due from acetone yielded a second solid product (900 mg.). Two recrystallizations of the second product from alcohol–ether gave colorless rods (740 mg.), m.p. 265–266° dec., $[\alpha]^{23}D$ −5° (*c* 1.25, pyr.), λ_{max} 246 mμ (ε 600).[20]

Anal. Calcd. for $C_{34}H_{51}O_9NS_2 \cdot HCl$: C, 56.84; H, 7.30; S, 8.93; Cl, 4.94. Found: C, 56.86; H, 7.80; S, 9.13; Cl, 5.11.

Desulfurization of 7-Dehydrogermine 3,16-Diacetate Propylene Thioketal Hydrochloride.—To a solution of 7-dehydrogermine 3,16-diacetate propylene thioketal hydrochloride (275 mg.) in alcohol (30 ml.) was added Raney nickel (3 g.) and the solution was heated under reflux for 11 hours. The suspension was filtered and the Raney nickel extracted twice with hot alcohol. The alcoholic solutions were combined and evaporated to dryness *in vacuo*. The residue crystallized slowly from acetone–ether; yield 30 mg. of rods, m.p. 253–255°. The melting point was not depressed by admixture of an authentic sample of zygadenine 3,16-diacetate and the infrared spectra of the respective samples were identical.

MADISON 6, WISC.

(20) *Cf.* D. J. Cram and M. Cordon, THIS JOURNAL, **77**, 1810 (1955).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF CIBA PHARMACEUTICAL PRODUCTS, INC.]

Rauwolfia Alkaloids. XXXI.[1] The Synthesis and Activity of Some Reserpine Analogs[2]

BY R. A. LUCAS, M. E. KUEHNE, M. J. CEGLOWSKI, R. L. DZIEMIAN AND H. B. MACPHILLAMY

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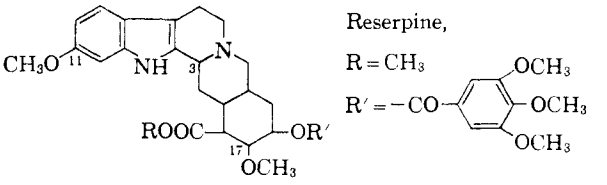
In an effort to separate the medically important hypotensive and sedative components of the action characteristic of reserpine, over 100 derivatives of methyl reserpate were prepared. Of these, two were outstanding; the carbethoxysyringate ester having a predominantly hypotensive effect with little sedation, and the 3-dimethylaminobenzoate ester which proved to be a fast acting sedative with little effect on the blood pressure. The physical properties and methods of preparation of the various derivatives are described.

The medical importance of the Rauwolfia alkaloid reserpine has stimulated considerable interest in determining the effect that variations in the chemical structure of this molecule might have upon the biological activity of the drug. It would be of theoretical interest if an analog of reserpine could be prepared with an activity such that either the hypotensive or sedative component of the action characteristic of reserpine predominated. This would then demonstrate that these actions, which have not previously been separated, could be dissociated. Such substances could also be of practical importance for in some clinical cases of hypertension the concomitant sedation produced by reserpine may not be desirable. While this side reaction can usually be adequately controlled by regulation of the dosage, a reserpine derivative with a hypotensive action considerably greater than its sedative effect would be clinically useful. On the other hand, the value of reserpine as a tranquilizer would be markedly increased if an analog could be prepared which had a strong sedative action of rapid onset. A de-emphasis of the hypotensive action in such a product would be desirable but not essential since reserpine does not lower the blood pressure of normotensive patients. With these considerations in mind we set out to prepare some substances derived from reserpine which might fulfill the above conditions.

Some information was already available on the biological effect of structural changes in the reserpine molecule. The naturally occurring 11-desmethoxy compound deserpidine[3] and the 11,17-didesmethoxy analog[4] both had typical reserpine-like activity. Substitution of the indole nitrogen with methyl and allyl groups[5] produced substances totally lacking in reserpine-like action. In fact their mild stimulant effect could be considered as antagonistic to reserpine. The N-oxide of the other more basic nitrogen in reserpine has a reserpine-like activity,[6] but the quaternary salt[7] was found to be completely inactive. This was also true of such degradation products as methyl reserpate, reserpic acid and its lactone.

Since none of the above-mentioned compounds showed any indication of an action which was either predominantly hypotensive or sedative, we initiated a program for the synthesis of reserpine analogs in which the R and R′ groups were varied.



Reserpine,

R = CH_3

R′ = $-CO-C_6H_2(OCH_3)_3$

We had previously prepared the compound in which R = ethyl and R′ = trimethoxybenzoyl[7] and this was found to have an activity comparable to reserpine. However, further variants in this direction were limited by the relative difficulty of preparation of the corresponding reserpic acid esters. The use of simple acid-catalyzed esterification is complicated by the known facile epimerization of reserpine derivatives at C-3 to the corresponding inactive iso-compounds[8] under acid conditions and is, therefore, not too adaptable. The action of reserpic acid lactone with alcohols did not give satisfactory yields of esters. The only sure method was that using the diazoalkanes, a

(1) Part XXX, J. M. Müller, *Experientia*, **13**, 479 (1957).

(2) Presented in part before the Division of Medicinal Chemistry at the 134th National Meeting of the American Chemical Society, Chicago, Ill., September 8, 1958.

