was filtered and repeatedly washed with hot methanol (15 ml.). The filtrate together with the washings was freed from the solvent. The viscid residue was taken up in ether (15 ml.), washed with sodium bicarbonate solution and dried over anhydrous sodium sulfate. Dry ether solution upon concentration deposited colorless needles of 1-methyl-2-keto-1,2-dihydro-4-quinazolone (0.18 g.), m.p. 255–258°. On several crystallizations from ethyl acetate, ethyl alcohol and benzene shining needles of constant m.p. 259–260° were obtained. It showed no depression in m.p. on admixture with the synthetic product of 1-methyl-2-keto-1,2-dihydro-4-quinazolone, m.p. 260°.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.55; N, 15.91. Found: C, 61.48; H, 4.61; N, 15.98.

Synthesis of 1-Methyl-2-keto-1,2-dihydro-4-quinazolone.—One gram of N-methylanthranilamide[13] prepared from isatoic anhydride was heated with freshly distilled ethyl chloroformate (2.0 g.) on a water-bath for 2 hours and then refluxed for 3 hours when 1-methyl-2-keto-1,2-dihydro-4-quinazolone separated out. It crystallized from alcohol in shining colorless needles (1.2 g.), m.p. 259–260°.

Anal. Calcd. for $C_9H_8O_2$: C, 61.36; H, 4.55; N, 15.91. Found: C, 61.52; H, 4.68; N, 15.79.

(13) Asima Chatterjee and Subhendu Ghosh Majumdar, THIS JOURNAL, **75**, 4365 (1953).

CALCUTTA, WEST BENGAL, INDIA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Rauwolfia Serpentina Alkaloids. I. Structure of Reserpine

BY NORBERT NEUSS, HAROLD E. BOAZ AND J. W. FORBES

RECEIVED DECEMBER 4, 1953

Hydrolysis of reserpine, a sedative principle of *Rauwolfia Serpentina* Benth., yielded 3,4,5-trimethoxybenzoic acid and reserpic acid. Reduction of reserpine afforded 3,4,5-trimethoxybenzyl alcohol and reserpic alcohol. Empirical formulas are proposed for reserpine and its degradation products. From the study of ultraviolet and infrared spectra of various indole derivatives, a possible structure of reserpine has been suggested.

Rauwolfia Serpentina Benth. is a genus of the *Apocyanaceous* family and has been used for centuries in India as a sedative. Its value as a hypotensive agent was discovered in the early thirties by Chopra, Gupta and Mukherjee[1] and since that time has been discussed by several pharmacologists.[2] The chemical investigation of the plant was first undertaken by Siddiqui and Siddiqui[3] and pursued later by several other investigators.[4] A renewed interest in the alkaloids of *Rauwolfia* was created by the isolation of a sedative principle of the plant, a crystalline alkaloid, named reserpine by Mueller, Schlittler and Bein.[5]

In our recent publication[6] it was shown that reserpine gives, upon hydrolysis with dilute alkali, 3,4,5-trimethoxybenzoic acid and an amino acid which we called reserpic acid. By reduction of reserpine, using lithium aluminum hydride, 3,4,5-trimethoxybenzyl alcohol and an amino alcohol, named reserpic alcohol, were obtained. These two reactions led to the establishment of empirical formulas of reserpine and its degradation products.[7] Based on data, both from ultraviolet and infrared spectra, it was proposed that reserpine has possibly a yohimbine-like nucleus with one methoxyl group at the 6-position of the indole moiety, corresponding to the 11-position of yohimbane.[8] The proof of that assumption came recently from the work of L. Dorfmann, *et al.*,[8] whose degradation studies, carried out on methyl reserpate, led to the isolation of yobyrine, the corresponding hydroxyyobyrine (probably a 7-hydroxy derivative) and 4-methoxyoxalylanthranilic acid. By preparation of a γ-lactone, the same authors established the relative position of the carbomethoxy group and hydroxy group in the ring E. Furthermore, the isolation of 5-hydroxyisophthalic acid from alkali fusion of methyl reserpate indicated the probable position of the second methoxyl group in ring E of reserpine.[9]

As starting material for isolation of reserpine, the oleoresin fraction[10] was used. By chromatography of this fraction on acid-washed alumina, using benzene–chloroform mixtures, a new alkaloid, tentatively called "*Rauwolfia* Alkaloid A" was isolated.[11] After changing to chloroform alone, reserpine was obtained. Repeated recrystallization of the alkaloid yielded long colorless prisms which gave satisfactory analytical results for a $C_{33}H_{40}N_2O_9$ compound. Preparation of a maleate salt and its analysis substantiated the empirical formula of reserpine. The molecular weight determination from X-ray data was also in excellent agreement with the above formulation.

