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SYNTHETIC ANALOGUES OF THE ALKALOID RESERPINE

S. G. Agbalyan

CONTENTS

I.	Introduction	526
II.	Effect of structural changes in the reserpine molecule on its biological activity	526
III.	Derivatives of yohimbine	528
IV.	Derivatives of β-carboline	529
V.	Derivatives of tryptamine	531
VI.	Derivatives of isoquinoline	531
VII.	Derivatives of cyclohexanol	531
VIII.	Derivatives of trimethoxybenzoic acid	532

I. INTRODUCTION

Most of the therapeutically valuable alkaloids have synthetic substitutes containing the same structural elements. They are simpler in structure and are manufactured on an industrial scale. At present the synthetic antimalarials (atebrin, bigumal), anaesthetics (promedol), local anaesthetics (novocaine), and other synthetic drugs are often superior in their properties to the natural ones and are favoured in medical practice.

In 1952, from the plant *Rauwolfia serpentina*, Müller, Schlittler, and Bein[1] isolated reserpine (I), an alkaloid of the indole group, with a sedative and hypotensive action.

The remarkable activity of reserpine and its wide applicability in medicine[2,3] for the treatment of hypertonia and mental diseases has attracted considerable interest. Its structure was established[4] in 1954, and in 1956 Woodward and his collaborators[5] carried out its complete synthesis.

Studies of the correlation between the structure of reserpine and its pharmacological activity were started in 1954. Yakhontov[6] discussed this subject in his review of the alkaloids from *Rauwolfia*.

A good deal of work is being done at present in an attempt to find simple analogues of reserpine. All efforts to synthesise a reserpine substitute are directed towards the preparation of various fragments of the reserpine molecule, *viz.* the derivatives of yohimbine, β-carboline, indole, isoquinoline, cyclohexanol, and trimethoxybenzoic acid.

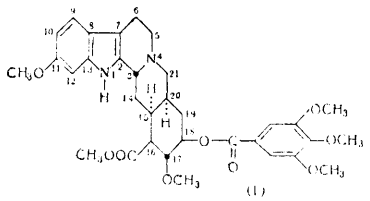
This review discusses all the attempts made so far to synthesise simple analogues of reserpine.

II. EFFECT OF STRUCTURAL CHANGES IN THE RESERPINE MOLECULE ON ITS BIOLOGICAL ACTIVITY

The pharmacological study of the alkaloids from *Rauwolfia* led to the discovery of an interesting type of action on the central nervous system, the so-called reserpine-like action, which is at once sedative and hypotensive.

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Reserpine is an alkaloid of very complex structure, which has 6 asymmetric carbon atoms. Its complex stereochemical formula, established by conformational analysis, is as follows (I):



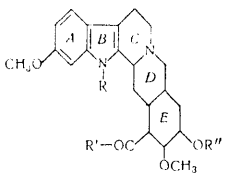
(I)

The biological properties of reserpine depend on steric factors, since its stereoisomer, 3-isoreserpine, is inactive[7]. The characteristic action of reserpine can be changed by small structural changes in its molecule. For example, its hypotensive properties are lost after hydrolysis into methyl reserpate (II) and trimethoxybenzoic acid[8].

Chatterjee and Talapatra[9,10] assumed that the biological activity of reserpine is due to the combined effect of all substituents in the rings. The same was observed by Huebner, Lucas, and their collaborators[11]. In order to establish the effect of changes in the reserpine structure on its properties, Huebner[12] alkylated the indole nitrogen in reserpine, and also prepared the reserpamide (V).

Methyl reserpate (II), in the form of its *N*-potassium derivative, was caused to react with methyl iodide and allyl bromide in liquid ammonia. The resulting *N*-alkylmethyl reserpates were then esterified with 3, 4, 5-trimethoxybenzoyl chloride giving (III)–(IV).

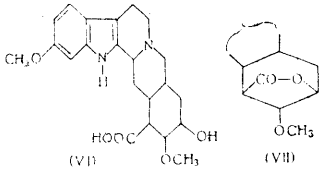
The action of an excess of sodamide upon reserpine in liquid ammonia results in the ammonolysis of both its ester linkages. Re-esterification of reserpamide with 3, 4, 5-trimethoxybenzoyl chloride yields the amide corresponding to reserpine (V):



where for (II) R = H, R′ = OCH_3, R″ = H; (III) R = CH_3, R′ = OCH_3, R″ = $COC_6H_2(OCH_3)_3$-3, 4, 5; (IV) R = CH_2–$CH=CH_2$, R′ = OCH_3, R″ = $COC_6H_2(OCH_3)_3$-3, 4, 5; (V) R = H, R′ = NH_2, R″ = $COC_6H_2(OCH_3)_3$-3, 4, 5.

The pharmacological investigation of these reserpine derivatives showed that they lack tranquillising and hypotensive properties. In fact, (II) acts as a reserpine antagonist.

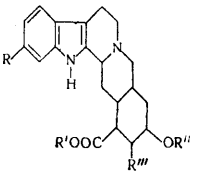
Without any activity whatsoever are the quaternary salt[13] and the products of degradation of reserpine: reserpinic acid and its lactone (VII):



(VI) (VII)

Certain functional groups of reserpine are of no importance for the biological activity of this alkaloid. The naturally occurring alkaloids deserpidine (VIII),[14,15] which is 11-desmethoxyreserpine, and *DL*-17-desmethoxydeserpidine (IX) also have the characteristic reserpine-like activity[16]. In fact the difference in the biological activity of deserpidine and reserpine is quantitative rather than qualitative[17]. Reserpine *N*-oxide also exhibits reserpine-like activity[18].

The reserpine homologue containing an ethyl instead of methyl radical (X) is comparable to reserpine in its activity[19]. Unfortunately, the homologue esters of reserpinic acid are relatively difficult to prepare. Esterification under acid conditions is complicated by the epimerisation at C_3 into corresponding inactive iso-compounds. The preparation of esters from lactones gives unsatisfactory yields. The only promising method for the preparation of esters is from diazoalkanes.



