.p. 89–92° (lit.,[20] m.p. 94°). The mixed melting point of this material was not depressed when mixed with an authentic sample of dimethyl 4-methoxyisophthalate. The infrared spectrum was also identical with that of the authentic sample when measured in potassium bromide.

(c) **Hydroxy Acid XII.**—Treatment of 306 mg. of hydroxy acid XII dissolved in 15 ml. of water with 2.25 g. of permanganate over a 4-hr. period did not result in complete decolorization of the permanganate even after 24 hr. Sodium sulfite was added to decompose the excess permanganate and then the same work-up procedure described above was used to yield 107 mg. of a white froth. A crystalline solid was obtained by sublimation for 3 hr. at 80° and 0.05 mm., and then resublimation under the same conditions, m.p. 173–175° (block). This was shown to be succinic acid by comparison of its infrared spectrum with an authentic sample. It did not depress the melting point of succinic acid.

The residue from the succinic acid sublimation was sublimed at 150° and 0.1 mm. to yield two bands of crystalline material and some oil. The yellow lower band was rinsed with chloroform to remove some color and was then resublimed at 130° and 0.01 mm. to give a white sublimate, m.p. 255–260° (lit.,[21] m.p. 269–271°). The m.m.p. of an authentic sample of 4-methoxyisophthalic acid melting at 258–263° was 255–262°. The infrared spectra of this sample and the authentic sample were identical. A semiquantitative ultraviolet spectrum determined on 0.6 mg. of this material [λ_{max} 253 mμ (ε 8260), λ_{min} 238 mμ (ε 7130), $\lambda_{inflection}$ 285 mμ (ε 1818)] exhibited the same maxima and minima as did 4-methoxyisophthalic acid.

4-Methoxyisophthalic Acid.—To a solution of 2.0 g. of 4-hydroxyisophthalic acid[22] in 15 ml. of 2.5 *N* sodium hydroxide was added 4 ml. of dimethyl sulfate and the mixture was allowed to stir overnight at room temperature. The solution was then acidified to pH 2 with sulfuric acid and the precipitate was filtered and washed with water and then crystallized from ethanol-water to yield 1.5 g., m.p. 258–260° (lit.,[21] m.p. 269–271°), λ_{max} 254 mμ (ε 11350), λ_{min} 238 mμ (ε 8500), $\lambda_{inflection}$ 285 mμ (ε 1946).

(19) G. Beckett and C. Wright, *J. Chem. Soc.*, **29**, 282 (1876).
(20) L. S. Fosdick and O. E. Fancher, *J. Am. Chem. Soc.*, **63**, 1277 (1941).
(21) S. Bien, *J. Chem. Soc.*, 4015 (1960).
(22) Aldrich Chemical Company, Milwaukee, Wis., m.p. 312°.

The dimethyl ester was prepared by treatment with diazomethane, crystallization from methanol, and sublimation at 100° and 0.05 mm., m.p. 95–96° (lit.,[20] m.p. 94°).

Hemipinic Acid Anhydride.—A sample of hemipinic acid[23] was heated to 180–190° for 5 min. and was then sublimed at 100° and 0.05 mm. for 5 hr., m.p. 160–162°, ν_{max} 1775 cm.$^{-1}$ and 1845 cm.$^{-1}$.

Dimethylverticillatine (IV).—Verticillatine (II) (300 mg.) slowly dissolved in a mixture of 10 ml. methanol and 20 ml. of ethereal diazomethane over a 3-day period at 0°. The solution was filtered, concentrated to dryness, and crystallized from methanol to yield 195 mg., m.p. 245–246°. An analytical sample was prepared by recrystallization from methanol, m.p. 243–245°, [α] +159° (c, 1.59), λ_{max} 280 mμ (ε 14200), λ_{min} 258 mμ (ε 10700), ν_{max} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; mol. wt., 449.5. Found (after drying to constant weight at 100° C.): C, 72.04; H, 6.86; mol. wt. (by titration), 452.

Dihydrodimethylverticillatine (VI).—A solution of 113 mg. of dimethylverticillatine (V) in 10 ml. of ethanol acidified with 2 drops of concentrated by hydrochloric acid and was hydrogenated using 67 mg. platinum oxide as catalyst. After 2 hr. 5.05 ml. of hydrogen was absorbed (theory 5.59 ml.). The solution was concentrated to dryness, taken up in water, made basic, and extracted into chloroform. The chloroform solution was dried over sodium sulfate and concentrated to dryness and the product was crystallized from ether to yield 81 mg., m.p. 180–182°. An analytical sample was prepared by crystallization from acetone–ether, m.p. 187–188°, [α] −99° (c, 1.13), λ_{max} 285 mμ (ε 4160), λ_{min} 258 mμ (ε 660), ν_{max} 1775 cm.$^{-1}$, pK_a' 8.3.

Anal. Calcd. for $C_{27}H_{33}NO_5$: C, 71.81, H, 7.20, mol. wt. 451.5. Found (after drying to constant weight at 100°): C, 71.38; H, 7.20; mol. wt. (by titration), 455.

