175 YEARS OF ISOQUINOLINE DRUGS[1]

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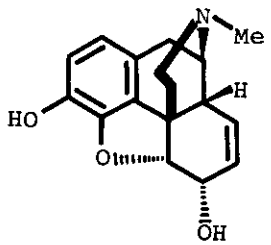
Morphine was isolated 175 years ago. At the occasion of this event it seemes appropriate to review isoquinoline drugs in general and to present some recent discoveries in this field. The following examples have been chosen for this purpose : 3-Deoxymorphines as analgesics, the bronchodilator trimetoquinol, the anthelmintic praziquantel and the discovery of "mammalian TIQ alkaloids" in the urine of Parkinsonian patients.

Morphine, one of the major opium alkaloids, is still indispensable in modern medical practice on account of its analgesic, hypnotic and sedative activity despite its habit-forming properties. The discovery of morphine by Sertürner 175 years ago, marks a milestone in natural products chemistry as well as in medicinal chemistry. The morphine molecule contains an isoquinoline unit, a finding that gave particular impetus to the search for additional natural and synthetic isoquinolines in order to explore their biological potential. Rather than review the chemistry of opium alkaloids, which is far better done by Bentley in Manske's text,[2] I have decided to discuss the development of some novel and very interesting isoquinoline compounds. However, before doing so, I feel that one should render respect to the remarkable alkaloid, called morphine, by briefly summarizing its chemical history in Table 1.

The various isoquinoline drugs presently on the market are compiled in Table 2, they are listed with their generic names. Analogs of morphine and papaverine which are also marketed are not listed. The drugs shown in the upper half of the Table 2 are CNS agents interfering in one way or another with the biochemistry mediated by brain amines. Those shown in the lower section are antiparasitic agents with an entirely different mode of action. Clearly, the isoquinoline moiety represents a valuable template which has led to the discovery of a variety of quite different drugs. It is interesting to note, that, thus far, no antibacterial or antitumor agent of proven clinical usefulness has emerged in this productive class of compounds.

Table 1



NATURAL (-)-MORPHINE

1803	Isolation of morphine by Sertürner from opium.
1925	Correct basic structure by Gulland and Robinson.
1955	Correct absolute structure by Bentley and Cardwell (1.22.1955).
1955	X-Ray of morphine.HI.$2H_2O$ by Dorothy Crowfoot Hodgkin.
1955	Absolute configuration by Jeger, Kalvoda and Buchschacher (10.12.1955).
1956	First total synthesis of natural morphine by Gates and Tschudi.

Table 2

ISOQUINOLINE DRUGS 1978

ANALGESICS	MORPHINE, CODEINE, HEROIN, LEVORPHANOL (ROCHE), ETORPHINE (RECKITT & COLMAN), PENTAZOCINE (STERLING-WINTHROP).
ANTAGONISTS	NALORPHINE (MERCK), LEVALLORPHAN (ROCHE), NALOXONE (ENDO), NALTREXONE (ENDO).
ANTITUSSIVES	CODEINE, DEXTROMETHORPHAN (ROCHE).
BRONCHODILATOR	TRIMETOQUINOL (TANABE).
SPASMOLYTIC	PAPAVERINE
TRANQUILIZER	TETRABENAZINE (ROCHE), BENZOQUINAMIDE (PFIZER).
ANTIDEPRESSANT	NOMIFENSIN (HOECHST).
HYPOTENSIVE	DEBRISOQUINE (ROCHE).
AMEBICIDE	EMETINE, DEHYDROEMETINE (ROCHE).
ANTHELMINTIC	PRAZIQUANTEL (E. MERCK & BAYER).
ANTIFUNGAL	HEDAQUINIUM CHLORIDE (ALLEN & HANBURYS)

1. 3-DEOXYMORPHINES : A NOVEL CLASS OF POTENT ANALGESICS.

