Anal. Calcd for $C_{13}H_8Cl_2O_2$: C, 58.45; H, 3.02; Cl, 26.55. Found: C, 58.00; H, 2.99; Cl, 26.02.

Decarboxylation of 2',3'-Dichloro-4-biphenylcarboxylic Acid (III).—A mixture of III (1.28 g, 4.79 mmoles), quinoline (7.0 ml), and basic cupric carbonate (100 mg) was heated rapidly to 240° with a free flame and maintained at 240–252° for 25 min. After cooling to room temperature, the mixture was diluted with 75 ml of ether and filtered. The filtrate was washed in succession with two 50-ml portions each of 2% sodium hydroxide, 1 *N* hydrochloric acid, and water, then dried over Drierite and concentrated *in vacuo* on a rotary evaporator. The residual oil weighed 0.66 g and gave an infrared spectrum (neat) differing from that of pure 2,3-dichlorobiphenyl in only minor respects. Analysis by gc (usual procedure, column A) showed that the oil contained 90% of this substance; thus, the yield was 0.59 g, or 55%.

Phenylation of *o*-Dichlorobenzene with Benzoyl Peroxide.—A solution of 12.1 g (0.0500 mole) of benzoyl peroxide in 60 ml of *o*-dichlorobenzene was added dropwise over a period of 75 min to 150 ml. of the solvent. The mixture was stirred rapidly during the addition and kept at 136–142°. After an additional 4 hr of stirring at 136–140°, the dark solution was worked up by a procedure similar to that used for most of the homolytic decarboxylation experiments. Analysis of fraction A by the usual gc technique showed that a mixture of 2,3- and 3,4-dichlorobiphenyl containing 64 ± 3% of the former isomer had been formed in 38% yield.

Preparation of 2,4',5-Trichlorobiphenyl.—A pasty mixture of *p*-chlorobenzoyl peroxide and dibutyl phthalate (Wallace and Tiernan "Luperco BDB") was extracted repeatedly with cold methanol to remove the ester. The residual peroxide, mp 142.5–143.5° (lit.[58] mp 138°), was shown by iodometry to be 98% pure. This material (15.5 g, 0.0500 mole) was added in small portions with stirring to 200 g of *p*-dichlorobenzene kept at 79–82°. The mixture was heated at 75–97° for 18 hr, cooled, diluted with 400 ml of benzene, filtered to remove 3.6 g of *p*-chlorobenzoic acid (mp 238–241°), and then processed in the usual way (*cf.* preceding experiment). Distillation of fraction A through a spinning band column afforded 8.37 g (32% yield) of 2,4',5-trichlorobiphenyl, bp 154° at 2.5 mm. The product solidified upon cooling and was recrystallized from ethanol to give slender, snow-white needles melting at 65.0–65.5° (lit.[59] mp 67°). The mass spectrum exhibited parent peaks at *m/e* 256, 258, 260, and 262; their intensities were in the ratio expected for a substance containing three atoms of chlorine.

Acknowledgments.—The author is indebted to the Esso Research and Engineering Company for permission to publish this work, and to Dr. R. H. Perry, Jr., for encouragement and support. Expert technical assistance was provided by Mr. H. J. Tarski.

(58) D. H. Hey and E. W. Walker, *J. Chem. Soc.*, 2213 (1948).
(59) V. Bellavita, *Gazz. Chim. Ital.*, **65**, 632 (1935).

Synthesis of Protoemetine. A New Total Synthesis of Emetine

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Received June 22, 1965

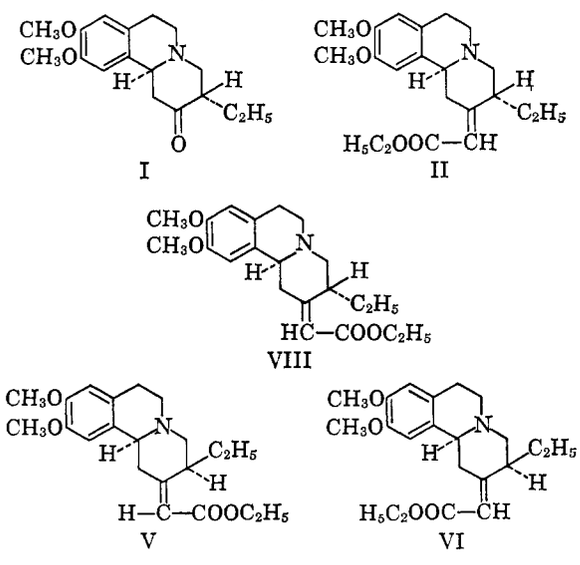
The reaction of 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (I) with phosphonoacetic acid esters, in the presence of potassium *t*-butoxide, gave different stereoisomers of the α,β-unsaturated esters, depending on the conditions used. Catalytic hydrogenation of the appropriate isomer and reduction of the product with diisobutylaluminium hydride gave protoemetine in excellent yield. Pictet–Spengler condensation of the latter with 3-hydroxy-4-methoxyphenethylamine produced cephaeline as the main product besides a small amount of isocephaeline. This suggests that the biogenesis of cephaeline must involve the action of enzyme. O-Methylation of the phenolic base yielded emetine. The above reaction series was carried out both with racemic and optically active compounds.