Hydrolysis of reserpine by hot dilute sodium hy-

(1) R. N. Chopra, J. C. Gupta and B. Mukherjee, *Indian J. Med. Res.*, **21**, 261 (1933); **29**, 763 (1941).

(2) Raymond-Hamet, *Bull. Acad. Med.*, **115**, 452 (1936); *Compt. rend. Acad. Sci.*, **223**, 927 (1946); H. J. Bein, *Experientia*, **9**, 107 (1953), and the references cited therein.

(3) S. S. Siddiqui and R. H. Siddiqui, *J. Ind. Chem. Soc.*, **8**, 667 (1931).

(4) *Cf.* A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **36**, 1143 (1953), and references cited therein.

(5) J. M. Mueller, E. Schlittler and H. J. Bein, *Experientia*, **8**, 338 (1952).

(6) N. Neuss, H. E. Boaz and J. W. Forbes, THIS JOURNAL, **75**, 4870 (1953).

(7) Independently, in this country and in Switzerland, A. Furlenmeier, R. Lucas, H. B. MacPhillamy, J. M. Mueller and E. Schlittler assigned the same empirical formulas to reserpine and reserpic acid, *Experientia*, **9**, 331 (1953). The identical formula for reserpine was also proposed by C. Djerassi, M. Gorman, A. L. Nussbaum and J. Reynoso, THIS JOURNAL, **75**, 5446 (1953). A different formula was suggested by M. W. Klohs, *et al.*, *ibid.*, **75**, 4867 (1953).

(8) L. Dorfmann, C. F. Huebner, H. B. MacPhillamy, E. Schlittler and A. F. St. André, *Experientia*, **9**, 368 (1953).

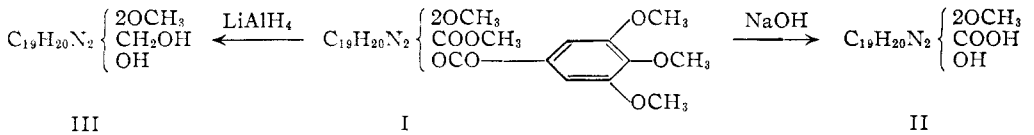
(9) An earlier announcement of these results by Dr. Schlittler (Symposium on hypotensive drugs, Boston, Massachusetts, September 14–15, 1953) prompted us to discontinue our work on structure elucidation of reserpine.

(10) A. Dutt, J. C. Gupta, S. Ghosh and B. S. Kahali, *Indian J. Pharm.*, **9**, 54 (1947); *J. Am. Pharm. Assoc.*, **36**, 416 (1947).

(11) Data concerning this and other alkaloids from *Rauwolfia serpentina* will be published later; N. Neuss, *et al.*, THIS JOURNAL, in press.

droxide, followed by acidification, yielded 3,4,5-trimethoxybenzoic acid. Upon addition of excess concentrated hydrochloric acid, the hydrochloride of reserpic acid separated. On recrystallization from methanol this amino acid hydrochloride analyzed well for a $C_{22}H_{28}N_2O_5 \cdot HCl \cdot CH_3OH$ compound. Lithium aluminum hydride reduction of reserpine yielded an amino alcohol, called reserpic alcohol, which gave good analyses for a $C_{22}H_{30}N_2O_4 \cdot H_2O$ compound. The mother liquors from crystallization of reserpic alcohol contained a small amount of an oil which was shown to be 3,4,5-trimethoxybenzyl alcohol.

As a result of these data, the following partial structures were suggested for reserpine (I), reserpic acid (II) and reserpic alcohol (III).[6]



III I II

Reserpine possesses a very characteristic ultraviolet spectrum. Its comparison with that of methyl 3,4,5-trimethoxybenzoate[12] indicates that the spectrum of reserpine consists of "MTB" and substituted indole. The nature of the substitution on the indole moiety was then studied by using various model substances, among them 2-methyl-3-carbethoxy-5-methoxyindole,[13] 5,6-dimethoxyindole,[14] 2,3-dimethyl-5,6-dimethoxyindole[15] and 2,3-dimethyl-6-methoxyindole.