Tetrahydrodimethylverticillatine (VIII).—To a partial solution of 182 mg. of dimethylverticillatine (V) in 40 ml. of ether was added 180 mg. of lithium aluminum hydride. The mixture was stirred for 18 hr. The excess hydride was then decomposed with water and the ether concentrated 194 mg. of a white froth which crystallized readily from benzene, m.p. 196–202°. An analytical sample was prepared by recrystallization from acetone m.p. 208–209°, [α] +7.5 (c, 1.20) λ_{max} 258 mμ (ε 15900), λ_{min} 248 mμ (ε 14850), $\lambda_{inflection}$ 280 mμ (ε 5260).

Anal. Calcd. for $C_{27}H_{35}O_5N$: C, 71.49; H, 7.78. Found (after drying to constant weight at 100° C.): C, 71.43; H, 7.56.

Diacetyltetrahydrodimethylverticillatine.—Tetrahydrodimethylverticillative (VIII) was dissolved in 1 ml. of pyridine. One milliliter of acetic anhydride was added and the mixture was allowed to stand at room temperature overnight. The solution was concentrated to near dryness, taken up in ether, and extracted into dilute hydrochloric acid. The acid solution was made basic with sodium carbonate and extracted into ether to yield 118 mg. of product. This was purified by elution from grade 3 alumina with benzene as an amorphous solid, λ_{max} 261 mμ (ε 12900), λ_{min} 247 mμ (ε 10900), $\lambda_{inflection}$ 281 mμ (ε 5650).

Anal. Calcd. for $C_{31}H_{39}NO_7$: C, 69.25; H, 7.31; 2-acetyl, 15.64. Found: C, 68.63; H, 7.40; acetyl, 15.53.

Hexahydrodesoxydimethylverticillatine (IX).—A solution of 51.2 mg. of tetrahydrodimethylverticillatine (VIII) was hydrogenated using 33 mg. of platinum oxide catalyst in acidified ethanol. Uptake of 4.08 ml. (theory for 1 mole 2.52 ml.) was complete in 15 min. The reaction mixture was filtered, concentrated, taken up in water, made basic, and extracted with ether. The ether was concentrated and 12 mg. of hexahydrodimethylverticillatine (VII) crystallized, m.p. 146–152°. The remainder of the material in the filtrate could not be obtained crystalline but could be converted to a methiodide on standing overnight in methyl iodide solution. A sample of hexahydrodesoxydimethylverticillatine methiodide (IX) recrystallized from methanol–ether melted at 197–201°, [α] −17° (c, 1.88 in CH_3OH), λ_{max} 285 mμ (ε 4956), λ_{max} 215 mμ (ε 57100), λ_{min} 260 mμ (ε 2830).

Anal. Calcd. for $C_{28}H_{40}NO_4I$: C, 57.83; H, 6.93; 1-C-CH_3, 2.59. Found: C, 57.61; H, 7.05; C-CH_3, 2.63.

Hexahydrodimethylverticillatine (VII).—To a solution of 325 mg. of dihydrodimethylverticillatine in ether was added 325 mg. of lithium aluminum hydride and the mixture was stirred at room temperature overnight. Water was added, the precipitate filtered and washed, and the filtrate concentrated to dryness and crystallized from acetone–methanol to yield 223 mg., m.p. 165–167°. An analytical sample was obtained from the same solvents, m.p. 167–169°, [α] −10° (c, 2.22), λ_{max} 281 mμ (ε 4770), λ_{min} 256 mμ (ε 1114).

Anal. Calcd. for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.19. Found: C, 71.39; H, 8.39.

An amorphous diacetate was prepared in the usual manner and was purified by chromatography on alumina and elution with benzene.

Anal. Calcd. for $C_{31}H_{41}NO_7$: C, 68.99; H, 7.66; 2-acetyl, 15.95. Found (after drying to constant weight at 50°): C, 68.87; H, 7.55; acetyl, 16.14.

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(23) K and K Laboratories, Jamaica, N. Y.

A Novel Rearrangement of Epoxyalkyl Esters[1]

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3,4-Epoxy-2,2,4-trimethylpentyl isobutyrate was found to undergo acid-catalyzed rearrangement predominantly to tetrahydro-2,2,4,4-tetramethyl-3-furyl isobutyrate. Such a rearrangement was indicated to be typical of 3,4-epoxyalkyl esters. Under similar conditions, a 4,5-epoxyalkyl ester underwent reactions typical of conventional epoxides. Mechanisms are proposed to explain the novel rearrangement.

In acidic media, epoxides generally undergo ring-opening reactions accompanied by addition of the acid or solvent molecules, or isomerization to a ketone or aldehyde. These typical reactions were observed in this investigation with 3,4-epoxyalkyl esters, but the predominant reactions with these epoxides were rearrangements to other types of compounds.

With the exception of 2,3-epoxypropyl esters, there is very little information on epoxyalkyl esters in the literature. Some assistance was forthcoming from the work of Gasson and associates, who reported the properties of epoxides with structures related to the epoxyalkyl groups which were the subject of this study.[2a,b,3] These workers found that 2,3-epoxy-2,4,4-trimethylpentane in the presence of sulfuric acid was converted mainly to 2,4,4-trimethyl-1-penten-3-ol, along with

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