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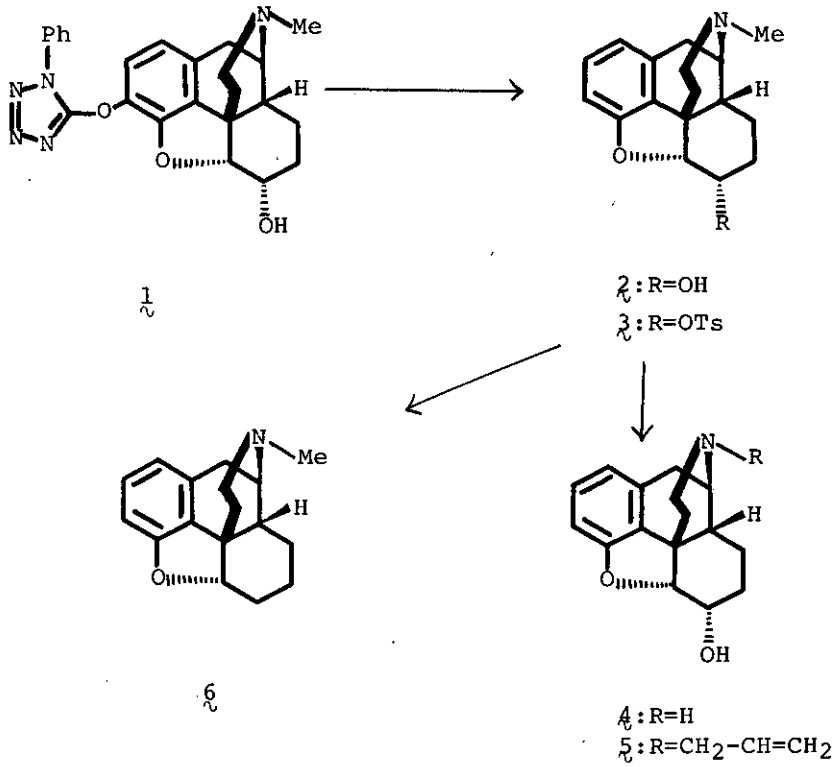
Few natural products have been studied as extensively as morphine. Almost every conceivable chemical manipulation has been carried out, often affording novel analgesics, such as the morphinans and the benzomorphans.[3] Taking all available data on opioids together, one can hardly claim to have uncovered how morphine works on the molecular level. The recent discovery of specific opiate receptors in the brain of animals and humans and their interaction with narcotic analgesics will undoubtedly provide valuable information in this respect.

From a structure-activity point of view it is interesting to note that the phenolic group in the 3-position of the morphine molecule has been considered essential for optimal analgesic activity[3,4,5]. This belief was possibly influenced by the finding that N-methylmorphinan is considerably less active than its 3-hydroxy derivative.[6] The facile removal of phenolic groups in a variety of natural products by catalytic reduction of their respective tetrazolyl ether derivatives,[7] prompted the preparation of 3-deoxydihydromorphine (2), a valuable compound for testing the aforementioned hypothesis. This compound was also obtained by Hungarian scientists through catalytic reduction of the 3-tetrazolyl ether of morphine.[8] Since compound 2 showed considerable agonist activity in our screening test we decided to study the group of 3-deoxymorphines and congeners in more detail. The

Chart 1

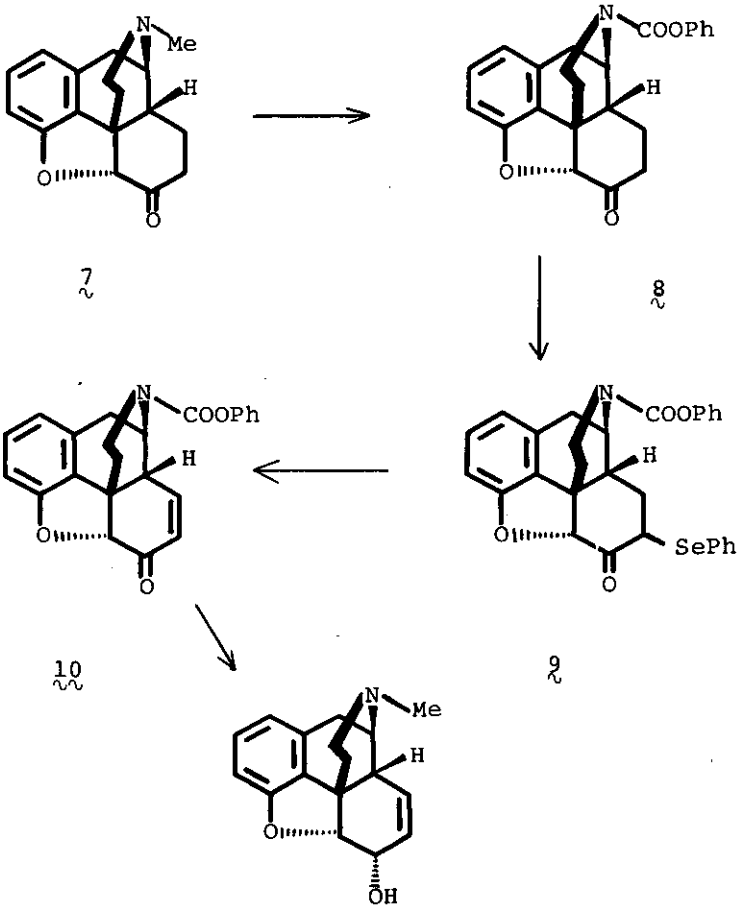


following is a summary of the work which has been accomplished, so far, in our laboratory.

The synthesis shown in Chart 1 illustrates the preparation of 3-deoxydihydromorphine (2), its N-desmethyl derivative 4 and the N-allyl compound 5. Elimination of the alcoholic hydroxy group in 2 via the tosylate 3 led to the preparation of 3,6-dideoxy-dihydromorphine (6), representing the basic pentacyclic ring system of morphine alkaloids. The synthesis of 3-deoxymorphine

Chart 2

SYNTHESIS OF 3-DEOXYMORPHINE



(11) itself, which involved a number of steps, including the important saturated ketone 7, is shown in Chart 2.

