Heating was continued for 90 min. On cooling a solid separated 33 [402 mg, 56%, mp 236–238°]. The melting point of this material was not depressed on admixture with a sample of material from the above experiment. The uv and ir spectra were identical.

Registry No.—1, 4414-88-4; 2, 14741-71-0; 4, 22712-49-8; 8, 22712-50-1; 9, 22712-43-2; 11, 22712-44-3; 12, 22712-45-4; 14, 22712-47-6; 15, 25183-97-5; 16, 22712-48-7; 17, 22776-80-3; 22, 25184-00-3; 23, 25184-01-4; 25, 25184-02-5; 26, 25184-03-6; 27, 25184-04-7; 31, 25184-05-8; 32, 25184-06-9; 33, 25184-07-0; 34, 25184-08-1; 35, 25150-05-4; N-ethyl-2-benzimidozoleacetonitrile, 25184-09-2; ethyl- 1-methyl-2-benzimidozoleacetic ester, 2735-61-7.

Acknowledgment.—We wish to acknowledge the support and encouragement of Dr. George deStevens and helpful discussions with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

Dihydro-Reissert Compounds

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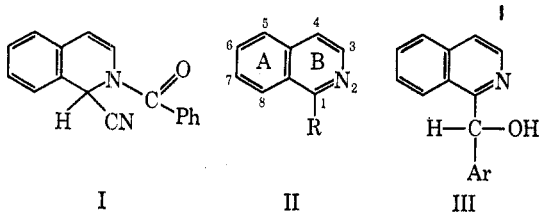
Received February 5, 1970

The dihydro-Reissert compound IV has been alkylated at C-1 to give VIIa, b, or c. Acid hydrolysis of VIIc afforded the acid amide VIII, from which the corresponding methyl ester amide IX could be derived. Hydrolysis of either VIIc or VIII in phosphoric acid furnished the amino acid X. Esterification to XII followed by N-benzoylation resulted in regeneration of the methyl ester amide IX. N-Methylation of the methyl ester XII could be achieved through reductive alkylation. But attempts at internal Friedel–Crafts acylation to obtain an ochotensimine analog did not yield any of the desired tetracyclic product.

Three practical procedures are presently available for the preparation of Reissert compounds,[1-3] and these methods allow for the synthesis of a wide variety of compounds related to structure I.

Two reactions of Reissert compounds have proven particularly useful in the synthesis of benzylisoquinolines. These are alkylation by alkyl halides followed by hydrolysis to yield C-1 alkylated isoquinolines (II),[4] and base-catalyzed condensation with aromatic aldehydes succeeded by hydrolysis to afford isoquinolines of type III.[5,6]



I II III

The literature is virtually devoid, however, of attempts aimed at expanding the Reissert approach to the direct synthesis of 1,2,3,4-tetrahydroisoquinolines. In fact, in only two cases have Reissert compounds lacking the C(3)–C(4) double bond been reported. These two cases are the preparation[6] of a compound tentatively identified as IV, a structure which we confirm in this report, and the synthesis of the amino alcohols V.[7] In neither instance were further reactions attempted on these species for which we now suggest the name "dihydro-Reissert compounds."

(1) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 11 (1955); F. D. Popp, *Advan. Heterocycl. Chem.*, 9 (1968).
(2) J. M. Groscheintz and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **63**, 2021 (1941).
(3) F. D. Popp and W. Blount, *Chem. Ind. (London)*, 550 (1961).
(4) F. D. Popp and J. W. Wefer, *Chem. Commun.*, 207 (1966).
(5) L. Walters, N. Iyer, and W. E. McEwen, *J. Amer. Chem. Soc.*, **80**, 1177 (1958).
(6) H. W. Gibson and F. D. Popp, *J. Chem. Soc. C*, 1860 (1966).
(7) W. Schneider and E. Kaemmerer, *Arch. Pharm.* (Weinheim), **299**, 817 (1966).

Our interest in dihydro-Reissert compounds arose from efforts to synthesize the spirobenzylisoquinoline alkaloid ochotensimine (VI) which incorporates a 1,1-disubstituted 1,2,3,4-tetrahydroisoquinoline skeleton. In the preparation of isoquinolines II and III, the elimination of cyanide ion under hydrolytic conditions is greatly facilitated by the concurrent aromatization of ring B. In dihydro-Reissert compounds, however, such complete aromatization is impossible, and it was surmised that hydrolysis of the cyano group and the amide could proceed without elimination.