(3) For a complete review of the Rauwolfia alkaloids see R. E. Woodson, Jr., H. W. Youngken, E. Schlittler and J. A. Schneider "Rauwolfia," Little, Brown and Co., Boston, Mass., 1957.

(4) F. L. Weisenborn, THIS JOURNAL, **79**, 4818 (1957).

(5) C. F. Huebner, *ibid.*, **76**, 5792 (1954).

(6) P. R. Ulshafer, W. I. Taylor and R. H. Nugent, *Compt. rend.*, **244**, 2988 (1957).

(7) L. Dorfman, *et al.*, *Helv. Chim. Acta*, **37**, 59 (1954).

(8) H. B. MacPhillamy, *et al.*, THIS JOURNAL, **77**, 1071, 4335 (1955).

procedure which does not lend itself to many variations.

However, the replacement of R′ in methyl reserpate (R = methyl, R′ = H) was relatively simple and amenable to the synthesis of a wide variety of compounds. Consequently, over 100 derivatives of methyl reserpate were prepared. These are listed in Table I. The great majority of the esters were made by the usual reaction of the corresponding acid chloride with methyl reserpate in pyridine solution, employing appropriate protecting groups when necessary. The time and temperature were on occasion important factors in obtaining satisfactory yields, and an investigation of the optimum reaction conditions with the invaluable aid of our Paper Chromatographic Laboratory was necessary in these cases.[9] The amino acid and dicarboxylic acid esters were best prepared by allowing the reactants to stand in methylene chloride solution. Low yields in many examples reflected the difficulty of isolation of the products. The intractable gums or sticky solids frequently encountered often became crystalline after passage in methylene chloride through a column of Florisil. In some cases regular aluminum oxide column chromatography was necessary and even then good analytical samples were difficult to prepare.

As might be expected three general types of activity were found: group I which included such compounds as 7, 38, 49, 72, 76 and 102 had a typical reserpine-like activity; group II, for example nos. 15, 24, 41, 56, 57 and 85 had a predominantly hypotensive action with relatively little sedative effect; while group III as represented by 11, 21, 32, 34, 71, 88, 99 and 101 demonstrated the reverse type action in which sedation was the prominent effect. It is obvious from the great variety of structures represented by the compounds cited above as the most prominent members of each group that no relationship could be discerned between structure and activity. One compound in group II (no. 57)[10] and one in group III (no. 11) were chosen as outstanding because of their relatively high oral activity. The carbethoxysyringate (no. 57) was almost equipotent to reserpine as a hypotensive but had only about one-twentieth its activity as a sedative, while the 3-dimethylaminobenzoate (no. 11) had approximately one-fourth the sedative effect of reserpine but with a much more rapid onset of action and yet it was only one-fortieth as potent as reserpine as a hypotensive agent. With the preparation of these two substances we felt that we had accomplished our purpose of synthesizing one reserpine analog with a predominantly hypotensive action and another whose activity was predominantly sedative, thus showing that the characteristic action of reserpine could be separated, at least to a significant degree, into its two most important components.

Acknowledgments.—We wish to express our appreciation to Dr. E. Schlittler for his continued interest and encouragement throughout this project. Many thanks are due to Mr. L. Dorfman and his associates for the microanalytical data and to Mr. B. Korzun and co-workers for running the paper chromatograms which greatly aided our work. The technical assistance of Miss Barbara Hensle and Mrs. Martha Windholz was gratefully appreciated. It is a special pleasure to acknowledge the close and valued coöperation of Dr. A. Plummer, Dr. W. Barrett and their colleagues in our Macrobiology Division who determined the biological action of our substances and who made many helpful suggestions.

(9) For details of the procedure see B. P. Korzun, A. F. St. André and R. P. Ulshafer, *J. Am. Pharm. Assoc. Sci. Ed.*, **46**, 720 (1957).

(10) For a fuller discussion of the pharmacology of this substance see Plummer, *et al.*, *Arch. intern. pharmacodynamie.* (In press).

Experimental

Melting Points.—Except where indicated melting points were determined in capillary tubes in an electrically heated aluminum block.

Methyl reserpate was prepared by methanolysis of reserpine according to the published procedures.[7]

Acid Chlorides.—Except for a few commercially available compounds acid chlorides were prepared by refluxing the acid in at least five times its weight of thionyl chloride for 30 minutes. After distillation of the bulk of the thionyl chloride *in vacuo* the last traces were removed by reevaporation with benzene and storage of the product over P_2O_5 and silica gel.

Preparation of Derivatives of Methyl Reserpate.—The general methods of preparation of compounds given in Table I are indicated below: (A) The principal method for preparation of esters of methyl reserpate is illustrated by the procedure for making methyl 18-O-(*p*-toluyl)-reserpate: Methyl reserpate (8 g., 0.019 mole) dissolved in 60 ml. of dry pyridine was mixed with 3.3 g. (0.021 mole) of *p*-toluyl chloride with cooling and shaking in a stoppered flask for 10–15 minutes. After standing overnight at room temperature the mixture was poured into water and the sticky product triturated until solid. It was filtered, water washed and recrystallized first from ethyl acetate and then from methanol–methylene chloride; yield 4.4 g. (43%).