The biological evaluation of these deoxymorphine derivatives

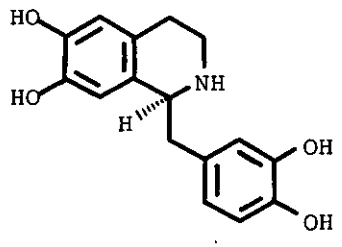
by classical analgesic screening methods involving mice as test animals revealed that compounds 2,6,7 and 11 are narcotic agonists with a potency similar to that of their natural 3-hydroxy analogs. The N-allyl derivative 5 is, as expected, a potent narcotic antagonist. Details on the pharmacological evaluation of these highly interesting compounds will be reported upon completion of the study.[9]

2. TRIMETOQUINOL : A POTENT ORALLY ACTIVE BRONCHODILATOR.

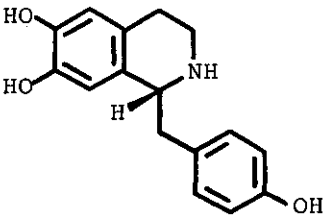
Tanabe Seiyaku Co., Ltd., Toda, Saitama, Japan.

Blood pressure lowering effects of isoquinolines containing catechol functions have been observed many years ago (Chart 3).[10] This prompted chemists from the Tanabe Company to look for improved compounds in the series of 1-benzyl substituted 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines.[11] These studies, carried out in

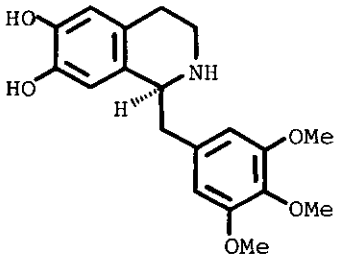
Chart 3



S-(-)-THP (Tetrahydropapaveroline)



Higenamine
(+)-Demethylcoclaurine



Trimetoquinol

Chart 4

SYNTHESIS OF TRIMETOQUINOL

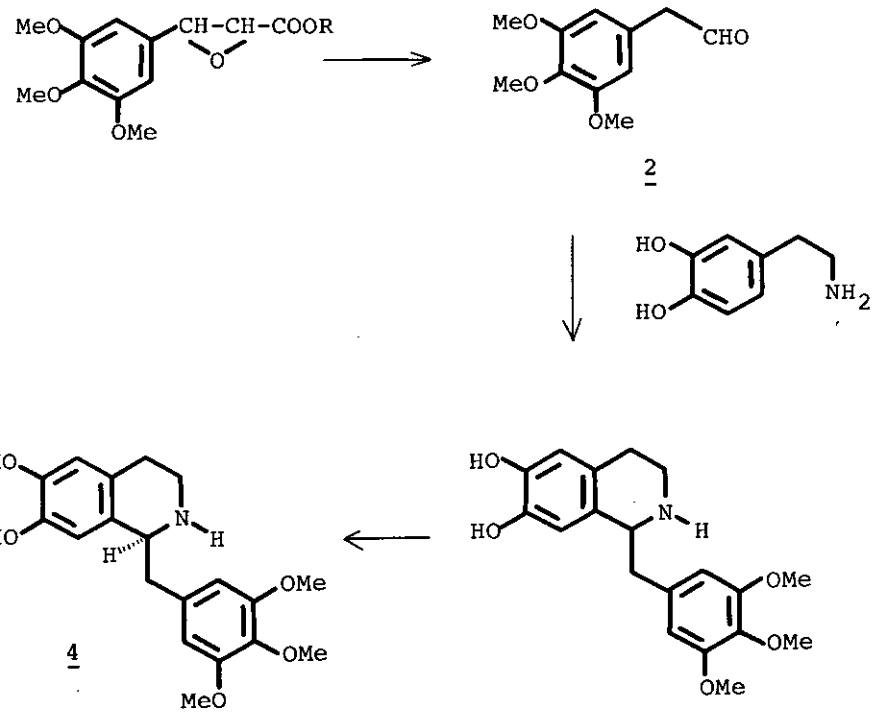
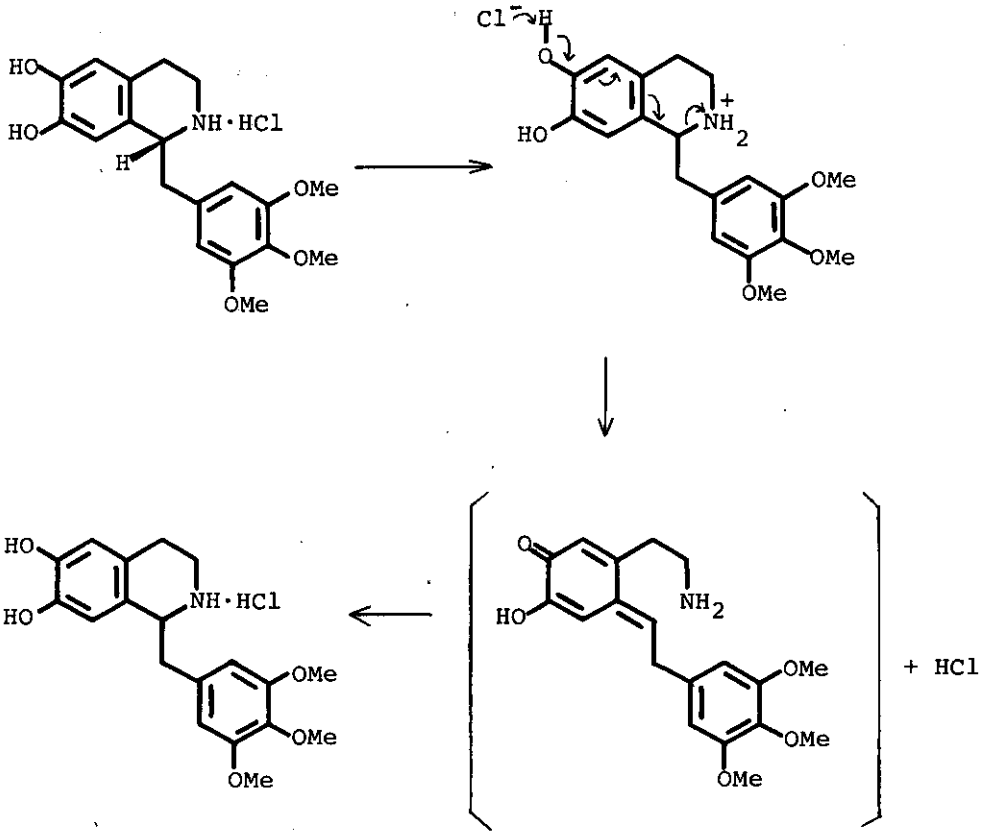