Reference to Tables I, II and III and to Fig. 1, suggests 2,3-dimethyl-6-methoxyindole as the best model. The summation of the spectrum of this compound and that of "MTB" gave a spectrum remarkably similar to that of reserpine. Furthermore, the ultraviolet absorption of 2,3-dimethyl-6-methoxyindole is very similar to that of reserpic alcohol. The slight discrepancies in the intensities can be explained by the presence of rings C, D and E.

These data clearly indicate that the ultraviolet chromophores in reserpine consist of 2,3-substituted-6-methoxyindole and 3,4,5-trimethoxybenzoate. An excellent agreement with such a formulation came from the infrared spectra.

The infrared spectrum of reserpine in chloroform solution has a free NH band at 2.87 μ, within 0.01 μ of similar bands in the spectra of indole, 5,6-dimethoxyindole, 2,3-dimethyl-5,6-dimethoxyindole, 2,3-dimethyl-6-methoxyindole and tetrahydroalstoniline.[17]

Comparison of these spectra also shows a characteristic group of bands, 6.13, 6.33, 6.67 and 6.84 μ, present in the compounds which have a methoxyl group in the 6-position only. The pattern of bands in this region in the 5,6-dimethoxyindoles is distinctly different. Two carbonyl bands in the spectrum of reserpine have wave lengths of 5.79 and 5.82 μ (0.01 to 0.02 μ greater separation when analytically resolved). Methyl cyclohexanecarboxylate and "MTB" have bands at 5.78 and 5.82 μ, respectively.

Relatively small interaction between the groups responsible for the more intense bands in the reserpine spectrum is illustrated by the composite spectra of four models at equimolar concentration in

TABLE I

ULTRAVIOLET SPECTRA OF INDOLE AND SUBSTITUTED INDOLES

Compound	λ_{max}, mμ	E	λ_{min}, mμ	E
Indole	216	33,100	238	1,600
	271	5,620		
	278	5,370		
5-Methoxyindole[16]	210			
	269	6,920	246	1,230
	289	4,370		
6-Methoxyindole[16]	265	4,570	242	1,590
	287	4,270	275	3,470
5,6-Dimethoxyindole	216	23,500	245	
	271	4,270	278	
	295	4,170		
2,3-Dimethyl-5,6-dimethoxyindole	227	25,700	255	3,310
	304	8,320	285 (shoulder)	5,250
2-Methyl-3-carbethoxy-5-methoxyindole	216	30,200	230	12,600
	242	18,200	272	8,510
	284	9,770		
2,3-Dimethyl-6-methoxyindole	228	32,400	252	3,240
	273	4,790	283	3,630
	298	5,500		

TABLE II

ULTRAVIOLET SPECTRA OF RESERPINE, ITS DEGRADATION PRODUCTS AND TETRAHYDROALSTONILINE

Compound	λ_{max}, mμ	E	λ_{min}, mμ	E
Reserpine	216	61,700	246	9,770
	267	17,000	287	10,000
	295	10,200		
Reserpic alcohol	228	35,500	252	3,800
	273	5,010	282	2,820
	298	6,170		
Reserpic acid HCl	225	26,900	249	3,470
	269	5,130	278	4,070
	295	6,460		
Tetrahydroalstoniline[17]	226	46,800	258	6,170
	273	7,410	280	6,030
	296	8,320		

(12) Throughout this discussion, methyl 3,4,5-trimethoxybenzoate shall be designated by "MTB."

(13) C. D. Nenitzescu, *Bull. soc. chim. Romania*, **11**, 37 (1929).

(14) A. E. Oxford and H. S. Raper, *J. Chem. Soc.*, **130**, 420 (1927).

(15) R. J. S. Beer, L. McGrath, A. Robertson and A. B. Woodier, *ibid.*, 2066 (1949).

(16) F. Pruckner and B. Witkop, *Ann.*, **554**, 127 (1943).

(17) Tetrahydroalstoniline is also a 6-methoxyindole derivative and has the structure A. R. C. Elderfield and S. L. Wythe, *J. Org. Chem.*, in press. We would like to thank Dr. R. C. Elderfield for this information and a sample of tetrahydroalstoniline.

