Acknowledgment. We wish to thank Mr. W. S. Zawacki for technical assistance, Messrs. T. P. Callan, C. W. Nash and their staffs for analyses, and Dr. H. L. Keil for fungicidal data.

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Simple Procedure for the Conversion of Aryl Halides to the Corresponding Phenols

M. FREDERICK HAWTHORNE

Received March 6, 1957

The use of two well known reactions in series has afforded a relatively rapid and efficient route from aryl halides to the corresponding phenols. The overall reaction sequence employed is illustrated in the following formulation.

$$ArX \longrightarrow ArMgX \xrightarrow[2.\ H_2O,\ H^+]{1.\ B(OCH_3)_3} \underset{+}{ArB(OH)_2} \xrightarrow{10\%\ H_2O_2} ArOH + B(OH)_3$$

$$Ar_2B(OH),\ \text{etc.}$$

The simplicity of the method lies in the fact that the arylboronic acid, which is produced along with varying amounts of other materials having aryl-boron bonds, need not be isolated. Treatment of the crude product (in ethereal solution) with 10% hydrogen peroxide readily degrades the product mixture to the corresponding phenol in 60–80% overall yield (based on aryl halide). The method has been applied to the preparation of phenol, α-naphthol and *p*-cresol which were obtained in 78, 75, and 60% yields, respectively.

EXPERIMENTAL

The experimental procedure is illustrated by the preparation of phenol. To a one-liter three-neck flask equipped with a stopcock on its bottom and carrying a reflux condenser, dropping funnel, stirrer, nitrogen inlet, and drying tube, was added 31 g. (0.33 mole) of pure methyl borate and 400 ml. of dry ether. The apparatus was flushed with dry nitrogen and 200 ml. of 1.5*M* phenylmagnesium bromide was added dropwise over a period of 1 hr. while the contents of the flask were cooled to −80° and rigorously stirred. After the addition the reaction mixture was warmed to room temperature and 200 ml. of 10% hydrochloric acid slowly run in with stirring under nitrogen. The stirrer was stopped and the lower aqueous phase separated by use of the stopcock in the flask bottom. The ether layer was washed twice more with water in this fashion. Two hundred milliliters of 10% hydrogen peroxide was slowly added from the dropping funnel with stirring at such a rate as to maintain gentle reflux. After the addition the mixture was stirred for 15 min. and the layers separated as before. The ether layer was washed with 10% ferrous ammonium sulfate and the phenol extracted by two portions of 10% sodium hydroxide solution. Acidification of the alkaline extract followed by extraction with ether and distillation afforded 22.0 g. (78% theory) of pure phenol, melting at 40–41°.

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Rauwolfia Alkaloids. V.[1] Stereochemical Correlation of Some Indole Alkaloids from the Infrared Spectra

NORBERT NEUSS AND HAROLD E. BOAZ

Received March 12, 1957

In a series of publications on Rauwolfia[2] alkaloids from these laboratories, we have used spectral data for deduction of structural features of reserpine,[3] reserpinine,[4] and deserpidine (recanescine).[5]

Our technique consisted of comparing the infrared spectrum of the naturally occurring alkaloid in chloroform solution[3] with the spectrum of an equimolar solution of a substituted methoxyindole and suitable component, bearing the remaining functional groups of the alkaloid. In the case of reserpinine, for example, it was pointed out that the identity of the wave lengths and intensities of most of the corresponding bands in the spectra of reserpinine and summation of 2,3-dimethyl-6-methoxyindole and tetrahydroalstonine strongly suggests the same steric configuration in these two alkaloids.[4]

After the compilation of the physical data of indole and dihydroindole alkaloids[6] we had on hand the infrared spectra of several heteroyohimbane derivatives in chloroform solution.

A close examination of these spectra permits the assignment of a methoxylated derivative to the tetrahydroserpentine or tetrahydroalstonine series.[7] The present paper deals with our observations in this class of indole alkaloids.

In our studies we have used the following indole alkaloids, derivatives of the heteroyohimbane ring system: aricine (VI),[8] reserpinine (III),[4] isoreserpiline (VIII),[8] raumitorine (VII),[9] tetra-

(1) For paper IV of this series, see S. C. Pakrashi, Carl Djerassi, Richard Wasicky, and N. Neuss, *J. Am. Chem. Soc.*, **77**, 6687 (1955).