Chart 5

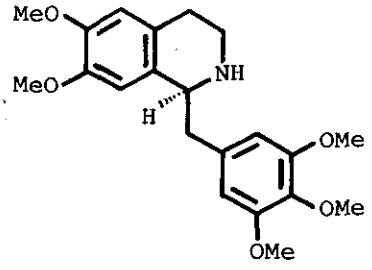
RACEMIZATION OF TRIMETOQUINOL ENANTIOMER



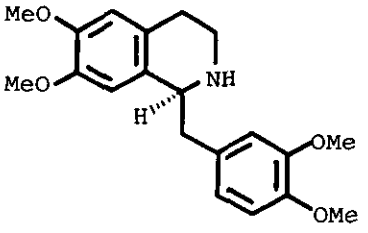
the sixties, resulted in the discovery of trimetoquinol which turned out to be a potent bronchodilator, acting on smooth muscles and comparing favorably to isoproterenol.[12] Trimetoquinol has practically no effect on the CNS system and acts like a clean β-sympathomimetic agent. The synthesis of trimetoquinol which

Chart 6

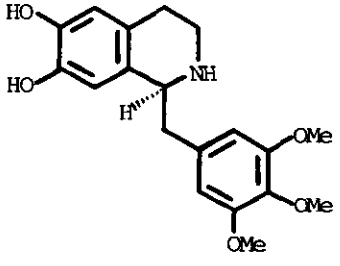
ABSOLUTE CONFIGURATION OF S-(-)-TRIMETOQUINOL



S-(-)-Trimetoquinol-O-dimethyl ether



S-(-)-Norlaudanosine



Trimetoquinol has S-(-)-Configuration.

involves classic manipulations for the preparation of many isoquinoline drugs is outlined in Chart 4.

The Pictet-Spengler synthesis is well suited for the preparation of TIQ's with catechol functions. In this case, 3,4,5-tirmethoxy-phenylacetaldehyde (2) is prepared in situ from the glycidic

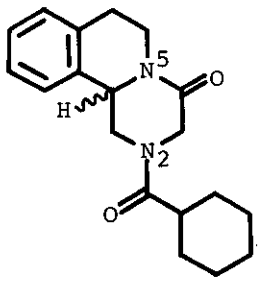
ester (Darzens synthesis) and reacted immediately, as the sodium salt of the free acid, with dopamine (DA) under acidic conditions. Since the biological activity resides in the (-)-isomer of compound 4 (trimetoquinol) optical resolution had to be carried out.[13] The unwanted (+)-isomer of 4 can be racemized by heating its hydrochloride. This process probably involves the formation of a quinone methide intermediate, as shown in Chart 5.