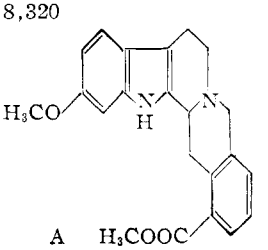


TABLE III

THE SUMMATION OF THE ULTRAVIOLET SPECTRA OF METHYL 3,4,5-TRIMETHOXYBENZOATE AND SOME SUBSTITUTED INDOLES IN A MOLE PER MOLE RATIO

Compound	λmax, mμ	E	λmin., mμ	E
Indole + "MTB"	214	64,600		
	266	15,000		
	288	6,760		
2-Methyl-3-carbethoxy-5-methoxyindole + "MTB"	214	66,100	Shoulder at 246 mμ	
	246	22,400		
	260	21,400		
5,6-Dimethoxyindole + "MTB"	216	47,900		
	267	12,300		
	293	7,590		
2,3-Dimethyl-5,6-dimethoxyindole + "MTB"	214	53,700	246	9550
	267	13,800	286	9120
	298	11,000	Shoulder at 225 mμ	
2,3-Dimethyl-6-methoxyindole + "MTB"	216	56,200	246	8510
	267	14,800	286	8320
	296	8,710	Shoulder at 228 mμ	

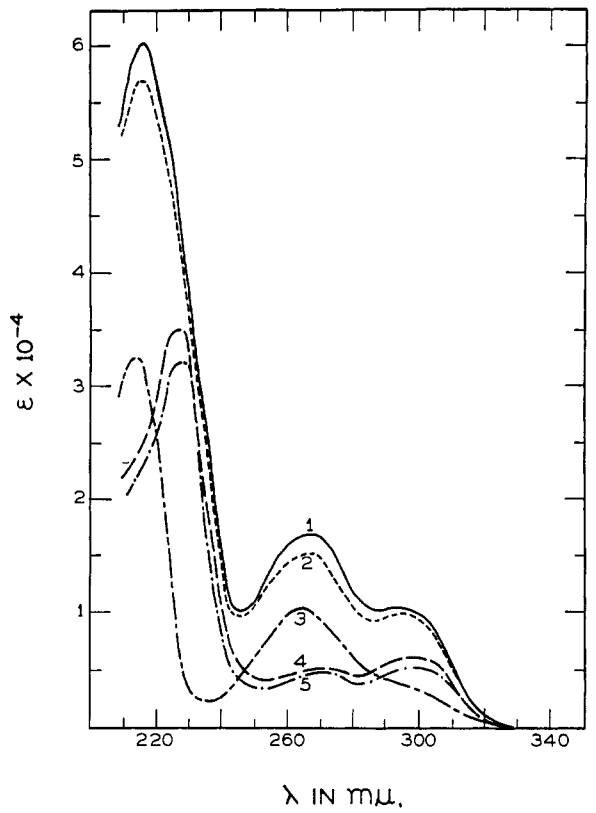


Fig. 1.—Comparison of the ultraviolet spectra of: 1, reserpine; 2, the sum of reserpic alcohol and methyl 3,4,5-trimethoxybenzoate in mole per mole ratio; 3, methyl 3,4,5-trimethoxybenzoate; 4, reserpic alcohol; 5, 2,3-dimethyl-6-methoxyindole. (All spectra were taken in methanol using a Cary Model 11 spectrophotometer.)

Fig. 3. In particular, the polarization of the indole system by a methoxyl group in the 6-position, as evidenced in the 6–7 μ region, leaves no doubt as to the position of the methoxyl group in the corresponding part of the reserpine molecule. The agreement of wave lengths and intensities of bands