In the last few years there has been quite extensive research activity in the field of the ipecacuanha alkaloids which are of chemical as well pharmacologic interest.[2]

By investigating the chemistry of the bases that can be obtained from heterocyclic imonium salts, we have been able to develop a simple method for producing in excellent yield[3] the benzo[*a*]quinolizine ring system, the common structural feature of ipecacuanha alkaloids. It therefore seemed feasible for us to participate in the efforts aimed at the development of a reasonable synthesis of these alkaloids. Brief mention of our results has already been made.[4,5] They are now presented in detail.

While 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (I) (Chart I) is obtained in good yield,[3] it has been rather difficult to utilize this compound by subjecting it to condensation reactions. It does not react with esters of malonic acid, while the condensation product[6] with malononitrile which is obtained relatively smoothly isomerizes under the conditions of hydrolysis to give a compound which contains the originally exocyclic double bond in

CHART I



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(2) In summary form, see (a) Cs. Szántay, *Magy. Tud. Akad. Kem. Tud. Oszt. Kozlemen.* (Contributions of the Department of Chemical Sciences of the Hungarian Academy of Science), **23**, 109 (1965); (b) Cs. Szántay in "Recent Development in the Chemistry of Natural Carbon Compounds," Vol II, Akademiai Kiado, Budapest, in press.

(3) D. Beke and Cs. Szántay, *Chem. Ber.*, **95**, 2132 (1962); *Magy. Kem. Folyoirat*, **68**, 426 (1962); Cs. Szántay and J. Rohály, *Chem. Ber.*, **98**, 557 (1965); *Magy. Kem. Folyoirat*, **70**, 478 (1964).

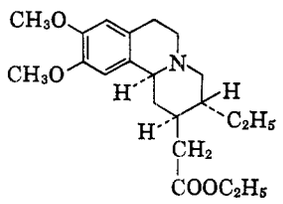
(4) Cs. Szántay, L. Töke and P. Kolonits, *Tetrahedron Letters*, 247 (1963).

(5) Cs. Szántay and L. Töke, *ibid.*, 1323 (1963).

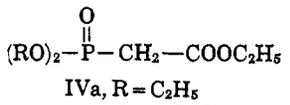
endocyclic form.[6,7] Hydrogenation of this compound, or of its derivatives, produces mixtures of epimers.[8,9]

The condensation reaction can be carried out effectively also with cyanoacetic acid ethyl ester.[6,9] However, the selective hydrogenation of the product proved that even during the condensation process epimerization occurs at the position 3 of the benzo[*a*]quinolizine system.[9,10] On the other hand Openshaw and Whittaker[10,11] obtained the unsaturated ester II in 58% yield by treating the ketone I with triphenylphosphorylideneacetic acid ester. This compound is excellently suited for further synthesis, because its catalytic hydrogenation affords the 2,3-*trans*-2-alkoxycarbonylmethyl-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (III) (Chart II) as a main product.

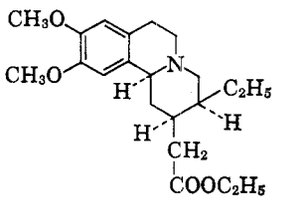
CHART II



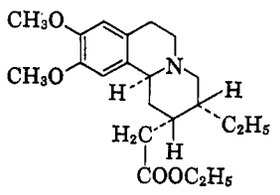
III



IVa, R = C_2H_5
b, R = *i*-C_3H_7



VII



IX

Results

We have studied the reaction of I with the phosphonoacetic acid esters (IV), which are good reagents to introduce an alkoxymethylene group in the place of the oxo function.[12]

The reaction of ketone I with phosphonic acid derivative IVa, when carried out in cold dimethylformamide (DMF) or in absolute ethanol in the presence of potassium *t*-butoxide, produced the expected ester II in good yield. From the mother liquor, the isomer V could be isolated. When the reaction was carried out using the base in excess, the main product was another stereoisomer (VI).