(VIII) R = H, R′ = CH_3, R‴ = OCH_3
(IX) R = OCH_3, R′ = CH_3, R‴ = H
(X) R = OCH_3, R′ = C_2H_5, R‴ = OCH_3
(XI) R = OCH_3, R′ = CH_3, R‴ = OCH_3

} R″ = $COC_6H_2(OCH_3)_3$-3, 4, 5

R″ = $COCH_2C_6H_2(OCH_3)_3$-3, 4, 5

Substitution of the trimethoxybenzoyl radical by a trimethoxycinnamoyl radical in the alkaloid rescinnamine[21,22] (XI) does not alter the pharmacological activity. Other acids could therefore probably be used for the acylation of methyl reserpate to give preparations with reserpine-like activity.

A series of pharmacologically active derivatives of similar type were patented in the United States[23–25]. Methylreserpate *O*-(β-cyclopentylpropionate)[23], methylreserpate *O*-acetoacetate[24], and methylreserpate-*O*-cathylate[25] are all strong hypotensive and sedative agents.

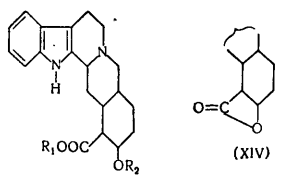
Lukas and his collaborators[19] prepared more than a hundred esters of methyl reserpate. These exhibited three types of activity: reserpine-like activity, hypotensive activity with a small sedative effect, and a predominantly sedative activity. For instance, 3, 5-dimethoxy-4-ethoxycarbonylbenzoic acid is almost equivalent to reserpine in its hypotensive activity, while showing only one-quarter of its sedative activity, 3-Dimethylaminobenzoic ester exhibits approximately one-quarter of the sedative activity of reserpine, with a more rapid onset, and only one-fortieth of its hypotensive activity.

The example of these two compounds shows that the characteristic activity of reserpine, consisting in the combination of hypotensive and sedative activity, can be effectively resolved into its main components. This is of interest because, by making some definite changes in the structure of reserpine, compounds with selective activity should result. Hypotensive preparations free of sedative properties are very important in clinical practice.

Investigations of the structure of reserpine showed that certain functions which have no effect on the characteristic activity of the starting alkaloid could be omitted in the synthesis of reserpine-like preparations, as for instance the methoxy groups at C_{11} and C_{17}, and that the trimethoxybenzoyl radical, acylating the hydroxyl group at C_{18}, could be changed.

III. DERIVATIVES OF YOHIMBINE

Reserpine is a 3, 4, 5-trimethoxybenzoyl ester of methyl reserpate (II). Methyl reserpate has the pentacyclic structure of yohimban, contained in the alkaloids from *Yohimba*. It is remarkable that in the transition from reserpine to yohimbine (XII) the pharmacological action undergoes a sharp change. Various stereochemical changes in the molecule of yohimbine considerably affect the biological activity of these substances[26-31]. Yohimbic acid (XIII), its amide, hydrazide, and lactone[32] (XIV) display no reserpine-like activity. The lactone shows a combination of adrenolytic and hypotensive activity, typical of yohimbine.



(XIV)

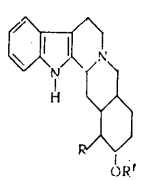
where for (XII) $R_1 = CH_3$, $R_2 = H$, and for (XIII) $R_1 = H$, $R_2 = H$.

Yohimbine was nevertheless used as starting material for the synthesis of reserpine substitutes, since the largest part of the reserpine molecule resembles yohimbine.

Huebner *et al.*[11] carried out the synthesis of a number of esters of yohimbine (XII) and its two stereoisomers corynanthine and α-yohimbine, with a view to obtaining reserpine substitutes. The esterification of these hydroxyl-containing alkaloids was carried out in pyridine at room temperature by reaction with acid chlorides. These authors obtained *O*-benzoyl-, *O*-anisoyl-, and *O*-veratroyl-3, 4, 5-trimethoxybenzoylyohimbines, as well as *O*-(3, 4, 5-trimethyloxybenzoyl)-α-yohimbine, *O*-(3, 4, 5-trimethoxybenzoyl)-corynanthine and *O*-acetylyohimbine. These esters were found not to exhibit any of the reserpine-like properties. Like other yohimbine derivatives, they had adrenolytic and hypotensive properties. Certain amongst them were relatively less toxic than reserpine.

Chatterjee and Talapatra obtained trimethoxybenzoyl and trimethoxycinnamoyl esters of α-yohimbine[33]. Both esters, which are the analogues of reserpine and rescinnamine, lower the blood pressure without having a sedative effect.

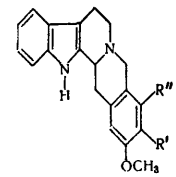
Esters (XVII) and (XVIII) were obtained[34] by the action of 3, 4, 5-trimethoxybenzoyl chloride upon yohimbol (XV) and 16-methylyohimbol (XVI):



where for (XV) R = H, R′ = H; (XVI) R = CH_3, R′ = H; (XVII) R = H, R′ = $COC_6H_2(OCH_3)_3$-3, 4, 5; (XVIII) R = CH_3, R′ = $COC_6H_2(OCH_3)_3$-3, 4, 5.

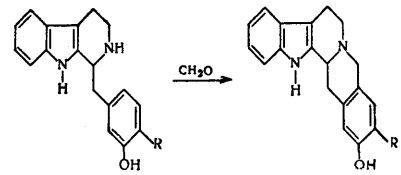
There are unfortunately no data as yet regarding the pharmacological activity of these compounds.