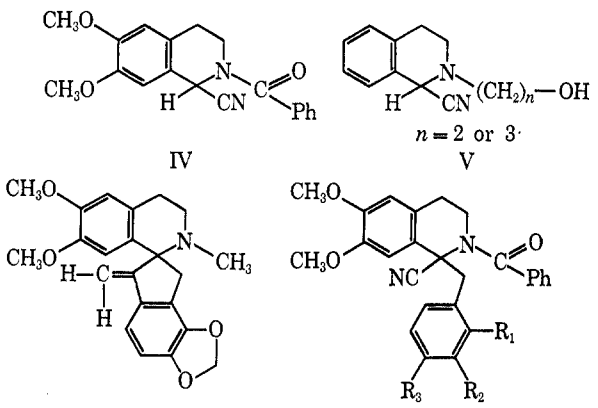
As described in the literature,[3,6] it was found that 3,4-dihydro-6,7-dimethoxyisoquinoline, prepared from N-formylhomoveratrylamine by the Bischler–Napieralski cyclization, could be condensed in the presence of potassium cyanide and benzoyl chloride to afford IV. Treatment of IV with 1 equiv of sodium hydride in dimethylformamide, followed by addition of deuterium oxide, gave starting material in which the hydrogen at C-1 had been completely exchanged for deuterium. It was then found that the anion of IV when treated with benzyl chloride gave a high yield of the tricyclic cyanoamide VIIa. This product was fully characterized spectroscopically. Its formation serves to demonstrate that alkylation of a dihydro-Reissert species proceeds for all practical purposes as readily as that of a Reissert compound.

Similarly prepared were the tricyclic cyanoamides VIIb and VIIc. The oxygenation pattern in the latter product is closely related to that for ochotensimine (VI), so that solely this material was employed in the subsequent investigations.

It was found possible to convert the nitrile function in VIIc to a carbonyl group by first complexing VIIc with zinc chloride in ether, and then hydrolyzing the complex in water. The resulting crystalline acid amide VIII (92% yield) was then esterified.

It will be recalled that loss of cyanide ion occurs readily upon hydrolysis of an alkylated Reissert compound to generate a C-1 substituted isoquinoline sys-

tem. With the alkylated dihydro-Reissert compound VIIc, on the other hand, hydrolysis with phosphoric acid, followed by dilution with water and neutralization, gave rise to a high yield of the desired amino acid X, also obtained by acid hydrolysis of VIII.



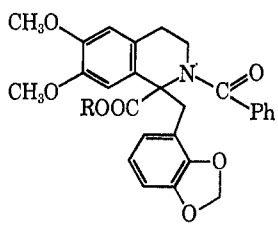
IV

$n = 2$ or 3

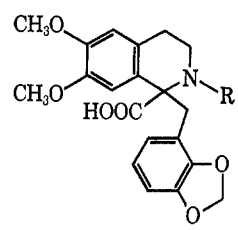
V

VI

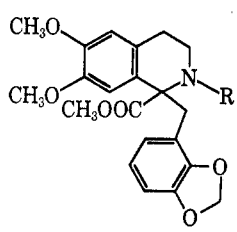
VIIa, $R_1 = R_2 = R_3 = H$
b, $R_1 = H$; $R_2 = R_3$ = methylenedioxy
c, $R_1 = R_2$ = methylenedioxy; $R_3 = H$



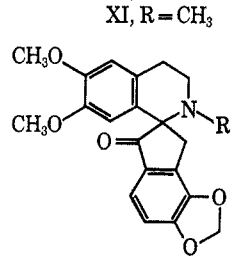
VIII, R = H
IX, R = CH_3



X, R = H
XI, R = CH_3



XII, R = H
XIII, R = CH_3



XIV

Although the insolubility of the amino acid X precluded full characterization, a number of derivatives were prepared. The methyl ester XII was formed by refluxing X in methanolic hydrogen chloride followed by column chromatography over silica gel. N-Benzoylation of this ester provided the methyl ester amide IX, which had earlier been prepared from the acid amide VIII.

N-Methylation of the methyl ester XII was achieved through reductive alkylation employing formalin over a palladium on carbon catalyst. The crystalline tertiary amine XIII was somewhat unstable to air. It could be hydrolyzed to the amino acid XI, and this material could in turn be reesterified to XIII.