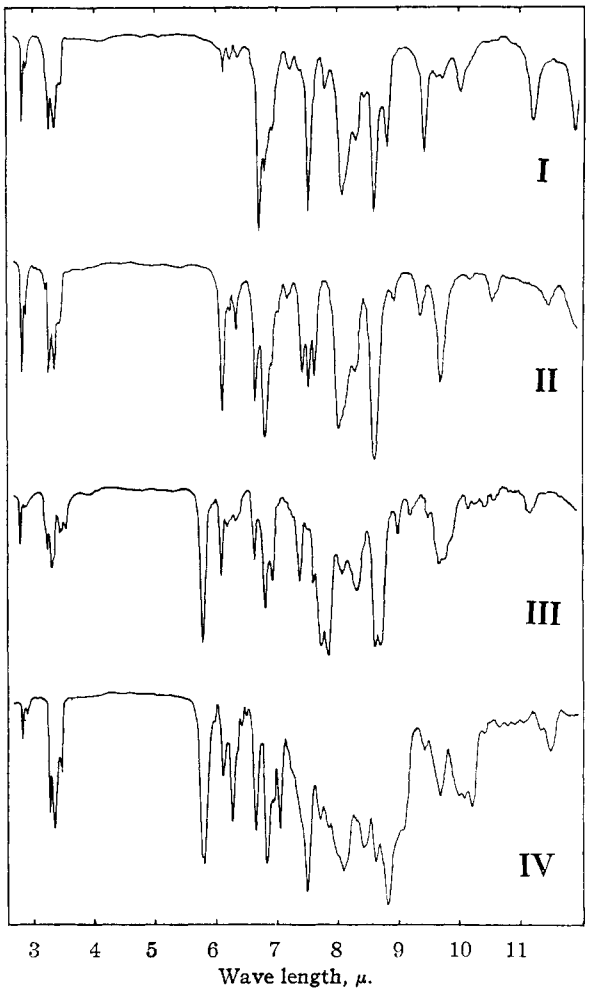
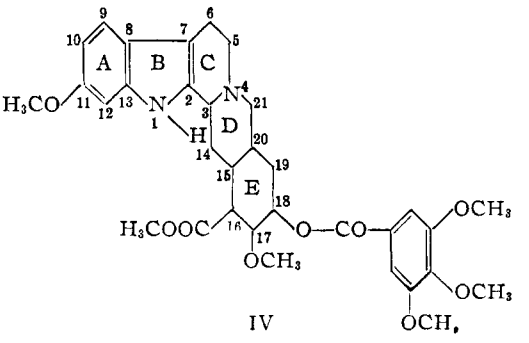


Fig. 2.—Infrared spectra of: I, 2,3-dimethyl-5,6-dimethoxyindole; II, 2,3-dimethyl-6-methoxyindole; III, tetrahydroalstoniline; IV, reserpine. (All spectra were taken in chloroform using a Beckman I. R. 2T instrument.)

in this region between the two spectra requires one of the methoxyl groups to be situated in the non-aromatic portion of the molecule. Absence of this methoxyl from the models is evidenced by significantly lower absorption at various points above 7.6 μ. The slightly greater separation of ester bands near 5.8 μ in reserpine than in the other spectrum suggests proximity of the methoxyl to the two ester groups.

Infrared spectra in mineral oil mull of reserpine, reserpic acid hydrochloride and reserpic alcohol also