(2) In strict usage and in compliance with the International Code of Botanical Nomenclature, the name should be spelled Rauvolfia, J. Monachino, *Economic Botany*, **8**, 349 (1954).

(3) N. Neuss *et al.*, *J. Am. Chem. Soc.*, **76**, 2463 (1954).

(4) N. Neuss *et al.*, *J. Am. Chem. Soc.*, **76**, 3234 (1954) and references cited therein.

(5) N. Neuss *et al.*, *J. Am. Chem. Soc.*, **77**, 4087 (1955).

(6) Lilly collection of Physical Data of Indole and Dihydroindole Alkaloids, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis 6, Ind., 1954 and 1956.

(7) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956), have just classified different indole alkaloids into normal and allo compounds and pseudo or epiallo compounds on the basis of presence or absence of certain bands in the 3.4–3.7 μ region. We would like to thank Dr. Wenkert for sending us the paper prior to its publication.

(8) A. Stoll, A. Hofmann, and R. Brunner, *Helv. Chim. Acta*, **38**, 270 (1955).

(9) Janot, Goutarel, Le Hir, and Poisson, *Compt. rend.*, **239**, 302 (1954).

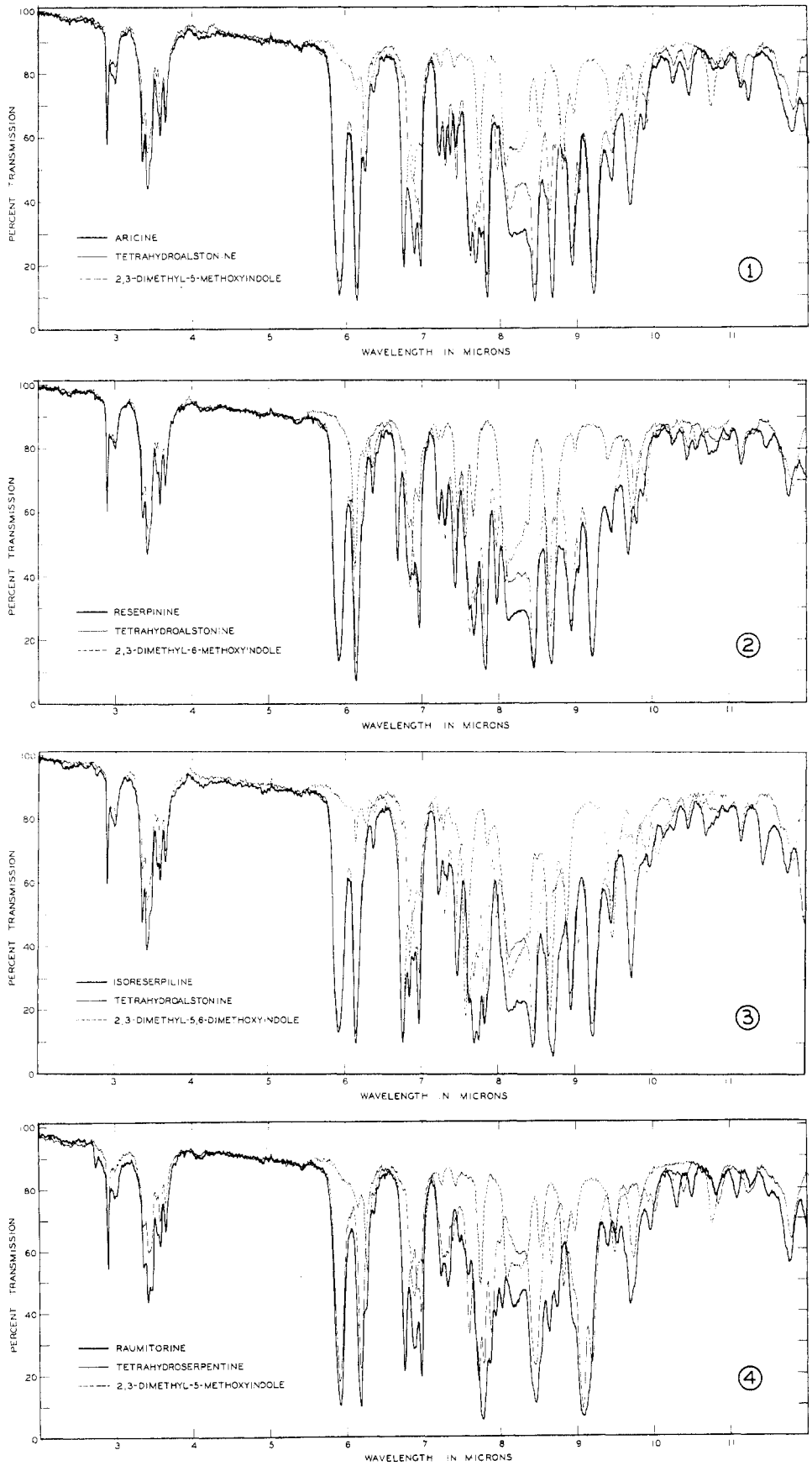
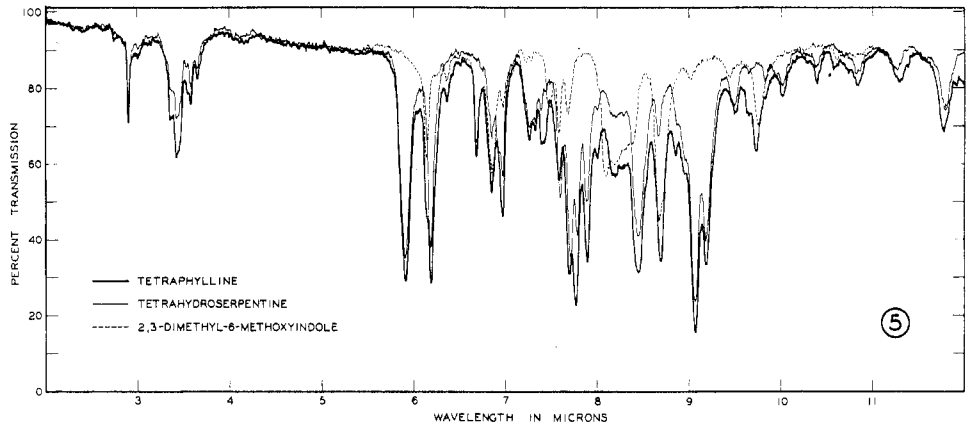
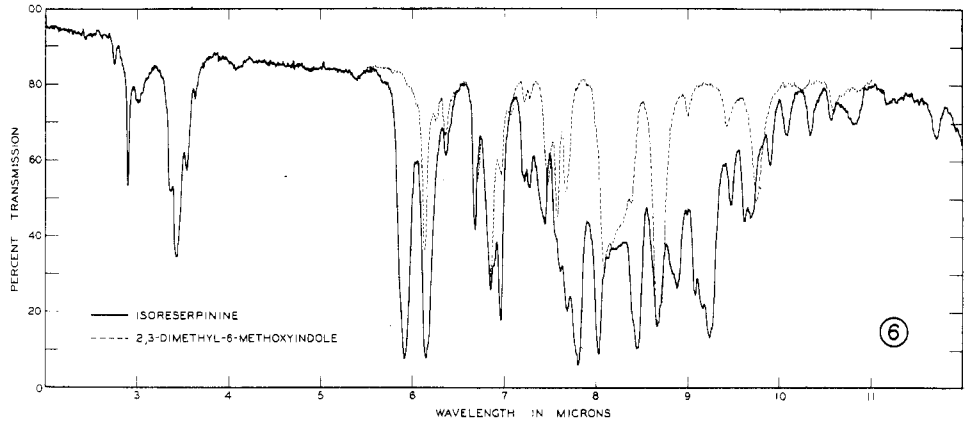
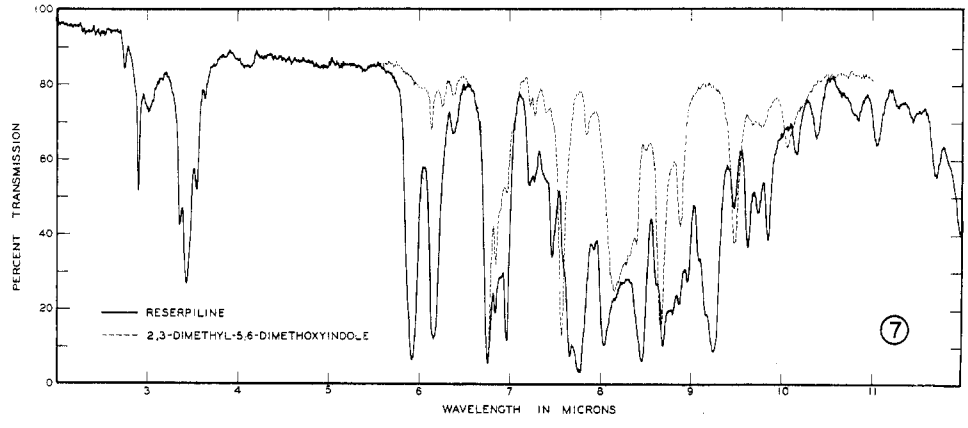
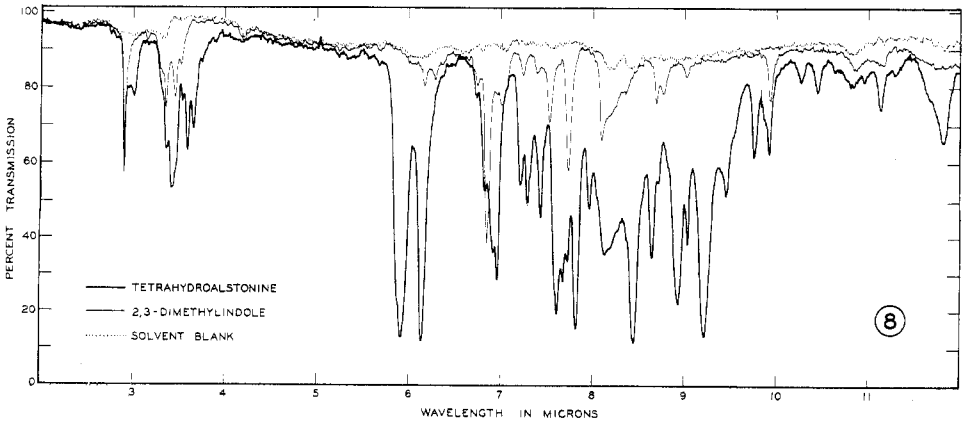