A number of attempts to cyclize the tricyclic 1,1-disubstituted benzylisoquinolines VIIc and VIII–XIII by internal Friedel–Crafts type acylation to obtain a species such as XIV were unsuccessful. The same difficulty has been noted by Uyeo in closely related systems.[8] However, Kametani has succeeded in carrying out a cyclization of this type,[9] although in poor yield. Our own efforts at Friedel–Crafts acylation were abandoned when it was found that a biogenetic approach to the spirobenzylisoquinolines of type XIV was more promising.[10]

In conclusion then, it can be stated that dihydro-Reissert compounds can be readily prepared from 3,4-dihydroisoquinolines. The C-1 alkylation of these derivatives proceeds in high yield, thus providing an alternate route to 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines. Finally, removal of the benzoyl group and modification of the cyano function of C-1 alkylated dihydro-Reissert compounds can be carried out without destroying the C-1,1 disubstitution pattern or altering the oxidation state of ring B.

Experimental Section

Standard Experimental Procedures.—All infrared spectra were obtained using a Perkin-Elmer 257 grating infrared spectrometer. The ultraviolet spectra were taken in 95% ethanol and were measured on a Coleman Hitachi 124 double beam spectrophotometer. The nmr data were recorded on a Varian A-60A spectrometer. Except where specified otherwise, deuteriochloroform was the solvent and tetramethylsilane was employed as an internal reference. All mass spectra were obtained on a AEI-MS-902 spectrometer at 70 eV.

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected.

Preparation of 2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (IV).—To 22.6 g (0.118 mol) of 3,4-dihydro-6,7-dimethoxyisoquinoline in 200 cc of methylene chloride was added 35 g (0.54 mol) of KCN in 80 ml of water. Then 48 g (0.34 mol) of benzoyl chloride was added dropwise over 3 hr. After stirring an additional hour, the methylene chloride layer was separated, washed with 10% HCl, 5% NaOH, and dried over magnesium sulfate. Filtration followed by removal of solvent gave a brown oil which after vacuum drying, scratching, and washing with cold methanol yielded white prisms, 25.4 g (67%), mp 215–216°, lit.[6] mp 212–213°; ir ($CHCl_3$) 6.08 μ (amide C=O) and 4.48 (C≡N).

Alkylation of IV.—In a 25-ml flask was placed a suspension of 644 mg (2 mmol) of IV in 4 ml of distilled dry DMF. To the mixture was added 380 mg (2.7 mmol) of benzyl chloride and no visible change was noted on this addition. The suspension was stirred and chilled in an ice bath and then treated with 48 mg (2.0 mmol) of sodium hydride. The ice bath was removed and stirring was continued for 3 hr during which some yellow color appeared in the mixture. The contents were poured into a large volume of water and extracted with chloroform. The chloroform was dried over magnesium sulfate and evaporated to give a white solid which after recrystallization from methanol provided 691 mg (84%) of 1-benzyl-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (VIIa). Mp 185–186°; ir ($CHCl_3$) 6.07 μ (amide C=O) and 4.48 (C≡N); nmr δ 3.88 (s, 6, $ArOCH_3$), 3.94 (AB, 2, ics = 53 Hz and J = 13 Hz, $PhCH_2$), 6.5 to 7.5 (m, 12, Ar-H).

Anal. Calcd for $C_{26}H_{24}O_3N_2$: C, 75.70; H, 5.87; N, 6.79. Found: C, 75.45; H, 5.98; N, 6.60.

Using the appropriately substituted benzyl chlorides, 1-(3′,4′-methylenedioxylbenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (VIIb) and 1-(2′,3′-methylenedioxybenzyl)-2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldonitrile (VIIc) were prepared in the same manner as VIIa. The following data were obtained for these compounds. VIIb: ir ($CHCl_3$) 6.07 μ (amide C=O), 4.48 (C≡N); mp 191–192°; uv max (95% C_2H_5OH), 285 mμ (log ϵ 3.68); nmr δ 3.92, 2.94 (s, 6, $ArOCH_3$), 5.90 (s, 2, $O\text{-}CH_2\text{-}O$), 6.1 to 7.5 (m, 10, ArH). VIIc: ir ($CHCl_3$) 6.07 μ (amide C=O), 4.48 (C≡N); mp 187–188°; uv max (95% C_2H_5OH), 284 mμ (log ϵ 3.70); nmr δ 3.82 (s, 6, $ArOCH_3$), 3,89 (AB, 2, ics = 48 Hz, J = 13.5 Hz, Ar–CH_2–C(CN)–), 5.53 (AB, 2, ics = 5 Hz, J = 1.3 Hz, $O\text{-}CH_2\text{-}O$),

(8) H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc. C*, 3051 (1968).