(B) Reaction products obtained by procedure A but which did not solidify when poured into water were extracted with chloroform or methylene chloride and washed with several portions of 2% HCl, 2% KOH and water. The extract was dried over Na_2SO_4 and filtered through a short column of Florisil. After evaporation of the solvent the crude ester was crystallized from either methanol, ethanol, acetone, ethyl acetate or ethyl acetate–petroleum ether (40–60°). Compounds difficult to purify and crystallize were subjected to chromatography in benzene solution over Woelm II-III activity neutral alumina. Elution with benzene containing small increments of methanol usually gave crystallizable product.

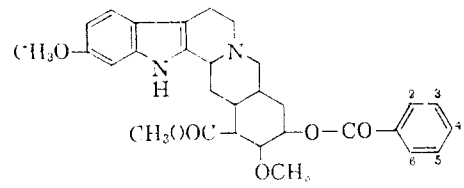
(C) This procedure is best illustrated by the preparation of methyl 18-O-(3,5-dimethoxy-4-hydroxybenzoyl)-reserpate. Methyl reserpate (8 g., 0.019 mole) dissolved in 60 ml. of pyridine was mixed with 6.5 g. (0.023 mole) of 3,5-dimethoxy-4-ethoxycarbonyloxybenzoyl chloride in 60 ml. of pyridine, with cooling and shaking. After standing overnight the mixture was poured into water. The gum which separated was heated for one hour with 200 ml. of a mixture of equal parts ethanol and 28% aqueous ammonia to remove the carbethoxy group. Upon cooling, the crude 3,5-dimethoxy-4-hydroxy benzoate ester crystallized readily and was recrystallized from ethanol; yield 8 g. (69%).

(D) The procedure for obtaining amino esters by hydrogenation of the corresponding nitro ester over palladium is illustrated by the preparation of methyl 18-O-(4-aminobenzoyl)-reserpate: Methyl 18-O-(4-nitrobenzoyl)-reserpate (5.0 g., 0.009 mole) was suspended in 200 ml. of methanol and hydrogenated at atmospheric pressure over 500 mg. of 10% palladium-on-charcoal until the theoretical amount of hydrogen was consumed during approximately 24 hours. The reaction mixture was filtered from catalyst, evaporated *in vacuo* and the product crystallized from acetone–petroleum ether (40–60°); yield 4.7 g. (98%).

(E) Acetylated phenolic or amino esters were prepared as follows: One gram of the phenolic or amino ester prepared as described in C or D was heated for 10 minutes in 100 ml. of benzene plus 5 ml. of pyridine and 5 ml. of the appro-

TABLE I

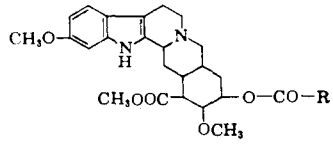
DERIVATIVES OF METHYL 18-O-BENZOYLRESERPATE

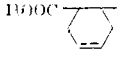
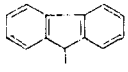
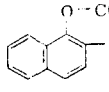
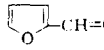
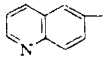