FIG. 1–4. INFRARED SPECTRA OF SOME INDOLE ALKALOIDS.



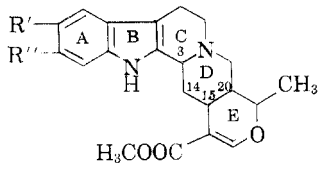






FIGS. 5–8. INFRARED SPECTRA OF SOME INDOLE ALKALOIDS.

phylline (IV),[10] isoreserpinine (V),[7] reserpiline (IX),[11] tetrahydroalstonine (I),[12] and tetrahydroserpentine (II).[4]



R′ = R″ = H; Tetrahydroalstonine (I), Tetrahydroserpentine (II)
R′ = H; R″ = OCH_3; Reserpinine (III), Tetraphylline (IV), Isoreserpinine (V)
R′ = OCH_3, R″ = H; Aricine (VI), Raumitorine (VII)
R′ = OCH_3, R″ = OCH_3; Isoreserpiline (VIII), Reserpiline (IX)

The most obvious features of the infrared spectra of methoxy substituted tetrahydroalstonines and their stereoisomers which can be correlated with the structure are the narrow and relatively intense bands in the 6 to 7 μ region. These bands arise from the peculiar polarization of the indole moiety.[4] Although interaction of the vibrations of this portion of the molecule with those of the conjugated ester vinyl ether in ring *E* of the heteroyohimbane may not be completely absent, it appears to be very small. Likewise there appears from the spectrum as well as from molecular models to be very little if any steric effect of methoxy groups in the 10 and 11 position upon rotational isomerism of the ester or methyl groups in ring *E*. Consequently one can regard in this group of compounds the infrared spectrum to a first approximation as the sum of the spectrum of the corresponding methoxy substituted 2,3-dimethylindole and the spectrum of tetrahydroalstonine or that of the corresponding stereoisomer. (See Fig. 1 to 7)

Deviations from simple summation of spectra between 6 to 7 μ are hardly observable. In the 7 to 12 μ region greater differences in wave length and intensity occur, but they raise little doubt as to which of the more intense bands arise from the indole moiety and which ones represent vibrations of the C-D-E ring system including the ester grouping. Examination of the spectrum of 2,3-dimethylindole (Fig. 8) shows that the contribution of the indole portion of tetrahydroalstonine in the 7 to 12 μ region of the spectrum is relatively small.