The absolute configuration of trimetoquinol, proved to belong to the S-(-)-series, was established by comparing its optical behavior with that of S-(-)-norlaudanosine of known absolute configuration (Chart 6).[14]

3. PRAZIQUANTEL : A BROAD SPECTRUM ANTHELMINTIC WITH EXCELENT ACTIVITY AGAINST SCHISTOSOMES AND CESTODES.

E. Merck, Darmstadt and Bayer AG., Ludwigshafen, Federal Republic of Germany.

PRAZIQUANTEL



(±)-2-Cyclohexylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinolin-4-one

It is estimated that some 200 million people are infected with Schistosomes and about 100 million with intestinal tapeworms (Cestodes). The economic loss of animals due to worm infections is considerable since none of the presently available drugs are suited for mass treatment.

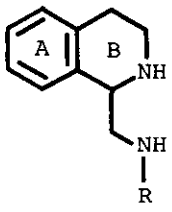
Praziquantel, an isoquinoline compound of unique structure, synthesized by chemists of the E. Merck Company, was found in the Laboratories of Bayer AG. to have outstanding properties[15]. Praziquantel was selected from hundreds of analogs because of its excellent activity and tolerance in experimental animals infected with Schistosomae and a variety of tapeworms. It is orally effective in a single dose treatment against most intestinal tapeworms in man and against a great variety of Cestodes in animals, including Echinococcus (recommended dose in animals 5 mg/kg).[16,17] Praziquantel exhibits remarkable activity against the three important Schistosomae species parasitic to man.[17] The drug is well tolerated, rapidly absorbed, intensively metabolized, and quickly excreted. No teratogenic or mutagenic activity has been observed. Praziquantel thus seems to meet most of the requirements of an ideal antiparasitic agent for use in human and veterinary medicine. The chemistry of this exceptional compound which is now being evaluated world-wide seems worth being summarized.

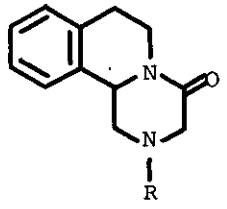
The easy preparation of the benzamide 1 from isoquinoline, benzoyl chloride and cyanide (Reissert compound), followed by high pressure reduction at elevated temperatures, has been reported.[18] The conversion of 1 into praziquantel (4) via the amino acid 2 and the important tricyclic oxo-hydropyrazino-isoquinoline 3,

shown in Chart 7, is of practical importance.