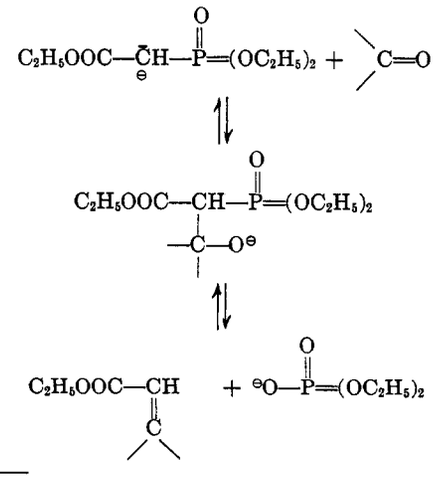
Catalytic hydrogenation of both unsaturated compounds V and VI produced the same saturated ester VII, which was identified in the form of its β-(3,4-dimethoxyphenyl)ethylamide.[13,14] Consequently, these derivatives (V and VI) must be *cis–trans* isomers with respect to the double bond. Configurations were assigned on the basis that the infrared spectrum of compound V exhibited the carbonyl bond at a higher frequency (1725 cm^{-1}) than that of compound VI (1714 cm^{-1}). This phenomenon was attributed to increased interference between ester and ethyl groups in V.

We came to similar conclusions by studying the nmr-spectra of the compounds in question. The aromatic proton at C-11 of ester V resonates at δ 6.66, whereas the corresponding signal of VI and II is found at a higher field (δ 6.83) due to the deshielding effect of ester-carbonyl group, while the signal of the other aromatic proton (C-8) remains unchanged. Furthermore, the two methoxyl groups of ester V appeared as a singlet (δ 3.83), but appeared at slightly different frequencies (J = 4 cps) in the spectrum of VI and II. The general validity of these observations has been proved in the case of several other model substances which will be published in detail, within a different context, in the near future.

The reaction of compound I with IV in 1,2-dimethoxyethane was investigated by Openshaw and Whittaker.[10] When the reaction was carried out in the presence of NaH, only two isomers (V and VI) of the desired compound (II) were isolated; compound II appeared only when $NaOCH_3$ was used as the base. From these results they concluded that the extent of the epimerization is directly dependent on the strength of the applied base.

On the strength of our observations, however, the above mentioned epimerization is dependent not on the strength but on the amount of excess base. The explanation for this may be found in a phenomenon similar to the "2-alkyl ketone effect."[15] The sp^2-hybridized carbon atom 2 is linked to carbon atom 3, which in turn is attached to the ethyl group. Consequently the ethyl group in the *e* position takes up a nearly eclipsed conformation in relation to the bulky groups adjacent to the olefinic bond.

Since the mechanism of the reactions of "PO-activated" compounds is very similar to that of the Wittig reaction,[16] where the addition of the reagent to the



(6) A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953).

(7) A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Wursch, F. Schneider, and O. Schnider, *Helv. Chim. Acta*, **42**, 772 (1959).

(8) A. Brossi, M. Baumann, and O. Schnider, *ibid.*, **42**, 1515 (1959).

(9) A. Brossi and O. Schnider, *ibid.*, **45**, 1899 (1962).

(10) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1461 (1963).

(11) H. T. Openshaw and N. Whittaker, *Proc. Chem. Soc.*, 454 (1961).

(12) L. Horner, H. Hoffmann, W. Klink, H. Ertel, and V. C. Toscano, *Chem. Ber.*, **95**, 581 (1962), and references therein.

(13) We express our sincere thanks to Dr. A. Brossi (Basel) and Dr. J. Osbond (Herts) for kindly supplying us with samples of compounds synthesized by them.

(14) Brossi, *et al.*,[8] originally presented a different configuration for ester VII from that of the formula illustrated above. Therefore in our preliminary communication[4] we also used the incorrect symbol. Eventually this has been cleared up, and the correct formula is given as above (VII). We are very grateful to Dr. H. Openshaw (Beckenham) for calling our attention to these facts and to Dr. Brossi for kindly allowing us to read the pertinent article before publication.