No.	Substituent	Method of prepn.	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	2-OH	C[a]	232–233	$C_{30}H_{34}N_2O_7$	67.40	66.88	6.41	6.49	5.24	5.23
2	2-OCH_3	A	202–203	$C_{31}H_{36}N_2O_7$	67.86	67.64	6.61	6.67	5.11	5.22
3	2-$OCOC_6H_5$	F	110–120	$C_{38}H_{38}N_2O_9 + H_2O$	63.45	63.83	6.45	6.10	4.48	4.48
4	2-COOH	M	191–193	$C_{31}H_{34}N_2O_8 + H_2O$	64.01	64.10	6.28	6.28	4.81	4.81
5	3-CH_3	A	231–234	$C_{31}H_{34}N_2O_8$	69.90	69.43	6.81	6.51	5.26	4.80
6	3-OH	C	181–182	$C_{30}H_{34}N_2O_7 + H_2O$	65.20	64.55	6.57	6.35	5.07	4.98
7	3-OCH_3	B	209–211	$C_{31}H_{36}N_2O_7 + H_2O$	65.71	65.28	6.76	6.78	4.94	5.04
8	3-$OCO_2C_2H_5$	B[b]	206–208	$C_{33}H_{38}N_2O_9$	65.33	65.01	6.31	6.39	4.62	4.49
9	3-NO_2	A	243–244	$C_{30}H_{32}N_4O_8$	63.93	63.38	5.90	5.82	7.46	7.24
10	3-NH_2	D	149–158	$C_{30}H_{36}N_4O_8$	67.52	67.66	6.61	6.88	7.88	7.76
11	3-$N(CH_3)_2$	F	205–208	$C_{32}H_{40}N_4O_8$	68.43	68.88	7.00	6.96	7.48	7.65
12	3-$NHCOCH_3$	E	248–250	$C_{32}H_{38}N_4O_9$	66.76	66.44	6.48	6.42	7.30	6.99
13	3-$NHCO_2C_2H_5$	E	235–237	$C_{34}H_{40}N_4O_{10} + \frac{1}{2}H_2O$	64.48	64.35	6.56	6.31	6.84	6.69
14	4-CH_3	A	246–248	$C_{31}H_{36}N_2O_8$	69.90	69.81	6.81	6.84	5.26	5.61
15	4-OH	C	249–252	$C_{30}H_{34}N_2O_7$	67.40	67.35	6.41	6.21	5.24	5.11
16	4-$OCOCH_3$	E	216–219	$C_{32}H_{36}N_2O_9$	66.65	66.36	6.29	6.09	4.86	4.67
17	4-$OCO_2C_2H_5$	E	180–182	$C_{33}H_{38}N_2O_9$	65.33	64.90	6.31	6.52	4.62	4.65
18	4-NO_2	A	242–244	$C_{30}H_{32}N_4O_8 + H_2O$	61.95	62.13	6.07	5.71	7.23	6.77
19	4-NH_2	D	208–212	$C_{30}H_{36}N_4O_6$	67.52	67.72	6.61	6.91	7.88	7.79
20	4-$N(CH_3)_2$	F	251–253	$C_{32}H_{40}N_4O_6$	68.43	67.69	7.00	7.09	7.48	7.23
21	4-$NHCOCH_3$	E	182–187	$C_{32}H_{37}N_3O_7 + 2H_2O$	62.83	63.09	6.76	6.72	6.87	6.91
22	4-$NHCO_2C_2H_5$	B	150–158	$C_{33}H_{39}N_3O_8$	65.44	64.66	6.49	6.36	6.94	7.06
23	4-$NHCONHC_6H_5$	G	250–251	$C_{37}H_{40}N_4O_7$	68.08	67.57	6.18	6.25	8.58	8.80
24	4-$N{=}NC_6H_5$	A	205–211	$C_{36}H_{38}N_4O_6$	69.43	68.29	6.15	5.80	9.00	9.26
25	2,3-$(OCH_3)_2$	B[c]	138–141	$C_{33}H_{36}N_2O_8$	66.43	65.61	6.62	6.60	4.84	4.69
26	2,5-$(OH)_2$	C[a]	180–185	$C_{30}H_{34}N_2O_8$	65.44	64.84	6.22	6.38	5.09	4.88
27	2,5-$(OCH_3)_2$	B[c]	180–182	$C_{33}H_{38}N_2O_8$	66.43	66.60	6.62	6.04	4.84	5.29
28	2,5-$(OCO_2C_2H_5)_2$	E	140–145	$C_{36}H_{42}N_2O_{12}$	62.24	61.57	6.10	6.09	4.03	4.07
29	2-OH, 5-NO_2	C	235	$C_{30}H_{33}N_3O_9$	61.95	60.88	6.07	5.75	7.23	7.29
30	2-OH, 5-NH_2	D	230–232	$C_{30}H_{35}N_3O_7$	65.56	65.50	6.42	6.35		
31	2-OCH_3, 5-NO_2	A	245–246	$C_{31}H_{35}N_3O_9$	62.72	62.48	5.94	5.85	7.08	7.07
32	2-OCH_3, 5-NH_2	D	148–153	$C_{31}H_{37}N_3O_7 \cdot CH_3OH$	64.52	64.94	6.94	6.65	7.05	7.04
33	2-OCH_3, 3-$N(CH_3)_2$	F	219	$C_{33}H_{41}N_3O_7$	66.98	66.84	6.98	7.09	7.10	6.87
34	2-OCH_3, 5-$N(CH_3)_2$	F	145–150	$C_{33}H_{41}N_3O_7$	66.98	66.67	6.98	6.93	7.10	7.27
35	3,4-$(OH)_2$	C	218–220	$C_{30}H_{34}N_2O_8 + \frac{1}{2}H_2O$	64.38	64.35	6.30	6.83	5.00	4.92
36	2-OCH_3, 3-NO_2	A	221	$C_{31}H_{35}N_3O_9$	62.72	62.47	5.94	6.05	7.08	7.16