Lɔgemann *et al.*[35] synthesised the yohimbine derivatives of the following general formula:

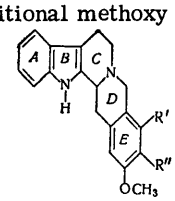


(XIX)	R′ = OH	R″ = H
(XX)	R′ = $OCOCH_3$	
(XXI)	R′ = $OCOCH_2CH_3$	
(XXII)	R′ = $OCOCH_2CH_2CH_3$	
(XXIII)	R′ = $OCOCH_2C_6H_5$	
(XXIV)	R′ = $OCOCH_2C_6H_5$	R″ = OCH_3

These compounds were prepared using the Hahn method[36-37] for the preparation of the derivatives of 15, 16, 17, 18, 19, 20-hexadehydroyohimban:



Compound (XIX) causes a sharp fall of the arterial blood pressure in anaesthetised dogs and rabbits. Compound (XXI) has a similar effect. The activity of compounds (XXIII) and (XXIV) is very low. The same authors[38] further studied the effect of introducing oxygen-containing groups into nucleus *E* on the pharmacological properties of the resulting compounds. They obtained 17, 19-dimethoxy-18-hydroxy-15, 16, 17, 18, 19, 20-hexadehydroyohimban (XXV), which contains an additional methoxy group in ring *E*:



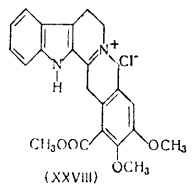
(XXV)	R′ = OCH_3,	R″ = OH
(XXVI)	R′ = OCH_3,	R″ = $OCOCH_2CH_3$
(XXVII)	R′ = OCH_3,	R″ = $OCOC_6H_2(OCH_3)_3$-3,4,5

This compound was obtained by the condensation of tryptamine with 3, 5-dimethoxy-4-hydroxyphenylpyruvic acid followed by the cyclisation of 1-(3, 5-dimethoxy-4-hydroxybenzyl)-1, 2, 3, 4-tetrahydro-β-carboline with formaldehyde. Its esters with propionic (XXVI) and trimethoxybenzoic acid (XXVII) were also prepared.

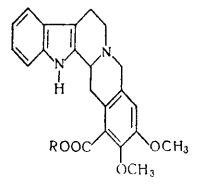
Pharmacological investigations showed that the introduction of an additional methoxy group changes the properties of the starting compounds; the resulting preparations are considerably less active than their desmethoxy analogues, trimethoxybenzoic ester being also less active than propionic ester.

Compounds containing substituents at the 16- and 18-positions of the yohimban skeleton, were also prepared as reserpine substitutes[39]. The condensation of a 2-methoxycarbonyl-3, 4-dimethoxy-6-chloromethylphenylacetate ester with tryptamine gave *N*-[2-(3-indolylethyl)]-3-oxo-5-methoxycarbonyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline. This was cyclised in the presence of phosphorus oxychloride into the unsaturated base (XXVIII), which was

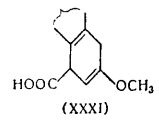
then reduced by platinum in methanol giving the saturated base (XXIX). The hydrolysis of (XXIX) by aqueous-alcoholic KOH yields the acid (XXX), which on reduction with sodium in liquid ammonia in the presence of isopropanol loses its methoxy group at position 17, and is further reduced to the enolic ester (XXXI). On hydrolysis (XXXI) yields the ketonic acid (XXXII), which, reduced in the presence of sodium borohydride, forms the hydroxy acid (XXXIII). Its lactone, (XXXIV), after treatment with sodium methoxide in methanol, formed 18-hydroxy-16--methoxycarbonyl-$\Delta^{15(20)}$-yohimbene (XXXV). There are no data on the biological properties of these compounds.



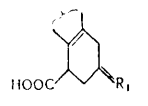
(XXVIII)



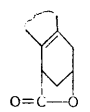
(XXIX) R = CH_3; (XXX) R = H;



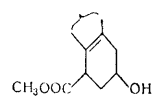
(XXXI)



(XXXII) R_1 = O; (XXXIII) R_1 = H, OH



(XXXIV)

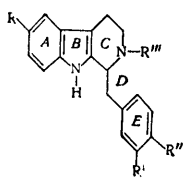


(XXXV)

IV. DERIVATIVES OF β-CARBOLINE

The synthesis of yohimbine derivatives is a laborious multistage process. Somewhat simpler is the preparation of the derivatives of yohimbine with the *D* ring open, and an aromatic or a cyclohexane ring *E*, as in reserpine. These compounds are the derivatives substituted in position 1 of 1, 2, 3, 4-tetrahydro-β-carboline, which can be obtained using the Bischler–Napieralski or Pictet–Spengler reactions.

Logemann *et al.*[35] obtained the derivatives of β-carboline (XXXVI–XLII) using the general method put forward by Hahn and his collaborators:

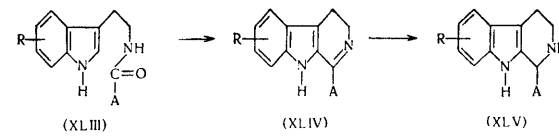


where for (XXXVI) R = R″ = R‴ = H, R′ = OH; (XXXVII) R = = R″ = H, R′ = $OCOC_6H_2(OCH_3)_3$-3, 4, 5, R‴ = $COC_6H_2(OCH_3)_3$--3, 4, 5; (XXXVIII) R = R‴ = H, R′ = OCH_3, R″ = OH; (XXXIX) R = H, R′ = OCH_3, R″ = $OCOCH_3$, R‴ = $COCH_3$; (XL) R = H, R′ = OCH_3, R″ = $OCOC_6H_2(OCH_3)_3$-3, 4, 5, R‴ = $COC_6H_2(OCH_3)_3$-3, 4, 5; (XLI) R = R′ = OCH_3, R″ = = OH, R‴ = H; (XLII) R = R″ = OCH_3, R′ = $OCOC_6H_2$. .$(OCH_3)_3$-3, 4, 5, R‴ = $COC_6H_2(OCH_3)_3$-3, 4, 5.

Only the compounds (XXXVI), (XXXVII), (XL), and (XLII) have any pharmacological interest, but in anaesthetised rabbits they only cause a temporary lowering of blood pressure in doses of 10–20 mg kg^{-1}.

A group of Czech chemists working under Protiva [40] are now making a systematic search for simple analogues of reserpine.

By acylation of tryptamine, 4-methoxytryptamine, and 7-methoxytryptamine the appropriate tryptamides (XLIII) were obtained, which upon the action of phosphorus oxychloride are cyclised forming 1-aralkyl-3, 4-dihydro-norharmanes (XLIV); on reduction with sodium in ethanol (XLIV) yielded 1-aralkyl-1, 2, 3, 4-tetrahydro-norharmanes (XLV).