(15) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).

(16) L. Horner, W. Klink, and H. Hoffmann, *Chem. Ber.*, **96**, 3133 (1963).

oxo compound is considered to be reversible,[17] we can postulate that the first step of this reaction occurs in an analogous manner.

The energy difference between the *a* and *e* positions of the C-3 substituent on I can be estimated to be only about 1.1 kcal/mol (*cf.* ref 15). Consequently, if thermodynamic equilibrium is attained in the presence of base, a significant proportion of I will be present in the form containing the ethyl group in the axial position and the reversible first reaction step postulated above occurs with both forms. With the ethyl group in the axial position, the possibility of stabilization of the intermediate in the direction of the end product is greater; therefore this form reacts more readily than the form containing the equatorial ethyl group despite the fact that the latter is present in much larger concentration. This would explain why V and VI are the main products of the reaction.

The epimerization of C-3 in the reaction of ketone I with cyanoacetic acid ester can probably be explained in a similar manner. Although the situation has not yet investigated, the product obtained by condensation of I with malononitrile would be expected to have the ethyl group in the axial position also.

The decisive influence of steric interactions seems to be supported by the fact that the isolation or chromatographic detection of a compound having the structure VIII was not possible. This opinion is also supported by our observation that increasing the steric bulk of the reagent (IVb) results in a much slower reaction rate and a significantly higher portion of the epimeric products V and VI.

The optically active ketone I*[18] needed for the production of optically active ester II* was obtained by resolving the racemic compound, using the excellent method of Openshaw and Whittaker.[10] Since excess of base promotes epimerization, the optically active ketone I* was treated with a large excess of the phosphonic acid derivative IVa; this led to the formation of ester II* in excellent optical purity. Hydrogenation of racemic ester II, and the optically active ester II*, afforded the saturated derivative III and III*, respectively, as described in the literature.[10,11]

It should be noted that besides the main product III we were able to isolate its epimer IX, in crystalline form. The methyl ester of the latter has been described as an oil.[10]

In order to accomplish the synthesis of protoemetine (X) it is necessary to reduce the saturated ester to the corresponding aldehyde. X, first isolated by Battersby, *et al.*,[19,20] is a very labile compound; therefore, its synthesis requires mild reaction conditions.

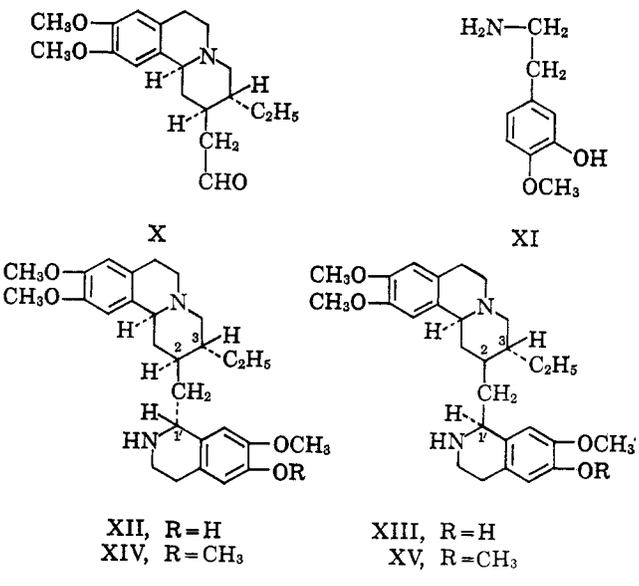
Among the methods recommended in the literature, the reduction with $LiAlH_4$[21,22] of the N-methylanilide or imidazolide derivative of ester III was unsuccessful. However, protoemetine was obtained in very good yield, both in its racemic (X) and its optically active (X*) form by using the method of Zakharin and Khorlina,[23] *i.e.*, by reduction of the corresponding ester (III or III*, respectively) at −60° in toluene solution with diisobutylaluminium-hydride.

Protoemetine occupies a key position among the ipecacuanha alkaloids because, according to a plausible hypothesis,[21] it is considered to be intermediate product in the biogenesis of emetine. The earlier concept of the essential role of a Pictet–Spengler reaction in the biogenesis of the isoquinoline alkaloids[24] seems to be strongly supported by the relatively recent isolation of protoemetine (X*), cephaeline (XII*), and emetine (XIV*) from the same ipecacuanha root.