(9) T. Kametani, S. Takano, and S. Hibino, *J. Pharm. Soc. Jap.*, **88**, 1123 (1968).

(10) M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, **91**, 4009 (1969).

6.2 to 7.5 (m, 10, Ar-H); mass spectrum M^+ at m/e 456 for $C_{27}H_{24}O_5N_2$.

1-(2′,3′-Methylenedioxybenzyl)-2-benzoyl-6,7-dimethoxy-1,2,-3,4-tetrahydroisoquinaldic Acid (VIII).—In a 500-ml flask was placed a mixture of the above VIIc (10 g, 0.022 mol), 200 cc of dry ether, and 10 g (0.074 mol) of anhydrous zinc chloride. The mixture was chilled to 0° and dry HCl was bubbled in for 8 hr during which time the formation of a yellow complex was noted. The mixture was then allowed to stand for an additional 10 hr and the ether evaporated to a yellow hygroscopic mass which was dissolved in water and chloroform. The chloroform layer was separated, washed with water, dried over magnesium sulfate, filtered, and evaporated. White crystals were obtained which recrystallized well from methanol. The yield of VIII by this procedure was 9.5 g (92%). Mp 216–218°; ir ($CHCl_3$) 5.79 to 5.85 μ (acid C=O), 6.13 (amide C=O); uv max (95% C_2H_5OH), 285 mμ (log ϵ 4.06); nmr δ 3.73, 3.78 (s, 6, $ArOCH_3$), 3.85 (AB, 2, ics = 40 Hz, J = 14 Hz, $Ar-CH_2-\underset{|}{\overset{|}{C}}-COOH$), 5.75 (AB, 2, ics = 7 Hz, J = 0, $O-CH_2-O$), 6.1 to 7.6 (m, 10, ArH); mass spectrum M^+ at m/e 475 for $C_{27}H_{25}O_7N$.

Anal. Calcd for $C_{27}H_{25}O_7N$: C, 68.20; H, 5.30; N, 2.98; O, 23.56. Found: C, 68.05; H, 5.35; N, 3.05; O, 23.90.

Preparation of 1-(2′,3′-Methylenedioxybenzyl)-2-benzoyl-1,2,-3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid Methyl Ester (IX). Method 1. Direct Esterification.—A mixture consisting of 500 mg of VIII, 10 cc of water, 10 cc of concentrated HCl, and 10 cc of methanol was refluxed together vigorously for 12 hr. During the reflux, the product (IX) separated from the reaction mixture as white crystals. It was collected by filtration and after drying the crude methyl ester was recrystallized from methanol–water, 413 mg (80%).

Method 2. Formation of Acid Chloride and Reaction with Methanol.—A sample of VIII which had been vacuum dried over P_2O_5 was stirred for 3 hr with 1 cc of purified thionyl chloride. The excess reagent was evaporated and 10 ml of methanol added. After standing for 1 hr, the methanol was evaporated to yield a white residue which was recrystallized as above to give 490 mg (95%) of IX.

The products produced by the above methods were identical in all respects and gave the following analytical data. Mp 215–216°; ir ($CHCl_3$) 5.79 μ (ester C=O), 6.13 (amide C=O); uv max (95% C_2H_5OH), 283 mμ (log ϵ 4.10); nmr δ 3.70 (s, 3, $COOCH_3$), 3.86, 3.92 (s, 6, $ArOCH_3$), 3.98 (AB, 2, ics = 46 Hz, $O-CH_2-O$), 6.1 to 7.5 (m, 10, Ar-H); mass spectrum M^+ at m/e 489 for $C_{28}H_{27}O_7N$.

Anal. Calcd for $C_{28}H_{27}O_7N$: C, 68.75; H, 5.58; N, 2.86; O, 22.91. Found: C, 68.52; H, 5.76; N, 2.80; O, 23.20.

1-(2′,3′-Methylenedioxobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid (X).—This amino acid can be prepared by the phosphoric acid catalyzed hydrolysis of either VIIc or VIII.