IV

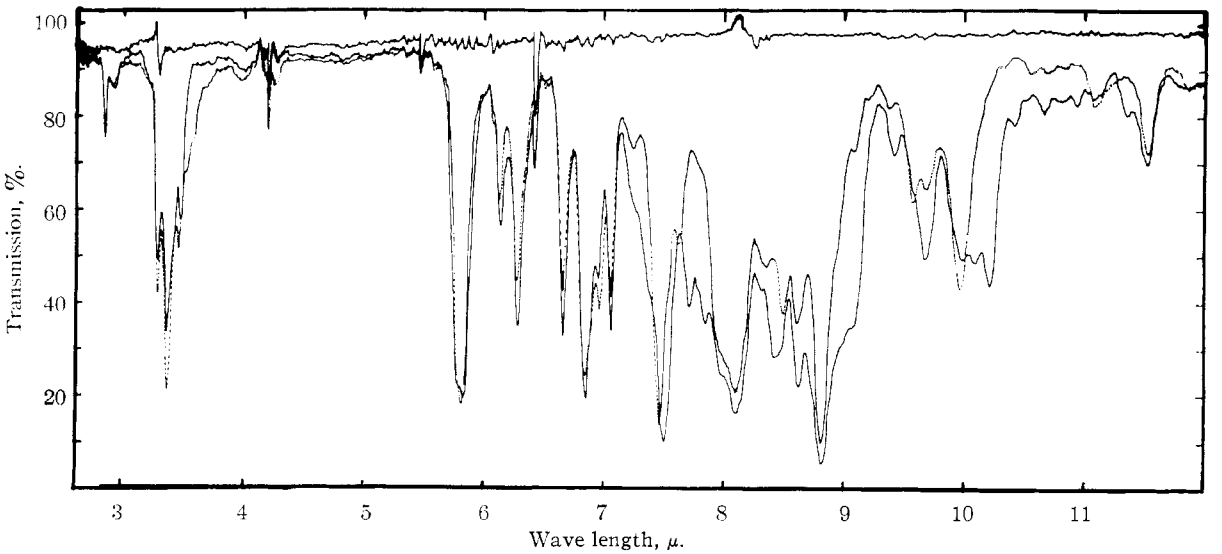


Fig. 3.—Infrared spectra of reserpine and an equimolar solution of 2,3-dimethyl-6-methoxyindole, methyl 3,4,5-trimethoxybenzoate, methyl cyclohexanecarboxylate and N-ethylpiperidine. The solid line spectrum is reserpine at 0.13 *M* in $CHCl_3$ in 0.100 mm. path. The spectrum distinguished by dotted portions is an equimolar solution of mentioned models at 0.10 *M* in chloroform in 0.100 mm. path. (The blank shows three calibration bands included in the standardization; CO_2 4.224 μ, H_2O 5.464 and 6.41 μ.)

show bands characteristic of different groupings in these molecules, but wave lengths and intensities in the crystal environments are not so useful in comparisons with models as those obtained from the spectra in chloroform solution.

Our analytical results and spectral data are in good agreement with the formula of reserpine proposed recently by L. Dorfmann, *et al.*, (IV).[8]

Acknowledgment.—We would like to thank Dr. R. B. Woodward for helpful suggestions during the course of this investigation. We gratefully acknowledge invaluable assistance by the following: Dr. H. A. Rose, X-ray data, Mr. E. H. Stuart, isolation of the oleoresin fraction; Messrs. W. L. Brown, G. M. Maciak and H. L. Hunter, elementary analyses and group determinations; Miss M. Hofmann, infrared spectra, Mr. D. O. Woolf, electrometric titrations and Mrs. Barbara B. Kehm, technical assistance.

Experimental[18]

Isolation and Characterization of Reserpine.—A solution of 70 g. of the oleoresin fraction[10] in 3 l. of benzene–chloroform (3:1) was chromatographed on a column (75 mm. in diameter) of acid-washed alumina, Merck (1625 g.). After elution of "*Rauwolfia* Alkaloid A"[11] with a total volume of 16 l. of benzene–chloroform mixtures, washing was continued with chloroform (12 l.) and a total of 18 g. of a second alkaloidal residue obtained.[19] This residue yielded 8.5 g. of slightly colored reserpine after crystallization from dilute acetone. Repeated recrystallization from methanol–chloroform and finally dilute, *methanol-free* acetone afforded long colorless prisms, m.p. 264–265° dec.

$[\alpha]^{26}D$ −115 (*c* 1.03 in $CHCl_3$)
$[\alpha]^{26}D$ −164 (*c* 0.96 in pyridine)
$[\alpha]^{26}D$ −168 (*c* 0.624 in dimethylformamide)

(18) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The substances were inserted at 150° unless otherwise mentioned. Electrometric titrations were determined in 66% dimethylformamide as a solvent.

(19) Fractions of 500 ml. were collected, evaporated under reduced pressure and crystallized. Certain crude fractions were combined according to similarity of color reaction with nitric acid, solubility properties and behavior in paper chromatography.

For analysis the sample was dried at 80° (0.05 mm.) for 8 hours.

Anal. Calcd. for $C_{33}H_{40}N_2O_9$: C, 65.11; H, 6.62; N, 4.60; OCH_3 (6), 30.59; mol. wt., 608.67. Found: C, 65.31, 65.11, 65.00; H, 6.88, 6.83, 6.68; N, 4.79; OCH_3 (6), 30.22; mol. wt., 586 ± 20 (electrometric titration pK'_a 6.6); 610 ± 12 (X-ray data).

Color reaction with concentrated nitric acid: greenish-blue, changing immediately to reddish-brown and finally to yellow. For ultraviolet spectra see Table II and Fig. 1, and for infrared spectra see Fig. 2.

Reserpine Maleate.—The maleate salt of reserpine was prepared by the usual procedure and recrystallized twice from chloroform–ethyl acetate, m.p. 226–227° dec.