37	3,4-$(OCO_2C_2H_5)_2$	E	162–164	$C_{36}H_{42}N_2O_{12}$	62.24	61.70	6.10	6.33	4.03	4.43
38	3,4-OCH_2O–	B	231–233	$C_{31}H_{34}N_2O_8$	66.18	66.03	6.09	6.09	4.98	5.12
39	3-OCH_3, 4-OH	C[c]	174–177	$C_{31}H_{36}N_2O_8 + \frac{1}{2}H_2O$	64.90	64.94	6.50	6.64	4.88	4.53
40	3-OCH_3, 4-$OCO_2C_2H_5$	E	140–142	$C_{34}H_{40}N_2O_{10} + \frac{1}{2}H_2O$	63.24	63.20	6.40	6.32	4.34	4.12
41	3-$OCO_2C_2H_5$, 4-OCH_3	A[b,c]	205–207	$C_{34}H_{40}N_2O_{10}$	64.14	63.80	6.33	6.26		
42	3,5-$(OCO_2C_2H_5)_2$	B[b]	200–206	$C_{36}H_{42}N_2O_{12} + \frac{1}{2}H_2O$	61.44	61.29	6.16	5.97	3.98	3.94
43	3,5-$(NO_2)_2$	A	235–239	$C_{30}H_{32}N_4O_{10}$	59.20	58.81	5.30	5.36	9.21	9.53
44	3,5-$(NH_2)_2$	D	186–188	$C_{30}H_{36}N_4O_6 + \frac{1}{2}H_2O$	64.61	64.55	6.69	6.70	10.05	10.48
45	3,5-$[N(CH_3)_2]_2$	F	260–261	$C_{34}H_{44}N_4O_6$	67.52	67.86	7.33	7.14	9.27	9.32
46	3,5-$(NHCOCH_3)_2$	E	210–215	$C_{34}H_{40}N_4O_8 + \frac{1}{2}H_2O$	63.63	63.04	6.44	6.37	8.73	8.88
47	3,5-$(NHCO_2C_2H_5)_2$	E	188–191	$C_{36}H_{44}N_4O_{10} + H_2O$	60.83	60.85	6.52	6.45	7.88	7.36
48	3,4,5-$(CH_3)_3$	A[d]	251–252	$C_{33}H_{40}N_2O_6$	70.69	70.66	7.19	7.08	5.00	4.93
49	3,4,5-$(OC_2H_5)_3$	B	209–211	$C_{36}H_{46}N_2O_9$	66.41	67.18	7.13	7.08	4.31	4.27
50	3,4,5-$(OCH_3CH_2CH_3)_3$	B[e]	145–147	$C_{39}H_{52}N_2O_9$	67.61	67.71	7.57	7.62	4.04	4.03
51	3,4,5-$(OCH_2CH_2CH_2CH_3)_3$	B[e]	162–163	$C_{42}H_{58}N_2O_9$	68.64	68.57	7.95	8.13	3.81	3.69
52	3,4-$(OCH_3)_2$, 5-OH	C[f]	228–233	$C_{32}H_{36}N_2O_8$	64.63	64.45	6.44	6.54	4.71	4.44
53	3,4-$(OCH_3)_2$, 5-$OCO_2C_2H_5$	E[f]	140–150	$C_{36}H_{42}N_2O_{11} + \frac{1}{2}H_2O$	62.21	61.80	6.41	6.58	4.15	4.23
54	3,5-$(OCH_3)_2$, 4-OH	C	190–192	$C_{32}H_{38}N_2O_9$	64.63	64.33	6.44	6.65	4.71	4.72
55	3,5-$(OCH_3)_2$, 4-$OCOCH_3$	E	233–236	$C_{34}H_{40}N_2O_{10}$	64.14	64.26	6.33	6.44	4.40	4.47
56	3,5-$(OCH_3)_2$, 4-OCO_2CH_3	E	231–232	$C_{34}H_{40}N_2O_{11}$	62.56	62.32	6.18	6.13	4.29	4.24
57	3,5-$(OCH_3)_2$, 4-$OCO_2C_2H_5$	E	175–179	$C_{35}H_{42}N_2O_{11}$	63.1	62.87	6.34	6.39	4.20	4.48
58	3,5-$(OCH_3)_2$, 4-$OCO_2(CH_2)_3CH_3$	E	182–183	$C_{37}H_{46}N_2O_{11}$	63.96	64.02	6.67	6.64	4.03	4.01
59	3,5-$(OCH_3)_2$, 4-$OCO_2(CH_2)_2CH_3$	E	183–184	$C_{36}H_{44}N_2O_{11}$	63.51	63.68	6.57	6.70	4.12	3.94
60	3,5-$(OCH_3)_2$, 4-$OCO_2CH_2CH(CH_3)_2 \cdot HCl$	E	224–225	$C_{37}H_{48}N_2O_{11} \cdot HCl + H_2O$	59.31	59.05	6.59	6.56	3.74	3.74
61	3,5-$(OCH_3)_2$, 4-$OCOC_6H_5 \cdot HCl$	E	230–234	$C_{39}H_{42}N_2O_{10} \cdot HCl + 1H_2O$	62.18	62.48	6.02	6.09	3.72	3.68
62	3,5-$(OCH_3)_2$, 4-$OCON(CH_3)_2 \cdot HCl$	A[g]	275	$C_{35}H_{43}N_3O_{10} \cdot HCl$	59.86	59.14	6.32	6.41	5.98	5.99
63	3,5-$(OCH_3)_2$, 4-$OCONHC_6H_5$	H	212–215	$C_{36}H_{43}N_3O_{10}$	63.2	63.57	6.50	6.45	6.30	6.21
64	3,5-$(OCH_3)_2$, 4-$OCONHC_6H_5$	H	192–196	$C_{36}H_{43}N_3O_{10}$	65.6	65.62	6.08	6.22	5.88	5.77
65	2-COOH, 3,4,5,6-Cl_4	M	207–208	$C_{31}H_{30}Cl_4N_2O_8 + 2H_2O$	50.49	50.22	4.64	4.28	3.80	3.49