In a 100-cc flask, 40 cc of 85% phosphoric acid was heated under N_2 in an oil bath to 100°. There was then added 5.0 g of powdered starting material (VIIc or VIII) and the mixture was heated for 10 min while stirring vigorously. Benzoic acid appeared on the inner walls of the flask. At the end of the heating period 40 ml of water was added, the mixture cooled, and the benzoic acid removed by filtration. The light yellow filtrate was carefully basified to pH 7 with concentrated ammonium hydroxide while cooling in an ice bath. This caused precipitation of a creamy mass which after collection, washing with water, and vacuum drying gave light tan crystals, mp 275° dec, which left no residue on ignition. Regardless of which starting material was used, the yield was 90%. Due to its extreme insolubility in all common solvents, little direct spectral data were obtained for the amino acid; ir ($CHCl_3$) 6.15 μ (amino acid C=O). Instead, the characterization of X rested on further chemical transformations.

1-(2′,3′-Methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid Methyl Ester (XII).—The above amino acid, X, 12 g (0.034 mol), was suspended in 300 ml of methanol and saturated for 4 hr with dry HCl. The resulting solution was refluxed for 60 hr under N_2, during which some darkening occurred. The brown reaction mixture was evaporated to dryness, water added, and the mixture basified with ammonium hydroxide and extracted with ether. After drying over magnesium sulfate, filtration, and removal of solvent, the crude ester was obtained as a brown oil. Purification by chromatography over a $1^1/_4$ in. × 4 ft silica gel column with ether eluent gave 8.2 g (66%) of XII as a light tan oil. Ir ($CHCl_3$) 5.80 μ (ester C=O); nmr δ 3.62 (s, 3, $COOCH_3$), 3.77, 3.83 (s, 6, $ArOCH_3$), 5.79 (s, 2, $O-CH_2-O$), 6.4 to 7.2 (m, 5, ArH); mass spectrum M^+ at m/e 385 correct for $C_{21}H_{23}O_6N$.

A sample of the tan oil was benzoylated with benzoyl chloride in the presence of triethylamine to give IX.

Anal. Calcd for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.15; H, 6.02.

1-(2′,3′-Methylenedioxybenzyl)-2-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinaldic Acid Methyl Ester (XIII).—The ester XII, 1.5 g (3.9 mmol), was dissolved in 70 ml of methanol, treated with 10 cc of formalin, and hydrogenated over 0.5 g of 5% Pd on carbon at room temperature for 12 hr. Crystallization of the product by trituration with ether gave 800 mg (51%) of white crystals which slowly turned yellow when exposed to air. Mp 112–114°; ir ($CHCl_3$) 5.82 μ (ester C=O); uv max (95% C_2H_5OH) 284 mμ (log ϵ 3.76); nmr δ 2.52 (s, 3, $N-CH_3$), 3.72 (s, 3, $COOCH_3$), 3.80, 3.82 (s, 6, $ArOCH_3$), 5.68 (AB, 2, ics = 12 Hz, J = 1.5 Hz, $O-CH_2-O$), 6.1 to 6.6 (m, 5, ArH); mass spectrum M^+ at m/e 399 for $C_{22}H_{25}O_6N$.

Anal. Calcd for $C_{22}H_{25}O_6N$: C, 66.15; H, 6.31. Found: C, 65.99; H, 6.25.

1-(2′,3′-Methylenedioxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,-4-tetrahydroisoquinaldic Acid (XI).—A solution of 700 mg (1.75 mmol) of XIII in 20 ml of methanol was mixed with 1.0 g of KOH in 20 ml of water and refluxed for 12 hr to give a pale yellow solution. The mixture was cooled and the methanol evaporated. The residual aqueous phase was washed several times with ether. The aqueous solution was then adjusted to pH 6 with phosphoric acid whereupon white crystals appeared. After collection on a filter and drying, the slightly tan crystals weighed 532 mg (79%). Mp 200–205° dec; ir ($CHCl_3$) 6.09 μ (acid C=O); nmr δ 2.90 (s, 3, $N-CH_3$), 3.84 (s, 6, $ArOCH_3$), 5.81 (s, 2, $O-CH_2-O$), 5.7 to 7.3 (m, 5, Ar-H), 7.8 (s, 1, COOH).

Reesterification of XI with methanol–HCl gave a 70% yield of XIII.

Registry No.—VIIa, 25186-58-7; VIIb, 25186-59-8; VIIc, 25186-60-1; VIII, 25186-61-2; IX, 25186-62-3; X, 25186-63-4; XI, 25186-64-5; XII, 25150-09-8; XIII, 25186-65-6.

Acknowledgments.—The authors are grateful to the National Institutes of Health for Research Fellowship 2 FO1 GM-33,013-03 to C. D. J., and for Research Grant 9 RO1 HE 12971-08 from the National Institutes of Health.