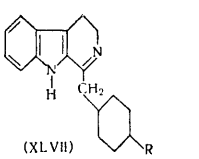
(XLIII) (XLIV) (XLV)

A = $CH_2C_6H_5$ (XLVI)
A = $CH_2C_6H_4(OCH_3)$-4
A = $CH_2C_6H_3(OCH_3)_2$-3,4
A = $CH_2CH_2C_6H_5$
A = $CH_2CH_2CH_2C_6H_5$
A = $C(CH_3)_2C_6H_5$
A-α-$C_{10}H_{11}$(5, 6, 7, 8-tetrahydronaphthyl)
A = $CH_2C_6H_5$, R = 6-OCH_3
A = $CH_2C_6H_5$, R = 8-OCH_3

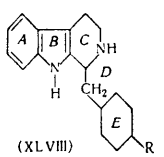
} R = H

Methane sulphonates of these compounds, which are more soluble than hydrochlorides, were used in their pharmacological assay. In doses of 1–5 mg kg^{-1} these methane sulphonates, introduced intravenously, lower the blood pressure by 10–70%. Compared with reserpine, their action is very rapid, but transient. As with reserpine, the lowering of the blood pressure is not based on adrenolytic action. Owing to its favourable hypotensive activity and low toxicity, preparation (XLVI), named "Phenoharmane" has been selected for clinical studies[41].

Protiva and his collaborators[42] also synthesised the simple reserpine analogues, containing a cyclohexane ring *E*. In their structure these compounds are more similar to reserpine than those obtained earlier, containing an open ring *D* and an aromatic ring *E*. For their preparation, cyclohexylacetic and 4-methoxycyclohexylacetic tryptamides were cyclised in the presence of phosphorus oxychloride and the resulting dihydrobases (XLVII) subsequently reduced with sodium in ethanol to form 1-cyclohexylmethyl-1, 2, 3, 4-tetrahydronorharmane (XLVIII) and 1-(4-methoxycyclohexylmethyl)-1, 2, 3, 4-tetrahydronorharmane (XLIX), respectively. Their hydrochlorides and methanesulphonates had hypotensive activity.

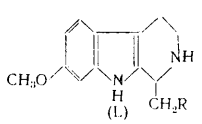


(XLVII) R = H or OCH_3



(XLVIII) R = H
(XLIX) R = OCH_3

An American patent[43] claims the synthesis of the compounds of general formula (L), which have sedative properties:

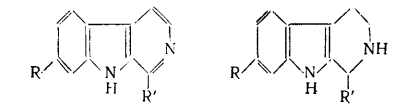


(L)

where R = 1-hydroxycyclohexyl; 1-hydroxy-2-methylcyclohexyl; 1-hydroxy-2, 6-dimethylcyclohexyl, and 1-hydroxycyclopentyl. These compounds were prepared by the condensation of the lithium compound of harmine with cyclohexanone, 2-methylcyclohexanone, 2, 6-dimethylcyclohexanone, and cyclopentanone. The reaction of the Li-derivative of 9--benzylharmine with 2-methylcyclohexanone gave 9-benzyl--1-(1′-hydroxy-2′-methylcyclohexylmethyl)-harmine. The

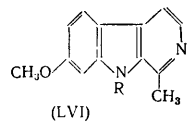
reserpine analogue was in this case obtained by starting from the more accessible alkaloid harmine (LI), which has practically the same structure as reserpine.

In addition to harmine (LI) and tetrahydroharmine (LII) as starting material in the synthesis of the β-carboline derivatives, a number of research workers[44-51] used synthetic harmane (LIII), tetrahydroharmane (LIV), and norharmane (LV). All these compounds contain the same *A*, *B*, and *C* rings as reserpine, and harmine and tetrahydroharmine also contain a methoxy group corresponding to the methoxy group in position 11 in reserpine.



(LI) R = OCH_3, R′ = CH_3; (LII) R = OCH_3, R′ = CH_3;
(LIII) R = H, R′ = CH_3; (LIV) R = H, R′ = CH_3;
(LV) R = H, R′ = H

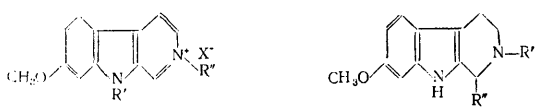
Zhelyazkov and his collaborators[44,45] obtained indole-*N*-alkyl derivatives (LVI) of harmine by reacting harmine-sodium with the appropriate chlorine derivatives:



(LVI)

where R = $CH_2C_6H_5$; $CH_2CH_2N(CH_3)_2$; $CH_2CH_2N(C_2H_5)_2$; CH_3; n-C_4H_9; $CH_2C_6H_4(OCH_3)$-4.

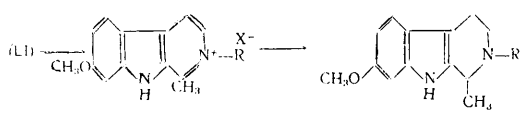
Koretskaya, Danilova, and Utkin[46] obtained several indole-*N*-alkyl- and pyridine-*N*-substituted-derivatives of harmine (LVII)–(LIX) and tetrahydroharmine (LX)–(LXI):



(LVII) R′ = H; R″ = $CH_2CH_2N(C_2H_5)$; X = Cl;
(LVIII) R′ = $CH_2C_6H_5$; R″ = CH_3; X = I
(LIX) R′ = $CH_2C_6H_5$; R″ = CH_3.
(LX) R′ = $CH_2CH_2N(C_2H_5)_2$; R″ = H;
(LXI) R′ = H, R″ = COOH;

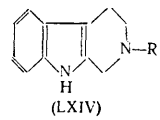
Pyridine-*N*-substituted tetrahydroharmines are closer in structure to reserpine than indole-*N*-derivatives of harmine.

Rubtsov and Yakhontov[47] developed a method for the reduction of the pyridine ring in harmine quaternary salts (LXII) using sodium borohydride which they applied to the synthesis of the pyridine-*N*-derivatives of tetrahydroharmine. In collaboration with Krasnokutskaya[48] they carried out the synthesis of pyridine-*N*-alkyltetrahydroharmines (LXIII) according to the following scheme:



(LXII) (LXIII)

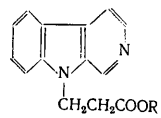
Pyridine-*N*-alkyl derivatives of β-carboline can be obtained by the reaction of tetrahydro-β-carbolines with appropriate chlorine compounds. For instance, by the reaction of tetrahydroharmane with 2-dimethylaminoethyl, benzyl, or 3-methoxybenzyl chlorides, the pyridine-*N*-substituted derivatives of 1, 2, 3, 4-tetrahydronorharmane (XIV) were obtained[49]. They all had hypotensive properties.