Chart 7

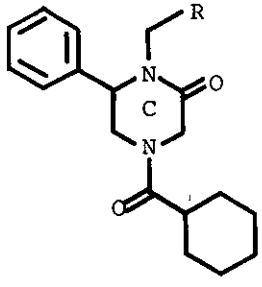
KEY INTERMEDIATES IN VARIOUS SYNTHESES OF PRAZIQUANTEL

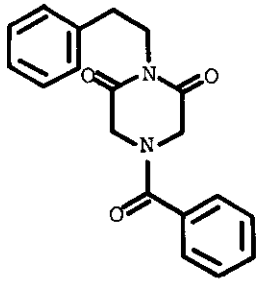




1: R=COPh
2: R=CH_2COOH

3: R=H
(±) 4: R =CO



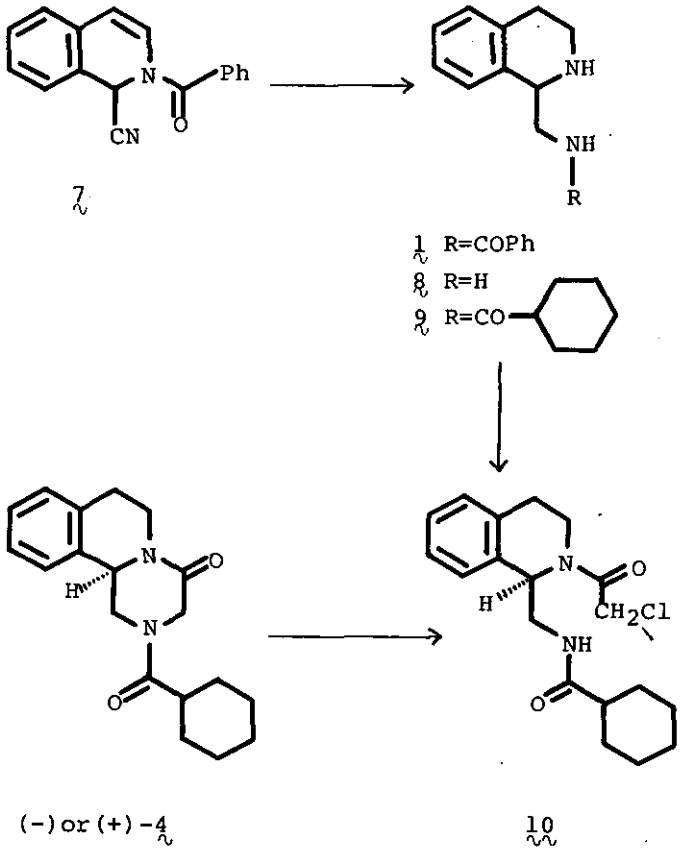


5: R=COOH

6

Chart 8

SYNTHES IS FROM REISSERT COMPOUND



7

1 R=COPh
8 R=H
9 R=CO

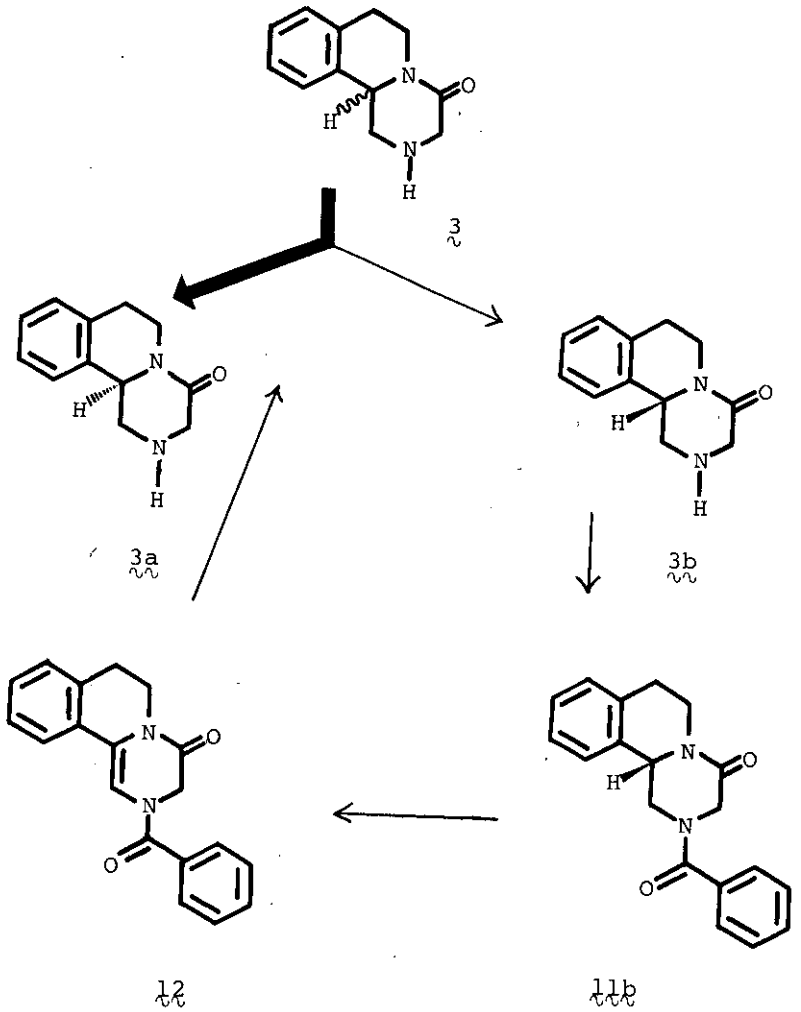
(-)or(+)-4

10

The syntheses of praziquantel (4) from 3-hydroxy-5-phenyl-pyrazine via the diamide 5 or from the dioxopiperazine 6, involving a Bischler-Napieralski cyclization, are of scientific interest. All of these sequences, published only in part, are covered by pending patent applications by the E. Merck Company. This also applies to the synthesis of praziquantel shown in Chart 8.

Chart 9

OPTICAL RESOLUTION AND RACEMIZATION OF PRAZIQUANTEL INTERMEDIATES



Optical resolution in this series is important since it has been shown that in praziquantel or its corresponding N-benzoyl analog the antiparasitic acitvity is almost exclusively concentrated in the (-)-isomers of yet unknown absolute configurations.[20]

The N-acylamino substituted TIQ's 1 and 9 can be resolved into their optical isomers prior to acylation with chloroacetyl chloride and cyclized to optically active praziquantel and analogs by treatment with strong bases.[19] Another scheme for accomplishing this objective is shown in Chart 9.

This synthesis involves as the most important step, the optical resolution of the tricyclic amine 3 together with a procedure for recycling the unwanted (+)-isomer into a compound used in the technical process. This could be achieved by acylation with benzoyl chloride, dehydrogenation with sulfur, and catalytic reduciton of the intermediate dehydro derivative 12.[21]

4. "MAMMALIAN TIQ-ALKALOIDS"

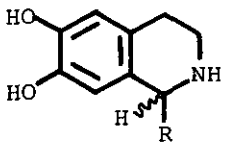
The medical use of L-dopa in Parkinson's disease resulted in the isolation of several 1,2,3,4-tetrahydroisoquinolines from urinary excretion products containing catechol functions. This group of compounds, including norsalsolinol (1), salsolinol (2, SAL) and tetrahydropapaveroline (3, THP, norlaudanosoline) have been named by several investigators "Mammalian TIQ Alkaloids". These isoquinolines have not been isolated from plant materials as yet but THP is an important intermediate in the biosynthesis of such well known "Plant TIQ Alkaloids" as laudanine, laudanosine

and papaverine[22]. The discovery of "Mammalian TIQ Alkaloids" gave immediate rise to speculations that their in vivo formation might provide an explanation for a variety of mental disorders observed in Parkinsonism, Alcoholism and perhaps also in Schizophrenia.[23] Such hypotheses received further stimuli by recent reports that L-dopa and THP cause rats to consume ethanol in preference to water.[24] Space is too small to summarize the biochemical and therapeutic implications resulting from the discovery of "Mammalian TIQ Alkaloids", discussed in detail by Cohen,[25] Davis,[26] Myers,[27] Sandler[28] and many others. The few TIQ's characterized unequivocally are shown in Chart 10.