TABLE I (*continued*)

DERIVATIVES OF METHYL RESERPATE



No.	Substituent	Method of prepn.	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
66	NH_2–	L	263–264	$C_{34}H_{31}N_3O_6$	63.00	63.18	6.83	6.80	9.19	9.42
67	C_6H_5NH–	I	264–265	$C_{40}H_{35}N_3O_6$	67.52	67.54	6.61	6.73	7.88	7.71
68	4-$NO_2C_6H_4NH$–	I	242–245	$C_{40}H_{34}N_4O_8 + {}^1/_2H_2O$	61.32	61.37	6.00	6.01	9.54	9.39
69	4-$NH_2C_6H_4NH$–	D	250–255	$C_{40}H_{36}N_4O_6$	65.67	65.10	6.61	6.63	10.21	10.42
70	2,5-$Cl_2C_6H_3NH$–	I	272–277	$C_{40}H_{34}Cl_2N_3O_6$	59.8	58.61	5.52	5.29	6.98	6.97
71	$CH_3CH{=}CH$–	B	236–238	$C_{37}H_{34}N_3O_6$	67.20	67.29	7.10	7.04	5.81	6.15
72	$(CH_3)_3C$–	B[h]	240–245	$C_{35}H_{38}N_3O_6$	67.44	66.99	7.68	7.59	5.62	5.76
73	$(CH_3)_2NCH_2$(=O)–	N	229–230	$C_{37}H_{37}N_3O_6$	64.90	64.72	7.46	7.42	8.41	8.37
74	$C_6H_5C(=O)NHCH_2$–	O	252–253	$C_{42}H_{37}N_3O_7 + 2CH_3OH$	63.83	63.85	7.09	6.74	6.57	6.23
75	$(CH_3)_2CH(CH_2)_2$–	B	223–226	$C_{39}H_{40}N_3O_6 + {}^1/_2H_2O$	66.77	66.76	7.92	7.71	5.37	5.47
76	C_6H_{11} (cyclohexyl)	B	223–225	$C_{39}H_{40}N_3O_6$	68.68	68.75	7.69	7.78	5.34	5.62
77	*trans*-C_6H_5OCONH-4-C_6H_{10}–	B[i]	140–150	$C_{48}H_{48}N_3O_8 + {}^1/_2H_2O$	64.06	64.16	7.17	7.31	6.79	6.66
78	$CH_3(CH_2)_7$–	B	208–211	$C_{33}H_{46}N_3O_6$	69.28	69.39	8.36	8.27	5.05	5.18
79	$CH_3(CH_2)_{14}$–	B	175–190	$C_{39}H_{60}N_3O_6$	71.74	72.12	9.26	9.31	4.29	4.23
80	HOOCCH=CH–	M	195–197	$C_{37}H_{33}N_3O_8 + {}^1/_2H_2O$	62.18	62.37	6.38	6.37	5.37	5.18
81	$HOOC(CH_2)_8$–	M	226–227	$C_{38}H_{39}N_3O_8$	63.62	63.66	6.86	6.96	5.30	5.11
82		M	214–215	$C_{51}H_{53}N_3O_8 + H_2O$	63.57	63.37	6.88	6.90	4.78	4.53
83	$C_{11}H_9OCH_2$–	B	206–212	$C_{45}H_{43}N_3O_7 + H_2O$	61.89	62.20	7.19	6.68	5.55	5.49
84	$C_2H_5OCO_2CH_2$–	B[a]	100–110	$C_{28}H_{36}N_2O_8$	61.75	59.37	6.66	6.16	5.14	5.61
85	$C_6H_5CH(OCH_3)$–	B	247–250	$C_{33}H_{33}N_3O_7$	68.31	67.67	6.81	6.78	4.98	5.06
86	$C_6H_5CH(OCO_2C_2H_5)$–	B[a]	220–227	$C_{34}H_{40}N_2O_9 + {}^1/_2H_2O$	64.85	64.78	6.72	6.47	4.45	4.09
87	2,5-$(OCH_3)_2C_6H_3CH_2$–	B[i]	190–192	$C_{33}H_{40}N_2O_8$	66.87	66.44	6.80	6.60	4.73	4.16
88	$(C_6H_5)_2CH$–	B	225–227	$C_{37}H_{40}N_2O_6$	73.00	73.88	6.62	6.83	4.60	4.75
89		B	205-210	$C_{37}H_{38}N_2O_6$	73.24	72.25	6.31	5.82	4.62	4.08
90	3,4-$(OH)_2C_6H_3CH{=}CH$–	C[k]	245	$C_{32}H_{36}N_2O_8$	66.65	66.45	6.29	6.28	4.86	5.01
91	3,4-$(OCH_3)_2C_6H_3CH{=}CH$–	C[k]	204–205	$C_{34}H_{40}N_2O_8$	67.53	67.42	6.67	6.66	4.63	4.62
92	3-OCH_3-4-$OCO_2C_2H_5C_6H_3CH{=}CH$–	E[k]	218–219	$C_{36}H_{42}N_2O_{10}$	65.24	64.94	6.39	6.35	4.23	4.36
93	3,4-$(C_2H_5OCO_2)_2C_6H_3CH{=}CH$–	E	203–205	$C_{38}H_{44}N_2O_{12}$	63.32	63.17	6.15	6.16	3.89	3.79
94	3,4-$OCH_2OC_6H_3CH{=}CH$–	B	235–237	$C_{33}H_{36}N_2O_8$	67.33	66.89	6.16	6.13	4.76	4.73
95	3,4-$OCH_2OC_6H_3CH{=}CH{-}CH{=}CH$–	B[k]	229–230	$C_{35}H_{38}N_2O_8$	68.39	68.14	6.23	6.01	4.56	4.51
96	3,4,5-$(OCH_3)_3C_6H_2(CH_2)_2$–	J	172–175	$C_{35}H_{44}N_2O_9$	66.3	66.17	6.98	7.24	4.42	4.63
97	3,4,5-$(OCH_3)_3C_6H_2(CH_2)_2$– (3-iso)	K	196–197	$C_{35}H_{44}N_2O_9$	66.3	65.6	6.98	7.13	4.42	4.31
98	β-Naphthyl	B	244–246	$C_{34}H_{36}N_2O_6$	71.81	71.67	6.38	6.29	4.93	4.51
99		B[a]	182–185	$C_{37}H_{40}N_2O_9 + H_2O$	65.86	65.08	6.27	5.99	4.15	4.31
100		A	239–243	$C_{30}H_{34}N_2O_7$	67.4	66.14	6.38	6.39	5.24	5.53
101		A	286–288	$C_{33}H_{33}N_3O_6$	67.03	67.39	6.40	6.36	8.09	8.22
102		B	220–225	$C_{36}H_{33}N_3O_6 + H_2O$	67.66	67.50	6.35	6.18	7.15	7.41