Battersby, *et al.*, had attempted to condense it (X*) with 3,4-dimethoxyphenethylamine in a Pictet–Spengler type of reaction, but neither emetine nor any similar product could be isolated from the reaction mixture.

We found that the reaction of the racemic protoemetine (X) (Chart III) with 3-hydroxy-4-methoxyphenethylamine (XI) under mild quasi-physiological conditions led to the formation of the hitherto unknown racemic cephaeline (XII); however, in addition, racemic isocephaeline (XIII, the C-1′ epimer of XII) was also obtained in small yield. The same reaction, using optically active protoemetine (X*) gave optically active cephaeline (XII*) and isocephaeline (XIII*). From this observation it can be concluded that the reaction is not completely stereospecific.

CHART III



In order to achieve full stereospecificity many different variations of the experimental conditions were attempted. These studies extended to variations of the pH (between 1 and 13 at 0.5 intervals) the concentration (between 0.1 mole/l. and 0.0001 mole/l.) and the type of acids used (hydrochloric acid, acetic acid, and oxalic acid). The reaction was carried out even in various organic solvents (changing their polarity between wide limits), although such conditions cannot correspond, of course, to the circumstances prevailing during biogenesis. The reaction was followed by

(17) H. J. Bestmann and O. Kratzer, *Chem. Ber.*, **95**, 1894 (1962).

(18) As customary, we have represented only one of the antipodes of the racemic compounds in our present article. In order to avoid any misunderstanding, we have used asterisks to symbolize those optically active compounds, where the formula exclusively denotes absolute configuration.

(19) A. R. Battersby, G. C. Davidson, and B. J. T. Harper, *Chem. Ind.* (London), 983 (1957).

(20) A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, 1748 (1959).

(21) F. Weygand and G. Eberhard, *Angew. Chem.*, **64**, 458 (1952); F. Weygand, *et al.*, *ibid.*, **65**, 525 (1953).

(22) H. A. Staab and H. Brauling, *Ann.*, **654**, 119 (1962).

(23) L. J. Zakharin and J. M. Khorlina, *Tetrahedron Letters*, 619 (1962).

(24) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).

paper chromatography, and it was established that the ratio of the two epimers, despite of the extreme variations of the reaction conditions, was almost invariably the same. The amount of the cephaeline in the final product varied between 60 and 80%, but at least 20% isocephaeline always appeared.

Analogous results were obtained with 3,4-dihydroxyphenethylamine or β-(3,4-dihydroxyphenyl)alanine was condensed with protoemetine.

From these results we conclude that the isoquinoline ring system in the plant is not formed through a simple Pictet–Spengler reaction, but we have to suppose the participation of enzymes in order to explain the stereospecificity of the biosynthetic reaction.

Cephaeline was transformed to emetine by methylation with diazomethane or trimethylphenyl ammonium hydroxide.[25] Thus a new and highly stereoselective total synthesis was achieved.

In addition to emetine its C-1′ epimer, isoemetine (XV), was also isolated in the form of its N-benzoyl derivative.

Experimental Section

Reaction of the Quinolizine (I) with Phosphonoacetic Acid Triethyl Ester (IVa) to Yield Unsaturated Ester (II).—A solution of IVa (52 ml, 0.26 mole) in 52 ml of dimethylformamide was added to solid potassium *t*-butoxide (prepared from 8 g, 0.2 mole, of potassium and *t*-butanol). The mixture was cooled to 0°, and a solution of ketone I (28.9 g, 0.1 mole) in 200 ml of dimethylformamide was added. The solution was allowed to warm to room temperature, stand for 30 hr, and was diluted with 2 l. of water. The aqueous layer was decanted from the resinous product which was then taken up in ether and washed with water, saturated sodium bisulfite, and water again. The ether solution was dried over magnesium sulfate and evaporated to dryness to give 35.5 g (99%) of partly crystalline, resinous product. This was recrystallized twice from ethanol to yield 21.2 g (59%) of II, mp 99–101°. The product showed infrared absorption at 1715 cm^{-1} (C=O) and nmr peaks at δ 6.83 (C-11 proton), 6.60 (C-8 proton), 5.67 (olefinic proton), 4.53 (C-11b proton, quartet with coupling constants of 2 and 14 cps), 4.20 (ester methylene protons, quartet, J = 7 cps), 3.89 and 3.82 (methoxy protons), 1.31 (ester methyl protons, triplet, J = 6.5 cps) and 1.07 (methyl protons, triplet, J = 6.5 cps).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.35; H, 8.22; N, 3.91.