Anal. Calcd. for $C_{33}H_{40}N_2O_9 \cdot C_4H_4O_4$: C, 61.31; H, 6.12; N, 3.86. Found: C, 61.57; H, 6.33; N, 3.83.

Hydrolysis of Reserpine and Isolation of Reserpic Acid Hydrochloride and 3,4,5-Trimethoxybenzoic Acid.—A solution of 300 mg. of reserpine in 3 ml. of a 4% sodium hydroxide solution, 9 ml. of methanol and 1.5 ml. of water was boiled under reflux for 30 minutes. After cooling, methanol was removed *in vacuo* and 3 ml. of water added. The reaction mixture was acidified with concentrated hydrochloric acid (acid to congo red paper) and allowed to stand for 2 hr. The crystalline material which separated (50 mg.) was collected and recrystallization from boiling water afforded 30 mg. of 3,4,5-trimethoxybenzoic acid, m.p. 175–176°. This material was identical with an authentic sample of the acid (X-ray patterns, ultraviolet and infrared spectra, m.p. and mixed m.p.).

The filtrate, after removal of the trimethoxybenzoic acid, was acidified with two more drops of concentrated hydrochloric acid and allowed to stand for 18 hours at room temperature in the dark. The crystalline solid which had separated, was removed by filtration (140 mg.) and washed with 25 ml. of ether. The product was recrystallized from methanol–ether and afforded 110 mg. of reserpic acid hydrochloride, m.p. 266–268° dec. The analytical sample was dried 3 hours at room temperature and 0.05 mm., and contained one mole of methanol of crystallization.

Anal. Calcd. for $C_{22}H_{28}N_2O_5 \cdot HCl \cdot CH_3OH$: C, 58.90; H, 7.09; Cl, 7.56; mol. wt., 468.93. Found: C, 58.84; H, 6.85; Cl, 7.53; mol. wt., 454 ± 20 (electrometric titration pK'_a 6.2 and 8.2).

For ultraviolet spectrum see Table II.

Reductive Cleavage of Reserpine; Isolation of Reserpic Alcohol and 3,4,5-Trimethoxybenzyl Alcohol.—To a stirred suspension of 600 mg. of lithium aluminum hydride in dry tetrahydrofuran was added dropwise a solution of 800 mg. of

reserpine in 30 ml. of dry tetrahydrofuran. The reaction mixture was boiled under reflux for 3 hours, then cooled and decomposed with 10 ml. of water. After heating under reflux for one hour, inorganic salts were removed by filtration. The filtrate was freed from solvent under reduced pressure at 30° and the partially oily residue crystallized upon addition of ethanol. The crude reserpic alcohol weighed 240 mg. The material was recrystallized twice from dilute alcohol and formed long, silky prisms, m.p. 217–218° dec. The compound was dried for analysis 2 hours at room temperature and 0.05 mm. and contained one mole of water of crystallization; $[\alpha]^{26}D$ −66.7, −67.9; (*c* 0.780 in dimethylformamide). The compound appeared to be optically inactive in pyridine.

Anal. Calcd. for $C_{22}H_{30}N_2O_4 \cdot H_2O$: C, 65.32; H, 7.97; N, 6.93; OCH_3 (2), 15.33; act. H, 5 moles; mol. wt., 404. Found: C, 65.12, 65.40; H, 7.99, 7.99; N, 6.67; OCH_3 (2), 15.07; act. H, 4.82 moles; mol. wt., 409 ± 10 (electrometric titration, pK'_a 7.7).

For ultraviolet spectra see Fig. 1 and Table II. After drying in a pig at 100° *in vacuo:* weight loss calcd. 4.45. Found: 4.63.

Anal. Calcd. for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82. Found: C, 68.33; H, 8.00.

The hydrochloride of reserpic alcohol was recrystallized twice from methanol–ether and melted at 258–260° dec. It was dried for analysis 16 hours at 80° and 0.1 mm.

Anal. Calcd. for $C_{22}H_{30}N_2O_4 \cdot HCl$: N, 6.62; Cl, 8.38. Found: N, 6.61; Cl, 8.16.