[a] Carbethoxy acid prepared according to published procedure: W. J. Hickenbottom, "Reactions of Organic Compounds." Longmans, Green & Co., Inc., New York, N. Y., 1948, p. 99. [b] Prepared according to the procedure of T. Heap and R. Robinson, *J. Chem. Soc.*, 2343 (1926). [c] Acid prepared from corresponding aldehyde by procedure given by I. A. Pearl, *Org. Syntheses*, **30**, 10 (1950). [d] Acid prepared according to O. Jacobsen, *Ber.*, **15**, 1855 (1882). [e] Acid prepared according to procedure of N. Rabjohn and A. Mendel, *J. Org. Chem.*, **22**, 986 (1957). [f] Acid prepared according to procedure of E. Fischer and K. Freudenberg, *Ber.*, **45**, 2716 (1912). [g] 3,5-Dimethoxy-4-dimethylaminocarbamyloxybenzoic acid was prepared according to the procedure of B. J. Ludwig and E. C. Piech, THIS JOURNAL, **73**, 5779 (1951), for synthesis of carbamates. [h] Trimethylacetyl chloride was distilled before use; b.p. 102–106°. [i] *trans*-4-Aminocyclohexanecarboxylic acid was prepared by Dr. L. H. Werner of these laboratories according to the procedure of E. Ferber and H. Brueckner, *Ber.*, **76**, 1019 (1943). [j] The acid was prepared by Dr. J. L. Marsh of these laboratories from 2,5-dimethoxyacetophenone by the Willgerodt reaction as described by H. Wolkowitz and M. S. Dunn, "Biochemical Preparations," Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 8. [k] These esters were prepared by Dr. J. M. Mueller of the CIBA Co., Basle, Switzerland. Melting points were determined in sealed capillary tubes.

priate acid chloride. The mixture was cooled, solvents evaporated almost to dryness *in vacuo;* water added and the gum triturated and washed with excess water yielding the desired compound in the form of its hydrochloride. Conversion of the crude salt to the free base was accomplished by slurrying in methanol solution for 10 minutes with an equal weight of silver carbonate. After filtration from silver salts and evaporation of the methanol the ester was crystallized from one of the solvents listed in B.

(F) The dimethylamino ester was prepared by reductive alkylation as illustrated by the preparation of methyl 18-O-(4-dimethylaminobenzoyl)-reserpate: Methyl 18-O-(4-aminobenzoyl)-reserpate (2.8 g., 0.005 mole) was dissolved in 200 ml. of methanol plus 4 ml. of 37% formaldehyde and subjected to reduction over 2 g. of 10% palladium-on-charcoal for two days until approximately the theoretical uptake of hydrogen was observed. The catalyst was removed by filtration and the solution evaporated *in vacuo* leaving the product as a pale yellow foam which was crystallized from ethanol–water; yield 0.35 g. (12%). (The nitro compound may be used instead of the corresponding amino ester.)

(G) Methyl 18-O-(4-aminobenzoyl)-reserpate (1 g., 0.0019 mole) was refluxed with 0.3 ml. (0.0027 mole) of phenyl isocyanate in 50 ml. of methylene chloride for 6 hours. The solution was evaporated *in vacuo* and the product recrystallized from acetone; yield 0.65 g. (52%).

(H) As an example of this preparation methyl 18-O-(3,5-dimethoxy-4-hydroxybenzoyl)-reserpate (2 g., 0.0034 mole) was refluxed for 2 hours in 50 ml. of methylene chloride with 0.4 ml. (0.0036 mole) of phenyl isocyanate. The reaction mixture was filtered to clarify and the filtrate evaporated *in vacuo*. The product was crystallized from acetone; yield 0.9 g. (37%).

(I) This preparation is illustrated by the reaction of methyl reserpate (4 g., 0.0097 mole) with 1.2 g. (0.01 mole) of phenyl isocyanate in refluxing methylene chloride (100 ml.). After one hour the mixture was filtered, the filtrate evaporated *in vacuo* and the product crystallized from acetone; yield 1.3 g. (24%).