(LXIV)

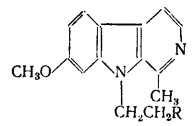
where R = $CH_2CH_2N(CH_3)_2$; $CH_2C_6H_5$; $CH_2C_6H_4(OCH_3)$-m.

A U.S. patent[50] described the preparation of the hydrochloride of indole-*N*-norharmanpropionic acid (LXV) and its ethyl ester (LXVI), and indicated their hypotensive properties.



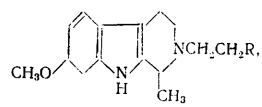
where for (LXV) R = H; (LXVI) R = C_2H_5.

Mndzhoyan and Agbalyan[51] prepared simple reserpine analogues by the reaction of harmine with acrylonitrile in the presence of trimethylbenzylammonium hydroxide, yielding indole-*N*-β-cyanoethylharmine (LXVII), and its hydrolysis product, the corresponding acid (LXVIII)



where for (LXVII) R = CN; (LXVIII) R = COOH.

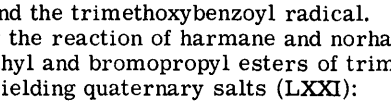
Pyridine-*N*-(β-cyanoethyl)tetrahydroharmine (LXIX) was obtained by the condensation of tetrahydroharmine with acrylonitrile without a catalyst, and was saponified to pyridine-*N*-(β-carboxyethyl) tetrahydroharmine (LXX)



where for (LXIX) R = CN; (LXX) R = COOH.

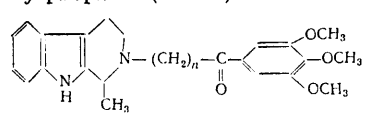
In addition to containing the *A*, *B*, and *C* rings of reserpine, the last two compounds contain the nitrile and carboxyl group at a distance from the salt-forming nitrogen, similar to that of the trimethoxybenzoyl radical in reserpine.

A U.S. patent[52] described certain pharmacologically active compounds which contained the *A*, *B*, and *C* rings of reserpine and the trimethoxybenzoyl radical. They were prepared by the reaction of harmane and norharmane with the bromoethyl and bromopropyl esters of trimethoxybenzoic acid, yielding quaternary salts (LXXI):



(LXXI)

The reaction of 1, 2, 3, 4-tetrahydroharmane with the bromoethyl or bromopropyl esters of the same acid gave the corresponding esters of tetrahydroharmylethanol and tetrahydroharmylpropanol (LXXII):

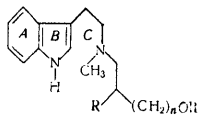


(LXXII)

V. DERIVATIVES OF TRYPTAMINE

The tryptamine derivatives synthesised as reserpine substitutes contain the indolyl fragment of reserpine, *i.e.* the rings *A*, *B*, with ring *C* opened.

Protiva *et al.*[49] synthesised several tryptamine derivatives containing the 3, 4, 5-trimethoxybenzoyl radical (LXXIII–LXXVII):

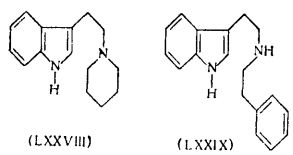


(LXXIII) R = H, n = 0
(LXXIV) R = CH_3, n = 0
(LXXV) R = H, n = 1
(LXXVI) R = H, n = 2
(LXXVII) R = H, n = 4

R′ = $COC_6H_2(OCH_3)_3$-3, 4, 5

By the addition of ethylene and propylene oxides to *N*-methyltryptamine, and the subsequent reduction of the resulting *N*-methyltryptamido-esters of malonic, succinic and adipic acids with lithium aluminium hydride, *N*-methyltryptamino-alcohols were prepared, and were further converted to esters by reaction with 3, 4, 5-trimethoxybenzoyl chloride.

The reaction of 3-indolylacetic acid or its chloride with piperidine and the subsequent reduction of the piperidide of 3-indolylacetic acid with lithium aluminium hydride gave 3-(2-piperidinoethyl)indole (LXXVIII). Similarly, *N*-(2-phenylethyl)tryptamine (LXXIX) was obtained from the tryptamide of phenylacetic acid[49].

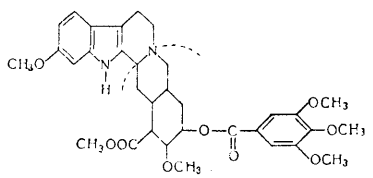


(LXXVIII) (LXXIX)

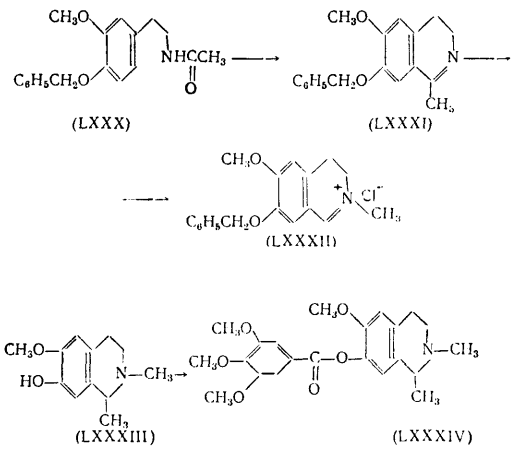
Nogradi[53] synthesised compound (LXXVIII) alongside other amino derivatives of the indole series. To judge from his results, (LXXVIII), as well as 3-(β-diethylaminoethyl)indole, display only one-thirtieth–one-fortieth of the activity of reserpine.

VI. DERIVATIVES OF ISOQUINOLINE

Considering that the reserpine molecule is a condensed ring system consisting of β-carboline and decahydroisoquinoline with functional groups in the appropriate positions, certain authors have synthesised simple reserpine analogues based on isoquinoline.