The mother liquor from the first crystallization of reserpic alcohol was evaporated under reduced pressure and 30° and a small amount of an oily residue (110 mg.) obtained. This oil was dissolved in 5 ml. of dry pyridine and reacted with *p*-nitrobenzoyl chloride. After the usual work up, the *p*-nitrobenzoate of 3,4,5-trimethoxybenzyl alcohol was obtained. The same derivative, m.p. 143°, was obtained from an authentic sample of the alcohol.[20] The m.p., mixed m.p. and infrared spectra were identical.

Anal. Calcd. for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.78; H, 5.02; N, 4.01.

Synthesis of 2,3-Dimethyl-6-methoxyindole.—A solution of 2 g. (0.0145 mole) of 3-methoxyphenylhydrazine (b.p. 160–162° (13 mm.))[21] and 1 g. (0.0139 mole) of methyl ethyl ketone was boiled under reflux for 15 minutes. The mixture was then cooled in ice, removed from the ice-bath and saturated with dry hydrogen chloride for 17 minutes. During this operation the solution turned red, then dark brown and a copious crystalline precipitate appeared. The reaction mixture was then cooled in ice and allowed to stand for 15 minutes. The 2,3-dimethyl-6-methoxyindole was collected (1.15 g.) and washed thoroughly with dilute ice cold alcohol. Two recrystallizations from dilute alcohol afforded colorless, shiny plates, m.p. 142–143°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.20; H, 7.57; N, 7.92.

For ultraviolet spectra see Table I and Fig. 1, for infrared spectra see Fig. 2.

(20) Kindly supplied by Dr. E. R. Shepard, of these laboratories. The alcohol was prepared by $LiAlH_4$ reduction of the corresponding acid.

(21) W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

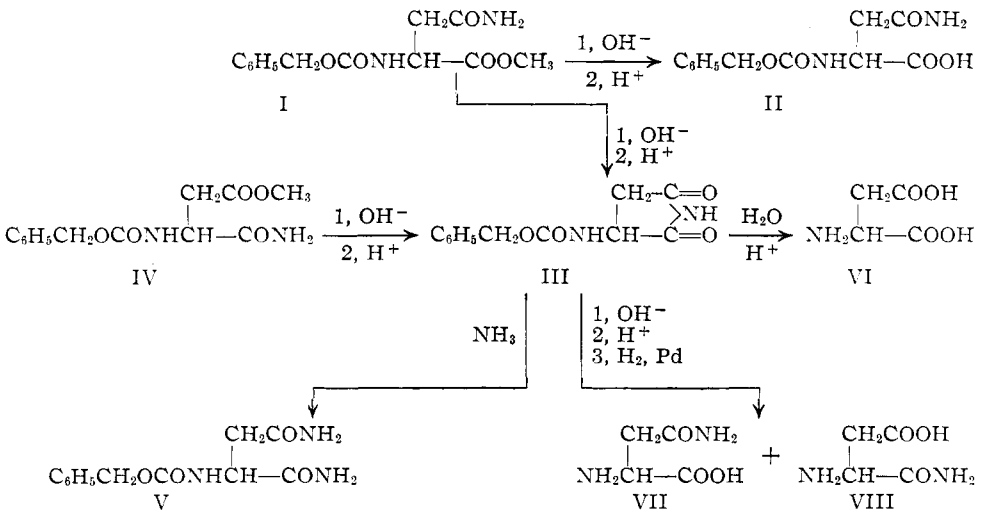
Imides from Asparagine and Glutamine[1]

BY ERNEST SONDHEIMER AND ROBERT W. HOLLEY

RECEIVED DECEMBER 22, 1953

Carbobenzoxy-L-aminosuccinimide (III) was obtained from carbobenzoxy-L-asparagine methyl ester by treatment with alkali. Hydrogenolysis of III gave L-aminosuccinimide (IX). Similar reactions take place in the glutamine series. The properties of these new compounds are described.

In the course of investigations of the synthesis of peptides of asparagine and glutamine, we had occasion to attempt to saponify carbobenzoxy-L-asparagine methyl ester (I). Contrary to expectations, the isolated material was not carbobenzoxy-L-asparagine (II), m.p. 165°, but a mixture, containing as its major component a compound (III), m.p. 79–81°, pK = 9.1 in aqueous methanol. Attempted saponification of carbobenzoxy-L-isoaspar-



(1) Journal Paper No. 958, New York State Agricultural Experiment Station. This investigation was supported in part by a research grant, G-3435, from the National Institutes of Health, Public Health Service.