(J) Methyl 18-O-(3,4,5-trimethoxycinnamoyl)-reserpate (5 g., 0.0079 mole) isolated from *Rauwolfia vomitoria* was hydrogenated at atmospheric pressure and room temperature in 300 ml. of methanol over 1 g. of 10% palladium-on-charcoal until the theoretical amount of hydrogen was absorbed during 16 hours. The solution was filtered from catalyst, evaporated *in vacuo* and the residue recrystallized from ethyl acetate–ether; yield 4.3 g. (85%) of methyl 18-O-[3-(3,4,5-trimethoxyphenyl)-propionyl]-reserpate.

(K) Hydrogenation of methyl 18-O-(3,4,5-trimethoxycinnamoyl)-reserpate (5 g., 0.0079 mole) in 300 ml. of methanol containing 5 drops of acetic acid over 1 g. of platinum oxide at room temperature and atmospheric pressure proceeded with the expected uptake of hydrogen during 4 hours. Removal of the catalyst by filtration and washing with methylene chloride and partial evaporation of the solvent *in vacuo* yielded 4.5 g. (90%) of crystalline methyl 18-O-[3-(3,4,5-trimethoxyphenyl)-propionyl]-isoreserpate.

Under the same conditions reserpine was approximately 20% converted to 3-isoreserpine.

(L) Methyl reserpate (3 g., 0.0072 mole) in 60 ml. of chloroform containing 1.27 g. (0.0068 mole) of antipyrene was treated with 0.48 ml. (0.68 g., 0.007 mole) of phosgene in 5 ml. of toluene at −10°. After standing overnight at room temperature the mixture was filtered and the filtrate cooled to 0° and treated with excess gaseous NH_3. The ammonium chloride was filtered, the solution washed with water, dried over K_2CO_3 and evaporated *in vacuo*. The brown gum was crystallized from ethanol; yield 0.2 g. (6%).

(M) The preparation of acid esters of methyl reserpate is illustrated by the preparation of the maleic acid ester: To a solution of 4.14 g. (0.01 mole) of methyl reserpate in 300 ml. of methylene chloride was added 0.02 mole of maleic anhydride and after 3 days at 25° the solution was evaporated to dryness *in vacuo*. Upon addition of 25 ml. of acetone and chilling the product crystallized and was recrystallized from acetone; yield 2.0 g. (39%).

(N) **N,N-Dimethylglycine Ester of Methyl Reserpate.**—A solution of 4.14 g. (0.01 mole) of methyl reserpate and 1.57 g. (0.010 mole) of the acid chloride–hydrochloride of N,N-dimethylglycine in 100 ml. of methylene chloride was stored in the dark for 7 days at 25°. The reaction mixture was then poured onto a column of 80 g. of alumina (Woelm, Activity III, basic). The crude ester collected in the first 200 ml. of methylene chloride eluate was recrystallized from methylene chloride–benzene giving 0.27 g. (5%) of product.

(O) **N-Benzoylglycine Ester of Methyl Reserpate.**—Methyl reserpate (4.14 g., 0.010 mole) and hippuryl chloride (2.2 g., 0.11 mole) were dissolved in 80 ml. of methylene chloride and stored in the dark at 25° for 18 days. At this time the concentration of ester, which was followed daily by paper chromatographic assay of aliquot portions of the reaction mixture, had reached a maximum and began to decrease. The mixture was now poured onto a column of 100 g. of alumina (Woelm, Activity III, basic) and eluted with 1000 ml. of methylene chloride. Concentration of the eluate and recrystallization of the residue from methylene chloride–methanol gave 0.73 g. (13%) of pure product.

SUMMIT, N. J.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Alkaloids of *Tabernanthe iboga*. Part VIII[1]

BY M. F. BARTLETT, D. F. DICKEL, R. C. MAXFIELD, L. E. PASZEK AND A. F. SMITH

RECEIVED OCTOBER 23, 1958

Iboluteine and iboluteine lactam were reduced and the dihydro compounds rearranged to yield the new indoles IX (or XII) and XIII.

In the course of our detailed study of the alkaloids of *Tabernanthe iboga* the reactions of iboluteine (I) were further investigated.

Goutarel, Janot, Mathys and Prelog[2] reported that ibogaine was obtained on reduction of iboluteine with lithium aluminum hydride.[3] This reaction has now been repeated but no ibogaine could be detected in the reaction mixture. The major product was dihydrodeoxyiboluteine (II) which was isolated in 85% yield. Dihydroiboluteine (III) was detected by paper chromatography as a minor component in the crude reaction product. Reduction of iboluteine with sodium borohydride gave a mixture of two diastereoisomers, dihydroiboluteine A (m.p. 150°) and dihydroiboluteine B (m.p. 184°), having typical dihydroindole ultraviolet absorption spectra and OH and NH absorption in the infrared. The molecular rotation differences between the two compounds and their common reduction product,

(1) Part VII, L. H. Werner and S. Ricca, Jr., THIS JOURNAL, **80**, 2733 (1958).

(2) R. Goutarel, M.-M. Janot, F. Mathys and V. Prelog, *Helv. Chim. Acta*, **39**, 742 (1956).

(3) However, Goutarel stated in his thesis that iboluteine was reduced to dihydrodeoxyiboluteine with lithium aluminum hydride but identified the product only by its ultraviolet absorption spectrum; R. Goutarel, These doc. sci. Paris, 1954.