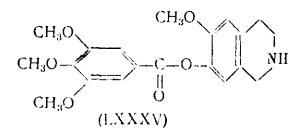
Strukov and Kolganova[54] synthesised and investigated pharmacologically derivatives of "salsoline". Acetylation of 3-methoxy-4-benzyloxyphenylethylamine gave the acetyl derivative (LXXX), which was converted to 1-methyl-6-methoxy-7-benzyloxy-3, 4-dihydroisoquinoline (LXXXI). 1, 2-Dimethyl-6-methoxy-7-hydroxy-1, 2, 3, 4-tetrahydroisoquinoline (LXXXIII) and its 3, 4, 5-trimethoxybenzoate (LXXXIV), were obtained from the iodo- or chloro-methylates derived from LXXXI (LXXXII).



(LXXX) (LXXXI) (LXXXII)

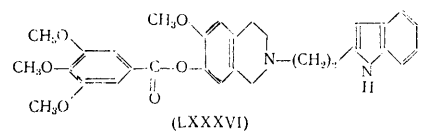
(LXXXIII) (LXXXIV)

The Japanese chemists Onda, Kawanishi, and Sasamoto[55] had earlier synthesised several isoquinoline derivatives as a route to the synthetic reserpine analogues. The condensation of 6-methoxy-7-hydroxy-1, 2, 3, 4-tetrahydroisoquinoline with trimethoxybenzoic acid in the presence of phosphorus pentoxide and 88% phosphoric acid yielded 6-methoxy-7-(3, 4, 5-trimethoxybenzoyloxy)-1, 2, 3, 4-tetrahydroisoquinoline (LXXXV):



(LXXXV)

The reaction of the same starting material with trimethoxybenzoyl chloride gave 2-(3, 4, 5-trimethoxybenzoyl)-6-methoxy-7-hydroxy-1, 2, 3, 4-tetrahydroisoquinoline. 2-[β-(3-Indolyl)ethyl]-6-methoxy-7-(3, 4, 5-trimethoxybenzoyloxy)-1, 2, 3, 4-tetrahydroisoquinoline (LXXXVI) was also prepared.

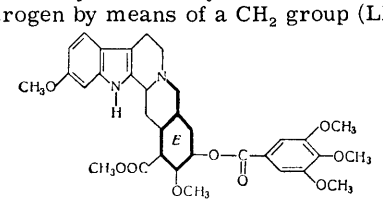


(LXXXVI)

This compound consists of three fragments of the reserpine structure: the indole ring, the *D* and *E* rings, and the trimethoxybenzoyl group.

VII. DERIVATIVES OF CYCLOHEXANOL

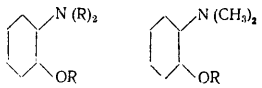
Reserpine contains in its molecule a cyclohexane ring *E*, which is acylated by trimethoxybenzoic acid and bound to the basic nitrogen by means of a CH_2 group (LXXXVII):



(LXXXVII)

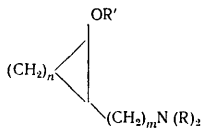
Esters of dialkylaminocyclohexanols (LXXXVIII) were prepared by a number of research workers[56–60]. In their effort to obtain reserpine substitutes, Dubravkova *et al.*[61]

prepared, and assayed the pharmacological activity of, the esters of dimethylaminocyclohexanol (**LXXXIX**) with aliphatic and aromatic acids (acetic, propionic, isobutyric, anisic, veratric, and trimethoxybenzoic).



(LXXXVIII) (LXXX1X)

The preparation of esters of trimethoxybenzoic acid with 2-aminocycloalkanols (**XC**) has also been described[62]:

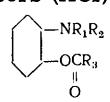


where R′ = $COC_6H_2(OCH_3)_3$-3, 4, 5.

R	n	m	R	n	m
CH_3	3	1	Piperidyl	4	1
C_2H_5	3	1	Morpholyl	4	1
Piperidyl	3	1	C_2H_5	4	2
CH_3	5	1	CH_3	4	1
			C_2H_5	4	1

The condensation of cyclic ketones with formaldehyde and secondary amines gave 2-aminomethylcycloalkanones, which on reduction with lithium aluminium hydride yielded the corresponding 2-aminocycloalkanols; these amino alcohols were subsequently esterified with trimethoxybenzoyl chloride.

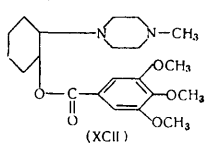
Shapiro *et al.*[63] prepared a series of the *trans*-2-amino-substituted cyclohexyl esters (**XCI**).



(XCI)

They prepared altogether 46 compounds containing various substituents in the amino group and various acyl groups. The final products were obtained by the reaction of the secondary amines with cyclohexene oxide forming substituted aminocyclohexanols, which were then esterified with various acid chlorides.

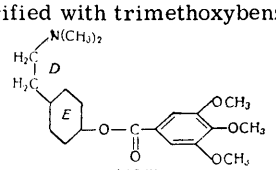
Hypotensive activity was displaced mainly by the derivatives of methylpiperazine. A relatively small number of compounds caused significant depression of the activity of the central nervous system; the only compound which exhibited this effect as well as the hypotensive effect was the ester of 3, 4, 5-trimethoxybenzoic acid (**XCII**):



(XCII)

The fact, however, that these compounds do not lengthen the period of sleep caused by evipan (hexenal) means that they are not completely reserpine-like in their action.

Hexahydrohordenine, obtained by hydrogenation of hordenine, was esterified with trimethoxybenzoic acid (**XCIII**):



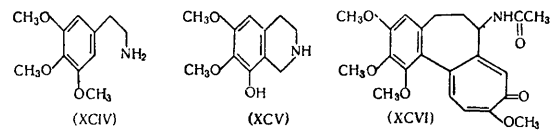
(XCIII)

This ester resembles the ring *E* of the reserpine molecule, with the trimethoxybenzoyl radical in the same position as in reserpine. The aminoethyl radical is reminiscent of the ring *D*. The hydrochloride derived from this ester had no hypotensive activity.