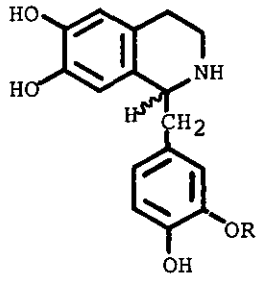
SAL (2) is proposed to be the condensation product of dopamine (DA) with acetaldehyde, whereas THP (3) is assumed to originate from DA and dopa aldehyde. SAL has been isolated in racemic form[29] and the question of whether its formation takes palce in the brain or in other tissues, perhaps even in the intestines or the urinary bladder, remains unanswered to data. It is unlikely that the major effects of acute ethanol intoxication can be attributed directly to the formation of sufficiently high concentrations of TIQ's. Experiments carried out 10 years ago by Robbins[30] do not exclude the formation of trace amount of TIQ's, especially at sites of localized high concentrations of the reactants. The heroic conditions applied by some investigators to demonstrate any in vivo accumulation of TIQ's in rat brain were often carried out under non-physiological conditions and these results are, therefore, not satisfactory. Recently, the TIQ 1-carboxylic acids 5 and 6 were detected in the urine of Parkinsonian

Chart 10

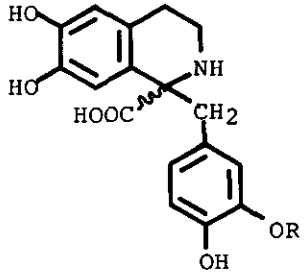
"MAMMALIAN ISOQUINOLINE ALKALOIDS" FROM PARKINSONIAN PATIENTS



1: R=H
2: R=Me (±)



3: R=H, (±)-THP
4: R=Me, (±)-THP-3'-O-methyl ether



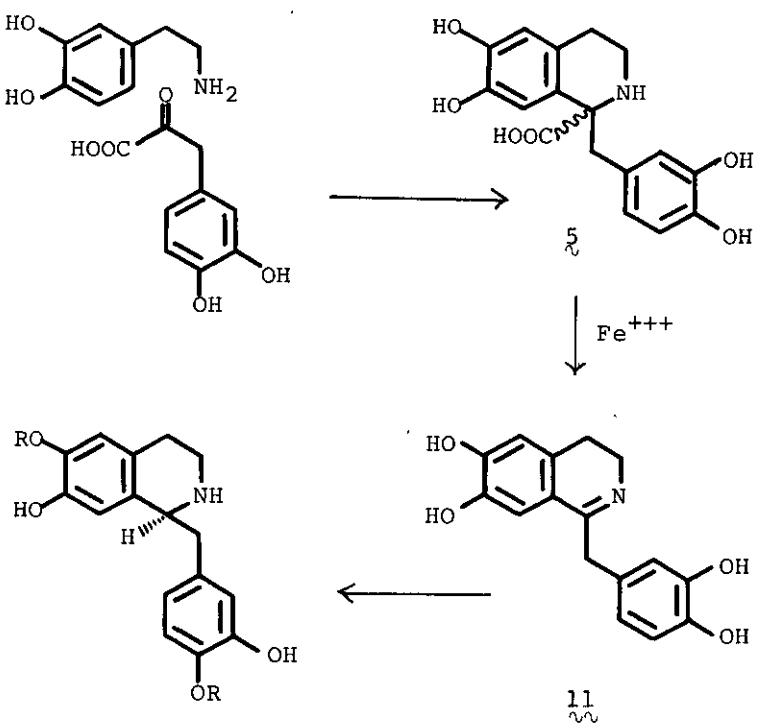
5: R=H, NLCA
6: R=Me, MNLCA

patients under L-dopa therapy.[31] The methoxy substituted carboxylic acid 6 is the major product and is obviously the result of the reaction of DA with 3-methoxyphenylpyruvic acid. The latter originates from the 3-monomethyl ether of L-dopa, a major metabolite of L-dopa in man.[32] The formation of TIQ 1-carboxylic acids under physiological conditions has been suggested by Hahn 50 years ago.[33] Some of these carboxylic acid derivatives occur in plants in O-

methylated form and are important precursors in the biosynthesis of isoquinoline Cactus alkaloids[34] and 1-benzyl-isoquinoline alkaloids.[35,36] The formation of THP from DA and the keto acid derived from L-dopa, as postulated by Hahn, is shown in Chart 11.