Synthesis of Optically Active II*.—Solid potassium *t*-butoxide (from 3.9 g of potassium, 0.1 mole, and *t*-butyl alcohol) was added to a solution of phosphonic ester IVa, (24 ml) in 24 ml of anhydrous dimethylformamide. The mixture, which warmed spontaneously, was cooled to 0° and a solution of (−) ketone I* (2.89 g, 0.01 mole) in 20 ml of cooled dimethylformamide was added. The solution was allowed to warm to room temperature and stand for 16 hr and was diluted with 500 ml of water and treated as described previously to give II*, mp 118–119° (lit.[10] 117–119°), $[\alpha]^{21}D$ +44° (*c* 1 in ethanol) (lit.[10] +44°), in 55% yield.

Isolation of the Ester V.—Racemic ketone I, was allowed to react with IVa as described for the optically active compound. The resinous material (3.6 g, 100%) from the dried ether extract was crystallized from 4 ml of ethanol to give compound II. The mother liquor from this crystallization was treated with 70% perchloric acid to yield 0.96 g of crystalline perchlorate. After recrystallization from ethanol, the melting point was 218–220°.

A suspension of 0.82 g of the perchlorate in 10 ml of water was basified with 5 ml of 10% sodium hydroxide and extracted with 30 ml of ether. The ether solution was dried over magnesium sulfate and evaporated to give 0.63 g of resinous material which was crystallized successively from ethanol and petroleum ether to yield 0.30 g of compound V, mp 79.5–80°. Compound V showed infrared absorption at 1725 cm^{-1} (C=O) and nmr peaks at δ 6.66 (C-11 proton), 6.60 (C-8 proton), 5.85 (olefinic proton), 4.19 (ester methylene protons, quartet, J = 7 cps), 3.86 (methoxyl protons), 1.31 (ester methyl protons, triplet, J = 7 cps) and 0.92 (methyl protons, triplet, J = 7 cps).

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.20; H, 8.03; N, 4.00.

Synthesis of the Ester VI.—Solid potassium *t*-butoxide (from 3.9 g, 0.1 mole of potassium and *t*-butyl alcohol) was dissolved in 16 ml (0.08 mole) of IVa and cooled to room temperature. The racemic ketone I, (11.6 g, 0.04 mole) in 80 ml of dimethylformamide was added and the mixture was allowed to stand for 70 hr. It was poured into 1 l. of water and treated as described in the first experiment above to yield 11.52 g (80%) of resinous product. Treatment of this with 36 ml of ethanol yielded 5.1 g (36%) of crystalline VI. Two recrystallizations from ethanol yielded 1.83 g, mp 108–109°, which showed infrared absorption at 1714 cm^{-1} (C=O) and nmr peaks at δ 6.83 (C-11 proton), 6.60 (C-8 proton), 5.77 (olefinic proton), 4.42 (C-11b proton, quartet, in part disturbed by ester methylene protons), 4.21 (ester methylene protons, quartet, J = 7 cps), 3.90 and 3.82 (methoxyl protons), 1.31 (ester methyl protons, triplet, J = 7 cps), and 0.82 (methyl protons, triplet, J = 7 cps).

Anal. Calcd for $C_{21}H_{29}NO_4$; C, 70.17; H, 8.13; N, 3.90. Found: C, 70.35; H, 8.22; N, 3.91.

Reduction of II to III and IX.—The unsaturated ester II was hydrogenated in the presence of 10% palladium on carbon to yield III in the yield and manner described in the literature.[10] After crystallization of III from ethanol, the mother liquor was allowed to stand at 5° for 2 weeks. Well-developed, water-clear crystals of IX formed and were collected. The original mp 58–60° rose to 61° after recrystallization from petroleum ether.

Anal. Calcd for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.90. Found: C, 69.79; H, 8.57; N, 4.13.

Racemic Protoemetine (I) (X).—A solution of 5.4 g of III in 120 ml of absolute toluene was cooled to −60° and 3.5 ml of diisobutylaluminum hydride was added under dry nitrogen. The solution was kept at −60° for 2 hr before saturated sodium bisulfite (80 ml) was added. The solution was allowed to warm to room temperature and the layers were separated. The toluene layer was extracted twice with 21-ml portions of bisulfite which were combined with the aqueous layer, basified with 2 *N* sodium hydroxide to pH 8–9 (with cooling) and extracted with ether. The ether was washed with water, dried, and evaporated to give 3.95 g (83%) of I as a colorless oil. The product was characterized by preparing a **semicarbazone**, mp 185–186°.