VIII. DERIVATIVES OF TRIMETHOXYBENZOIC ACID

Investigations of the derivatives of trimethoxybenzoic acid are among the most important in the search for reserpine substitutes. The great number of papers on this subject is probably due to the fact that the derivatives of trimethoxybenzoic acid are easier to obtain than the types of compounds discussed so far.

Of all the *Rauwolfia* alkaloids only reserpine contains the trimethoxybenzoyl radical. Cases are known, however, of the accumulation of methoxy groups in other physiologically active substances, *e.g.* the anhalonine alkaloids mescaline (**XCIV**) and anhalamine (**XCV**), as well as colchicine (**XCVI**) and other alkaloids.



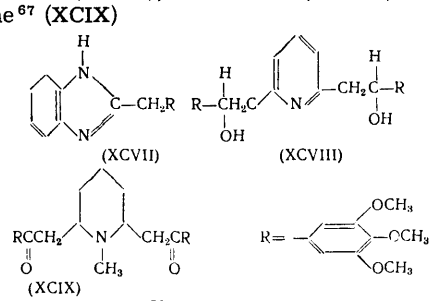
(XCIV) (XCV) (XCVI)

Mescaline, the alkaloid from *Kaktee anhalonium L.*, is known to act on the central nervous system causing hallucinations, but in doses from 0.006–0.008 mg kg^{-1} it displays a hypotensive activity[64].

The methoxy groups obviously play an important part in the action upon the central nervous system; the trimethoxybenzoyl radical is therefore considered by several authors to be one of the most vital components in the manifestation of reserpine activity.

Of all the imidazoline derivatives which cause an increase in blood pressure, 3, 4, 5-trimethoxybenzylimidazoline (Phedrasin) has the strongest effect. This may be accounted for by the accumulation of methoxy groups[65].

For a comparative study of the effect of methoxy groups on the well-known pharmacological preparations containing a phenyl radical, compounds of similar structure, but containing the 3, 4, 5-trimethoxyphenyl radical, were synthesised: for example the trimethoxy analogues of 2-benzylbenzimidazole[66] (**XCVII**), lobeline[67] (**XCVIII**) and lobelanidine[67] (**XCIX**)



(XCVII) (XCVIII)

(XCIX)

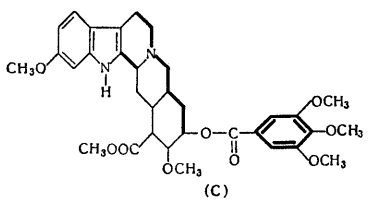
Miller and Weinberg[68] came to the conclusion that the trimethoxybenzoyl radical, though important, is not alone sufficient to account for the pharmacological effect of reserpine. On the basis of existing information regarding the pharmacological activity of nitrogen-containing compounds, these authors synthesised various esters of trimethoxybenzoic acid containing a nitrogen atom in positions 2 or 3 with respect to the oxygen atom in the carboxylic

group. Of all the esters they synthesised, only the tertiary diethylaminopropyl ester had reserpine-like activity (one--third). The corresponding primary aminopropyl ester and the tertiary aminoethyl ester were inactive. On the basis of their results they concluded that oxygen and nitrogen must be separated by three carbon atoms, and that the nitrogen must be tertiary.

This communication was followed by numerous preparations of various amino-esters, as well as the amino-amides of trimethoxybenzoic acid. It is known that the pharmacological effect can sometimes be made to last longer by replacing the ester linkage by an amide linkage.

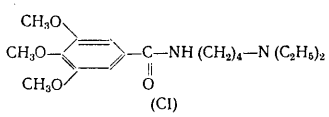
Dialkylaminoethyl esters of 3, 4, 5-trimethoxybenzoic acid, synthesised by Rabjohn and Mendel[69] had only local anaesthetic activity, but no activity characteristic of reserpine.

Sastry and Lasslo[70], starting from the premise that the diethylaminobutyl ester of trimethoxybenzoic acid has a structure closer to that of reserpine than the diethylaminopropyl ester, synthesised the former ester in the hope of obtaining a compound with biological properties similar to those of reserpine.



(C)

By substituting the ester by the amide linkage they also obtained N-[4-($N'N'$-diethylaminobutyl)]-3, 4, 5-trimethoxybenzamide (CI).

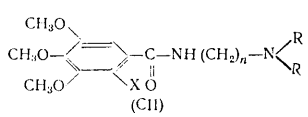


(CI)

The ester- and amino-amide were prepared by the reaction of trimethoxybenzoyl chloride with 4-N,N-diethylaminobutanol and N-(4-N',N'-diethylamino) butylamine, respectively.

Lunsford, Murphey, and Rose[71] also prepared 4-dialkylaminobutyl esters of 3, 4, 5-trimethoxybenzoic acid and found them devoid of any reserpine-like activity.

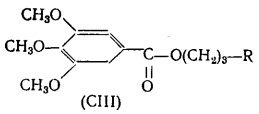
Shiemenz and Engelhard[72] synthesised the amino-amides of 3, 4, 5-trimethoxybenzoic and 2-bromo-3, 4, 5-trimethoxybenzoic acids because their structure was similar to those of the dialkylaminoalkyl esters obtained earlier by others. Amino-amides were obtained by the reaction of the appropriate primary–tertiary diamines with the mixed anhydride of monoethylcarbonate and trimethoxybenzoic acid. This anhydride reacts readily with dialkylaminoalkyl amines forming compounds of the general formula (CII).



(CII)

where X = H, Br; n = 2, 3; R = CH_3, C_2H_5.

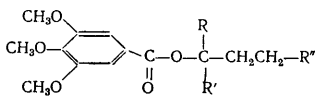
In addition to esters with aliphatic amino alcohols, trimethoxybenzoates containing nitrogen in a ring were also prepared (CIII):



(CIII)

where R = N-pyrrolidyl, N-morpholinyl, and N-piperidyl[73,74]. The condensation of acid chlorides with the appropriate diamines gave amino-amides containing the same heterocyclic radicals[73].