All these observations clearly indicate that aricine (VI), reserpinine (III), and isoreserpiline (VIII) are 10-methoxy-, 11-methoxy-, and 10,11-dimethoxytetrahydroalstonine respectively; similarly raumitorine (VII) and tetraphylline (IV) are 10-methoxy- and 11-methoxytetrahydroserpentine. Finally, isoreserpinine (V) and reserpiline (IX) are 11-methoxy- and 10,11-dimethoxy derivatives of a base which is neither tetrahydroalstonine nor tetrahydroserpentine, but resembles tetrahydroalstonine more than tetrahydroserpentine.

The examination of the infrared spectra in carbon disulfide solution of these alkaloids leads also to the conclusion that they can be divided into three groups. (Fig. 9 to 14)

In the first group, including tetrahydroserpentine and tetraphylline, there is a relatively simple ester band[13] at 8.45 μ. (Fig. 9 and 10)

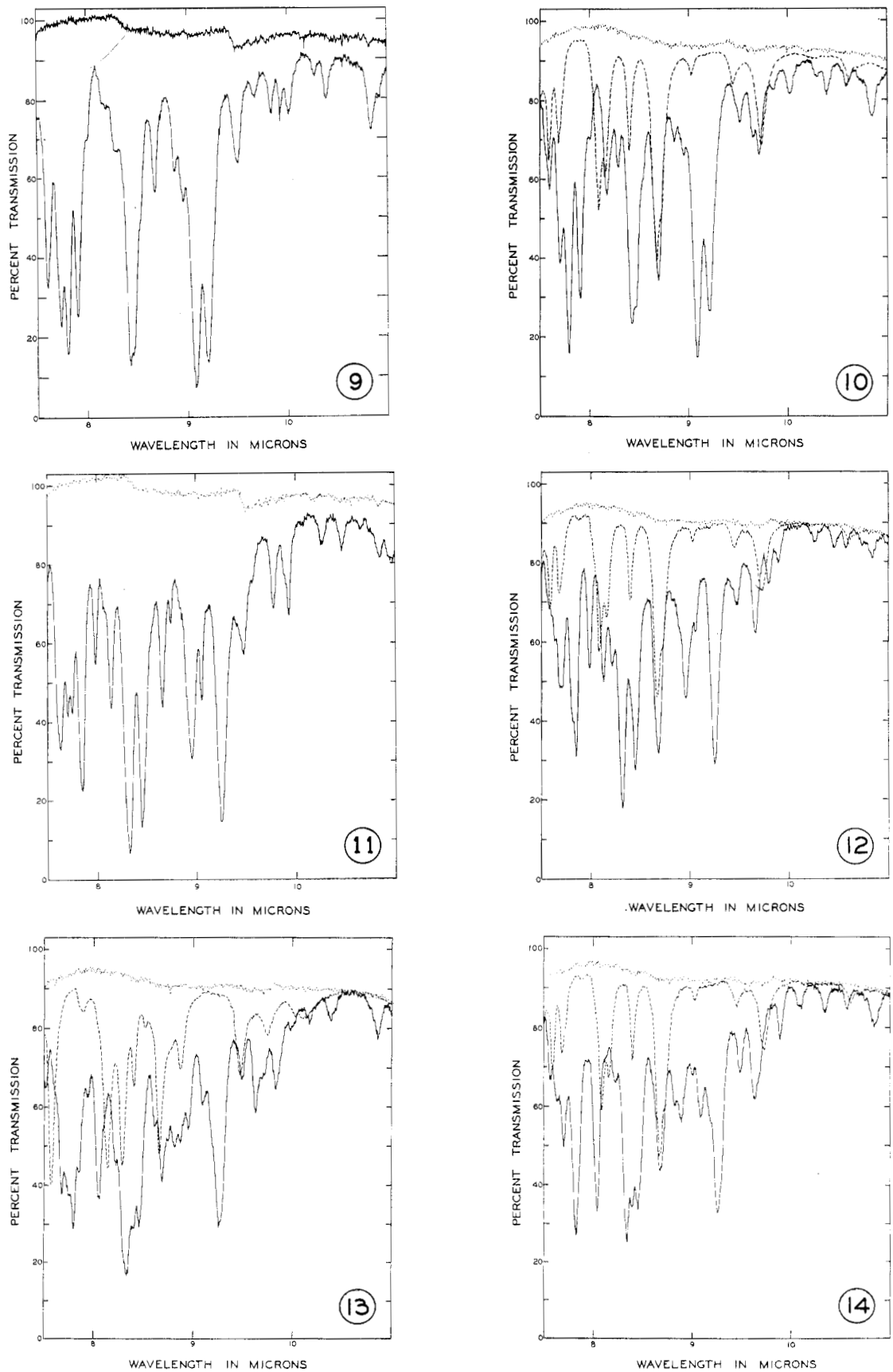
In the second group represented by the spectra of tetrahydroalstonine and reserpinine there appear three distinctly resolved bands at 8.15, 8.32, and 8.45 μ. (Fig. 11 and 12)