Anal. Calcd for $C_{20}H_{30}N_4O_3$: C, 64.1; H, 8.1; N, 14.9. Found: C, 63.9; H, 8.0; N, 14.9.

When the toluene was evaporated to dryness under vacuum, 0.3 g of starting material was obtained.

(−)-Protoemetine (X*).—Optically active III* was obtained from optically active II* by reduction over palladium.[9] The hydride reduction of (−) III* as described above yielded (−)-protoemetine (I*) identical in every respect with naturally occurring protoemetine.[19,20] The compound was further characterized as a **semicarbazone** and as a **perchlorate**.

The perchlorate was prepared by adding one part of 70% perchloric acid to a solution of one part of base in ten parts of 50% aqueous ethanol. Partial evaporation of the solution yielded the crystalline perchlorate. The properties of the derivatives were identical (infrared spectra, melting point, and optical rotation) with those reported.[19,20]

Racemic Cephaeline (XII) and Isocephaeline (XIII).—A solution of 1.11 g (3.5 mmoles) of racemic X and 0.58 g (3.5 mmoles) of 3-hydroxy-4-methoxyphenethylamine (XI)[26,27] in 10 ml of ethanol was boiled under reflux for 10 min and evaporated to dryness. The residue was warmed on a steam bath with 5 ml of 5% hydrochloric acid for 4 hr, cooled, and basified with 5% sodium carbonate. The precipitate was collected, dissolved in 16 ml of methanol, and treated with 0.4 g of anhydrous oxalic acid. After standing at room temperature for 2 days, 0.8 g of pure (paper chromatography[29]) crystalline racemic cephaeline oxalate, mp 215–217°, precipitated. Recrystalli-

(25) See M. M. Janot in "The Alkaloids," Vol III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1953, p 363.

(26) K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **75**, 5119 (1953).

(27) To exclude the possibility that some 3-methoxy-4-hydroxyphenethyl amine impurity was present, we also prepared the amine XI, starting from pure isovanillin.[28] The Picket–Spengler condensation led also in this case to the same result.

(28) D. Beke and Cs. Szántay, *Acta Chim. Acad. Sci. Hung.*, **14**, 325 (1958).

zation from methanol did not alter the melting point. A portion of the oxalate was treated with 5% hydrochloric acid to yield the **hydrochloride**, mp 258–260°. The ultraviolet spectrum and R_f (paper chromatography) were identical with those of naturally occurring cephaeline hydrochloride.

Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot 2HCl \cdot 2H_2O$: C, 58.5; H, 7.4; N, 4.9. Found: C, 58.3; H, 7.2; N, 4.9.

The free base was prepared from the oxalate and recrystallized from 150 parts of ether to give woolly fine needles, double mp 115–116 and 150°.

Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot H_2O$: C, 69.7; H, 8.3; N, 5.8. Found: C, 69.9; H, 8.2; N, 6.0.

The mother liquor from the cephaeline oxalate was evaporated to dryness, converted to the hydrochloride, and recrystallized repeatedly from ethanol–water until a paper chromatogram showed only one spot with an R_f corresponding to isoemetine. In this manner, 50 mg of isocephaeline hydrochloride, mp 270°, was obtained.

Anal. Calcd for $C_{28}H_{38}N_2O_4 \cdot 2HCl$: C, 62.3; H, 7.5; N, 5.2. Found: C, 62.0; H, 7.5; N, 5.0.

Isocephaeline base, mp 176°, was obtained from the hydrochloride and recrystallized from about 1000 parts of ether.

Methylation of racemic cephaeline and isocephaeline bases with diazomethane yielded products which were similar to those (infrared spectra, paper chromatography, and derivatives) of authentic emetine and isoemetine.

Racemic Emetine (XIV).—The crude mixture of cephaeline and isocephaeline as obtained above was methylated with diazomethane to yield a mixture of emetine and isoemetine. This mixture was separated by crystallization of the oxalate salts as described.[8] The yield of pure emetine was 50% based upon protoemetine.