The synthesis has also been described of the esters of the following general formula (CIV):

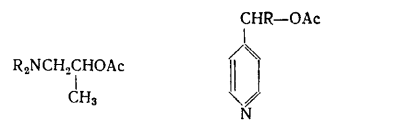


R	R′	R″
H	H	1-methylpiperazyl
C_6H_5	C_6H_5	pyrrolidyl
C_6H_5	C_6H_{11}	pyrrolidyl
C_6H_{11}	C_6H_{11}	pyrrolidyl

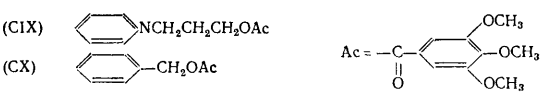
In the paper by Vejdělek and Trćka[75], the reserpine--like activity of the esters of 3, 4, 5-trimethoxybenzoic acid was discussed in some detail. The authors noted that the activity of the 3-diethylaminopropyl ester of 3, 4, 5-trimethoxybenzoic acid bears some resemblance to that of the alkaloid reserpine. They therefore synthesised the esters of this acid with amino-alcohols in which the tertiary atom is separated by 2, 3, or 4 carbon atoms from the oxygen atom. Using the normal method for the preparation of amino-esters, *viz.* the reaction of trimethoxybenzoyl chloride with various amino-alcohols, they obtained 11 esters, which were simple reserpine analogues. They were all assayed for hypotensive activity.



(CV) R = CH_3; (CVI) R = C_2H_5 (CXI) R = H; (CXII) R = CH_3



(CVII) R = CH_3; (CVIII) R = C_2H_5 (CXIII) R = H; (CXIV) R = CH_3



(CIX)

(CX)

The piperidine ring in these compounds may be considered as ring C of the reserpine molecule. In many cases the distance between the nitrogen and oxygen atoms is shorter than in reserpine, *viz.* two carbon atoms instead of three. The authors point out, however, that the *cis*-condensation of rings D and E in reserpine is more important for the linear distance between tertiary nitrogen and oxygen and shortens it.

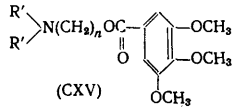
As a result of the pharmacological investigations, the active compounds were found to be the dialkylaminopropyl and dialkylaminoisopropyl esters of 3, 4, 5-trimethoxybenzoic acid (CV–CVIII).

The most active preparations contain a normal propyl radical. Diethylamino derivatives act longer and more deeply than their dimethyl analogues; the most active

preparation was the diethylaminopropyl ester (CVI). The increased length and branching of the chain between N and O atoms, as well as the increased size of the substituent bound to tertiary nitrogen, result in a shortening of the time of action and an increase of toxicity. All the enumerated compounds have a sedative effect.

On the basis of their results the authors concluded that none of these esters approaches reserpine in hypotensive activity or length of action. The finding that the diethylaminopropyl ester had one-third of the reserpine activity the authors regard with some doubt.

Solov'ev, Arendaruk, and Sklodinov[76] prepared a series of esters of trimethoxybenzoic acid (CXV):

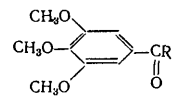


(CXV)

R'R"N	n	R'R"N	n
$(CH_3)_2N$	2	$(C_2H_5)_2N$	3
$(C_2H_5)_2N$	2	$(C_2H_5)_2N$	4
$C_5H_{10}N$	2	$C_5H_{10}N$	4
$O[(CH_2)_2]_2N$	2	$(CH_2)_6N$	4
$(CH_2)_6N$	2	$O[(CH_2)_2]_2N$	4

including the diethylaminopropyl ester. On pharmacological investigation this last ester made only one-quarter of the reserpine sedative activity (it was one-third according to Miller and Weinberg). None of the amino-esters had hypotensive activity, and only a few had a sedative effect.

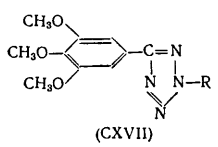
With a view to preparing reserpine-like compounds, various amides, amino-amides, and ureides of trimethoxybenzoic acid were prepared (CXVI) by the reaction of the acid chloride with various amines and substituted ureas. The authors were prompted by the data on the sedative, hypotensive, and narcotic activity of innumerable acylamides and ureides:



R = NHC_4H_9; NHC_6H_5; NHC_6H_5; $NHCH_2COOC_2H_5$; $NHCH_2CONH_2$; $NHCH_2CH_2N(C_2H_5)_2$; $NHCONHCH_3$; $NHCONHC_4H_9$; $NHCOC_6H_{11}$; $NHCONHC_6H_5$.

2-Substituted 5-(3,4,5-trimethoxyphenyl)tetrazoles (CXVII)[77], in which the nucleus is alkylated by dialkylaminoalkyl groups, have also been prepared as reserpine analogues. The authors were encouraged by the fact that disubstituted tetrazoles might be pharmacologically similar to the corresponding amino-esters.

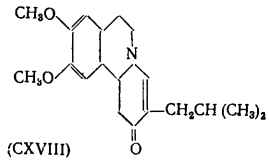
To prepare the tetrazoles, trimethoxybenzonitrile was reacted with sodium azide and acetic acid in boiling butanol. Alkylation was carried out with the chlorides derived from amino-alcohols in aqueous acetone in the presence of caustic soda:



(CXVII)

where R = H; $CH_2CH_2N(C_2H_5)_2$; $(CH_2)_3N(CH_3)_2$; $(CH_2)_3N.(C_2H_5)_2$.

Owing to the inadequacy of the data at present available on the pharmacological activity of simple reserpine analogues it cannot be said with certainty which of the types of compounds examined are likely to be the most promising as regards reserpine-like activity. It is not inconceivable that compounds most similar in activity to reserpine may be structurally very dissimilar to it. Compound (CXVIII)[78] is very interesting in this respect.



(CXVIII)

The pharmacological investigations showed that, like reserpine, various synthetic derivatives of 1,2,3,4,6,7--hexahydrobenzo-(a)-quinolizine cause the liberation of serotonine in the organism, and have a sedative effect free of any hypnotic effect, which recalls the action of the alkaloids from *Rauwolfia*.

One thing is certain, and that is that the development of the current investigations on the synthetic substitutes of reserpine[80-90] may – and indeed should – result in the discovery of compounds highly effective in their reserpine--like activity, as well as their sedative and hypotensive action.

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