The last group contains reserpiline and isoreserpinine. Instead of the characteristic ester bands mentioned in the first two groups there is a broad band at 8.26 μ (Fig. 13 and 14). Our attempts to reconstitute the spectra of these two alkaloids by summation of either tetrahydroalstonine or tetrahydroserpentine and the corresponding substituted indole were unsuccessful.[14] However, the superposition of the spectrum of tetraphylline (Fig. 10), reserpinine (Fig. 12), and isoreserpinine (Fig. 14) clearly shows a much greater similarity of the latter compound to reserpinine than to tetraphylline. Actually the bands at 8.32, 8.45, and 9.25 μ nearly coincide both in wave length and relative intensity in the spectra of these two compounds.[15]

The examination of molecular models (Stuart-Briegleb) of tetrahydroserpentine shows that with a D/E ring junction *cis*, no hindrance to rotation of the carbomethoxy group is evident. Accordingly the infrared spectrum of this alkaloid shows only a small splitting of the ester band. This is in agreement with the findings of Chatterjee *et al.*,[16] who have postulated a *cis* configuration for the D/E ring junction on the basis of the unusual stability to acid of the enol ether linkage of the dihydropyran ring in the ring *E*.

By assembling the molecular model with a *trans* D/E ring junction one observes a restricted rotation of the ester carbonyl hindered by the $C_{(14)}$ methylene hydrogens. As a result the carbon-carbon double bond is in a different plane than the ester carbonyl. In agreement with this configuration the spectrum of tetrahydroalstonine shows a large splitting. Bader has reported the instability of alstonine toward acid and the ease of formation of the 2,4-dinitrophenylhydrazone with a simultaneous fission of the oxygen bridge,[17] and Elderfield

(10) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *J. Am. Chem. Soc.*, **79**, 1217 (1957).
(11) Klohs *et al.*, *Chemistry & Industry*, 1264 (1954).
(12) E. Schlittler, H. Schwarz, and F. Bader, *Helv. Chim. Acta*, **35**, 271 (1952).
(13) This band is missing in the spectrum of tetrahydroserpentinol in pyridine solution.
(14) Mayumbine and akuammigine have been reported to be isomeric with tetrahydroalstonine. Unfortunately we were unable to obtain these alkaloids for this study.
(15) Isoreserpinine is a $C_{(3)}$ epimer of reserpinine. We thank Dr. C. Djerassi for this information prior to publication.
(16) A. Chatterjee and S. K. Talapatra, *Science and Culture (India)*, **20**, 568 (1955).
(17) F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1953).



FIGS. 9–14. INFRARED SPECTRA OF: 9, tetrahydroserpentine; 10, tetraphylline; 11, tetrahydroalstonine; 12, reserpinine; 13, reserpiline; 14, isoreserpinene.

has confirmed this instability for tetrahydroalstonine.[18]

The greater acid stability of tetrahydroserpentine as compared to that of tetrahydroalstonine can be attributed to the difference in configuration at the D/E ring junction.[19]

Additional evidence for these configurations of the C/D ring junction in tetrahydroalstonine and tetrahydroserpentine is furnished by the wave lengths of the C=C bands in the infrared spectra in chloroform solution. This band is found at 6.14 μ in the former and at 6.19 μ in the latter.