(−)-Emetine (XIV*).—An aqueous suspension of optically active protoemetine (X*) perchlorate (3.0 g) was covered with an ether layer and basified with sodium hydroxide, with cooling. The layers were separated and the aqueous layer was extracted many times with ether. The combined ether extracts were washed with water, dried, and evaporated to dryness under vacuum to yield 2.16 g of an oily product. This material was combined with 60 ml of water, 3 g of 3-hydroxy-4-methoxyphenethylamine (XI) hydrochloride, and 6.6 ml of acetic acid. The solution (pH 4–4.5) was allowed to stand at 25° until a negative protoemetine test (2,4-dinitrophenylhydrazine) was obtained (44 hr). The aqueous solution was basified with solid sodium carbonate and the base that precipitated was collected and dried over phosphorus pentoxide to yield 2.25 g, mp 85–130°. An additional 0.51 g was obtained by partially concentrating the mother liquor under nitrogen and *in vacuo*. Further concentration yielded the excess of XI originally added. Paper chromatography showed that both fractions (total, 2.76 g, 87%) were identical and that each contained about 75% cephaeline and 25% isocephaeline.

A sample of the mixture of bases (1.7 g) was dissolved in 20 ml of ethanol and treated with an excess of ethereal diazomethane. The solution was allowed to stand overnight and evaporated to dryness. The residue was dissolved in ether, washed with 2 *N* sodium hydroxide and water, dried, and evaporated to yield 1.60 g of a resinous product which was dissolved in 10 ml of methanol and acidified with 48% hydrobromic acid. The solution was kept at 5° overnight and the crystals which precipitated were collected to yield 1.12 g of crude emetine hydrobromide, mp 228–240°. Repeated recrystallization from methanol yielded pure product, mp 244–245°, lit. 243–245[32] and 250–254°.[10]

When the hydrobromide was dissolved in water and basified with ammonium hydroxide, emetine base was obtained: $[\alpha]^{21}D$ −49.2 ± 1° (*c* 2.8 in chloroform), lit.[28] $[\alpha]^{23}D$ −49.2 ± 1° (*c* 3.56 in chloroform). The synthetic products, both salts and free base, were identical (melting point, mixture melting point, infrared spectra, and paper chromatography) with natural materials.

The mother liquor from the crystallization of emetine hydrobromide was evaporated to dryness and the residue was dissolved in water and basified with ammonium hydroxide. The precipitated base was dried, dissolved in 5 ml of pyridine and treated with benzoyl chloride (0.2 ml). The reaction mixture was processed in the usual manner to obtain 0.060 g of N-benzoylisoemetine, mp 202°, lit.[26] 201.5–203°.

Acknowledgment.—We are indebted to Mrs. Ilona Balogh and Mrs. Sarolta Viszt for the microanalyses and to Dr. P. Sohar for the infrared spectra. The work was supported by the Hungarian Academy of Sciences and the Chinoin Pharmaceutical Works.

(29) The paper chromatography was carried out in the system: 2 *N* hydrochloric acid, methyl ethyl ketone, applying descending technic.[7,30] The chromatography was evaluated for 24 hr and the spots were developed with platine iodide solution. For comparison, parallel experiments were conducted in each case with emetine and isoemetine (prepared according to the literature[31]); the R_f value of these two compounds show the ratio 1:0.62.[31] The cephaeline has the same R_f value as emetine, while the isocephaeline shows the same migration as isoemetine.

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Griseofulvin Analogs. I. 5′,7′-Dimethoxyspiro(cyclohexane-1,2′-indan)-1′2,4-trione, the Ring-B Carbon Analog of Dechlorodemethylgriseofulvic Acid

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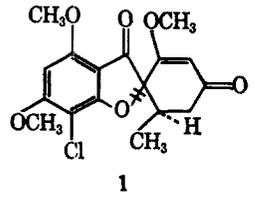
Received November 22, 1965

The synthesis of the title compound is described.

The potent antifungal properties of the mold metabolite griseofulvin (1)[1] made it of interest to prepare some related compounds for biological evaluation.



1

Since no work on structural variations in ring B had been reported,[2] we decided to direct our efforts toward the modification of this part of the molecule. Spe-

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(2a) NOTE ADDED IN PROOF.—Very recently, Mulholl, *et. al.* [*ibid.*, 4939 (1965)], reported on the preparation of ring B sulphur and nitrogen analogs of griseofulvin-like compounds in which ring A was either unsubstituted or mono chlorinated.