Chart 11

PLANT BIOSYNTHESIS OF THP RELATED TETRAHYDROISOQUINOLINES



3a:R=H, S-(-)-THP

7a:R=Me, S-(-)-Norreticuline

The decarboxylation of TIQ 1-carboxylic acids to afford 3,4-dihydroisoquinolines has recently been accomplished by electrochemical oxidation[37] and by oxidative chemical decarboxylation.[38] The 3,4-dihydroisoquinolines and their quaternary equivalents[39] are established intermediates in the biosynthesis of plant alkaloids; chirality is developed through asymmetric reduction at this stage. The unlikely possibility that SAL or THP originate in vivo by the TIQ 1-carboxylic acid pathway has, however, to be considered and would constitute an interesting parallel in the synthesis of TIQ's from plant and mammalian origin.

The in vitro formation of nor-reticuline (7) and possibly isosalsoline (8) from THP and SAL, respectively, with catechol O-methyltransferases (COMT) is illustrated in Chart 12 and may constitute another bridge between the TIQ's of plant, mammalian and human origin.[40]

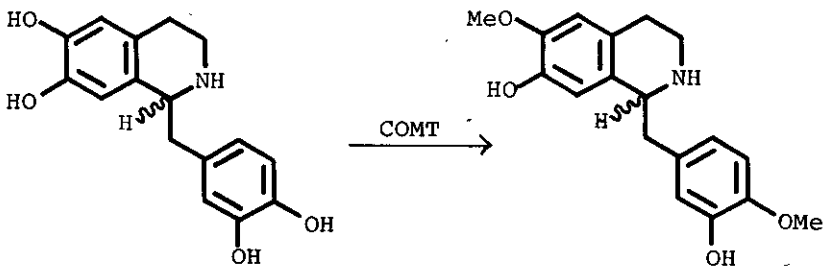
A third connection between the TIQ's of different origin is supported by the isolation of the two isomeric catechol-substituted berbines 9 and 10, detected in the urine of Parkinsonian patients as shown in Chart 13.[26] Their formation implies that THP may be the intermediary metabolite. THP can, however, undergo further biotransformations, before or after formation of the berbine bridge, affording various O-methylated and O,O-methylenated TIQ derivatives. The report of Kametani that racemic reticuline is converted into a variety of rather complex isoquinolines by rat liver homogenates stimulated with oxygen and cofactors, is well in line with such assumptions.[41] Since the two optical isomers of THP show considerable differences in their biological activities, marking the S-

(-)-enantiomer as the active isomer,[42,43] such investigations should be repeated with optically active materials.

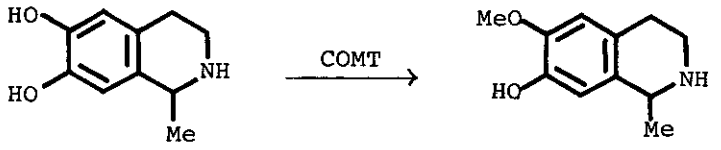
In summary, the following conclusions regarding these interesting "Mammalian TIQ Alkaloids" seem appropriate: they have, thus far, not been detected in normal individuals and their formation most likely occurs during L-dopa therapy. It is interesting to note that mammals and humans, as well as plants, seem to biotransform L-dopa, in principle, in a very similar way, with the notable difference, that "Mammalian Alkaloids" are often excreted as

Chart 12

IN VITRO O-METHYLATION OF THP AND SAL WITH "COMT"



3 7: (±)-Norreticuline

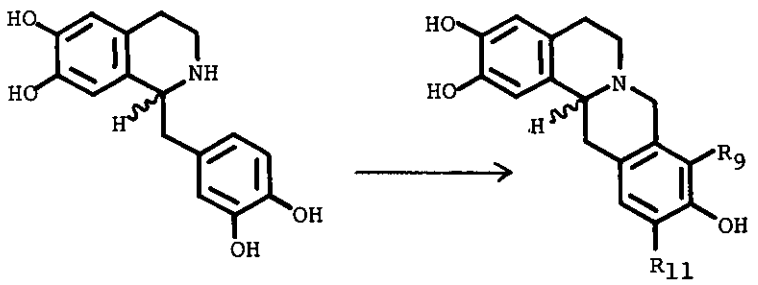


2 8: (±)-Isosalsoline

catechols or catechol conjugates, whereas "Plant TIQ's" have mostly been isolated in form of O-methylated congeners. It would be interesting to study the in vivo biotransformation of other biologically important amino acids, given in excessive amounts, to explore whether they would be transformed along similar pathways. It is very probable that through such investigations the groups of the so-called "Mammalian Alkaloids" would grow considerably.

Chart 13

CYCLIZATION OF THP TO BERBINES IN PARKINSONIAN PATIENTS



3

9: R_9=H, R_{11}=OH

10: R_9=OH, R_{11}=H

Acknowledgement

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