The ultraviolet spectrum also corroborates the C/D ring junction as *cis* for tetrahydroserpentine and *trans* for tetrahydroalstonine. Thus the differential ultraviolet spectrum of tetrahydroalstonine *vs.* yohimbane shows distinctly two bands whereas the corresponding differential spectrum of tetrahydroserpentine has only a simple symmetrical band. (Fig. 15)

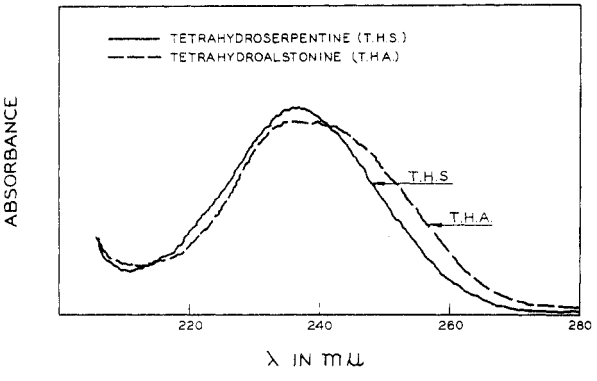
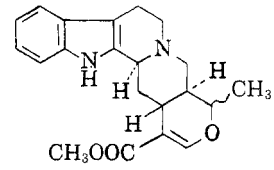


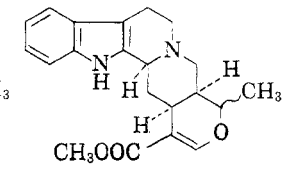
FIG. 15. DIFFERENTIAL U. V. SPECTRUM OF T. H. A. AND T. H. S. VERSUS YOHIMBANE

The configuration at C_3 and C_{15} in tetrahydroserpentine has already been proposed as *syn* by Weisenborn.[20] More recently Wenkert[7] has classified various indole alkaloids into *normal* and *allo* products with an α-hydrogen at $C_{(3)}$ and *pseudo* or *epiallo* compounds containing a β-hydrogen at $C_{(3)}$. This assignment was given on the basis of presence or absence of certain bands in the 3.4–3.7 μ region in chloroform solution. In this classification tetrahydroserpentine and tetrahydroalstonine have an α-hydrogen at $C_{(3)}$.

All these data indicate the most probable configuration of tetrahydroalstonine (X) and tetrahydroserpentine (XI) at $C_{(3)}$, $C_{(15)}$, and $C_{(20)}$ and are represented by formulae X and XI, respectively:



X



XI

On the basis of this evidence together with that cited above aricine, reserpinine, and isoreserpiline should be assigned the tetrahydroalstonine and raumitorine and tetraphylline the tetrahydroserpentine configurations.

EXPERIMENTAL

Spectra in chloroform solution were obtained in 0.11 mm. path; solutes are at concentrations of 0.18–0.2*M*. Spectra in carbon disulfide solution were obtained in 3 mm. path; solutes are at concentrations of 0.003–0.005*M*. All spectra were recorded using Perkin-Elmer, double-beam I.R. spectrophotometer, Model 21.

Acknowledgment. We would like to thank Drs. C. Djerassi, M. M. Janot, and A. Hofmann for the samples of some of the alkaloids used in this study.

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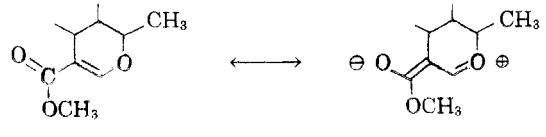
(18) We gratefully acknowledge this information from Professor Elderfield (1953).

(19) A system consisting of fused 6-membered rings with a double bond adjacent to a ring juncture has a lower energy when that juncture is *cis* than when it is *trans*. [D. A. H. Taylor, *Chemistry & Industry*, 250 (1954); Andre S. Dreiding, *Chemistry & Industry*, 1419 (1954).] If it is assumed that the disposition of atoms in dihydropyran is not unlike that in cyclohexene, then tetrahydroserpentine (*cis* D/E) should be the more stable. Resonance stabilization of the vinyl ether system will be greater in this alkaloid where the free rotation of the carbomethoxyl group allows complete coplanarity of the carbonyl and ethylenic functions:



We would like to thank Dr. G. B. Kline of these laboratories for this explanation.

(20) F. L. Weisenborn *et al.*, *Chemistry & Industry*, 375 (1954).

Metal-Catalyzed Condensations of Esters of Acetonedicarboxylic Acid

P. N. GORDON

Received March 18, 1957

Evidence is presented which suggests that the conversion of dimethyl acetonedicarboxylate (DMADC) to methyl 2,4-dicarbomethoxy-3,5-dihydroxyphenylacetate (I) proceeds through the initial formation of a metal chelate compound. Among the reported reactions of esters of acetonedicarboxylic acid are the self-condensations of these substances to esters of 2,4-dicarboxy-3,5-dihydroxyphenylacetic acid, I, II, III, and IV, under simple experi-