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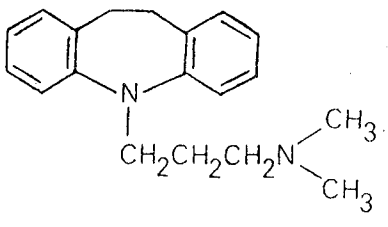
Chemistry of Sintamil—a new dibenzoxazepine derivative with antidepressant activity

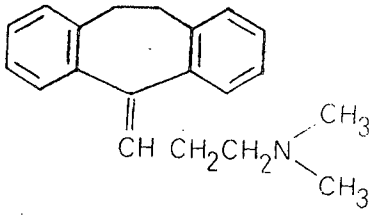
by K. NAGARAJAN

The astute observations of KUHN in 1957 during clinical trials of some dibenzazepine derivatives led to the discovery of the antidepressant activity of imipramine (I) and to a spurt in the synthesis and evaluation of several tricyclic systems (II-XIII) (Chart 1) for this indication (KAISER and ZIRKLE, 1970; PROTIVA, 1970). As one typical example of the outcome of this work, I should

Chart 1



I



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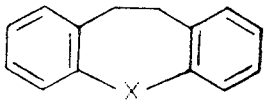
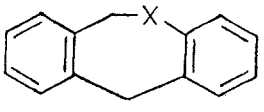


III X=O

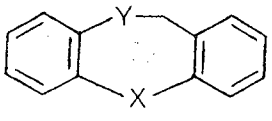
IV X=S



V X=O

VI X=S

VII X=N



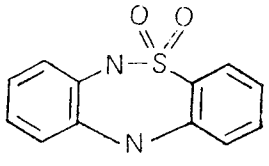
VIII X=O Y=N

IX X=S Y=N

X X=Y=N

XI X=N Y=O

XII X=N Y=S

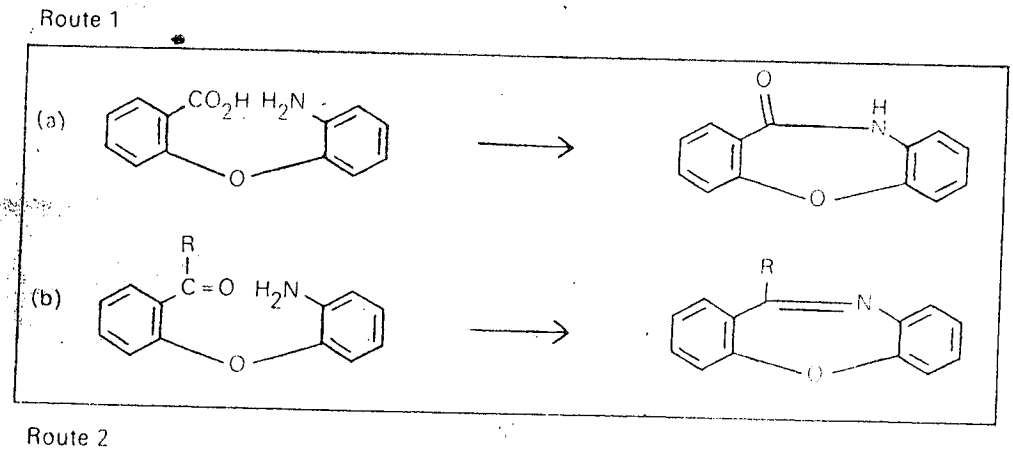


XIII

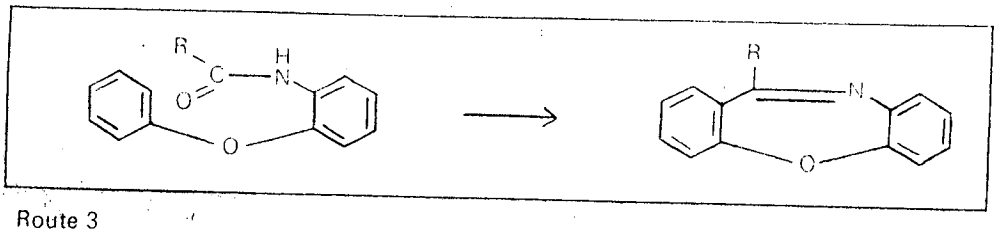
like to mention amitriptyline (II). It has a dibenzocycloheptane nucleus with the central ring devoid of a heteroatom and was introduced as an antidepressant in 1961 (HOFFSOMMER et al, 1962). In 1963, when we started working in this field, we planned to investigate tricyclic systems with two heteroatoms in the central ring and noted that the potentiality of the dibenz [b, f] [1, 4] oxazepine ring (VIII) had not been exploited[1]. Further impetus was given by our discovery at the Research Centre of a new and facile synthesis of system VIII. Earlier syntheses of VIII were through one of the following three routes (Chart 2):

Chart 2.

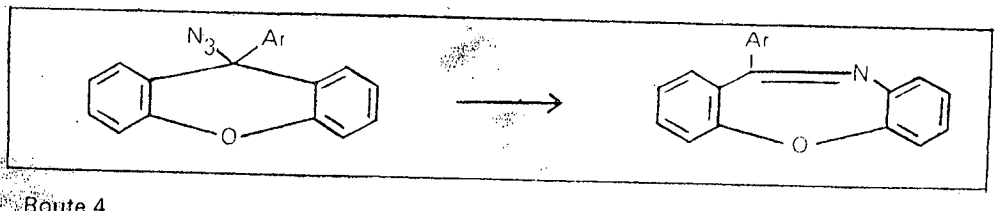
Route 1



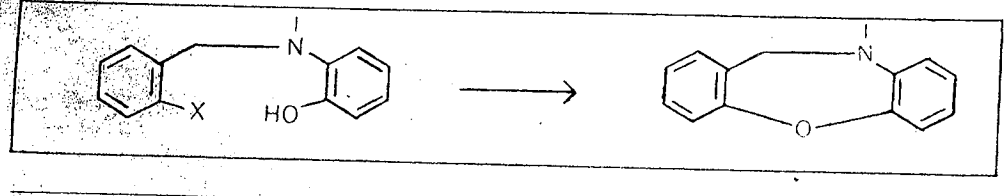
Route 2



Route 3



Route 4



[1] Chemical Abstracts records 8 publications on the chemistry of this ring system prior to 1963; subsequently there are 80 references to its chemistry and biology in the period 1963-72.

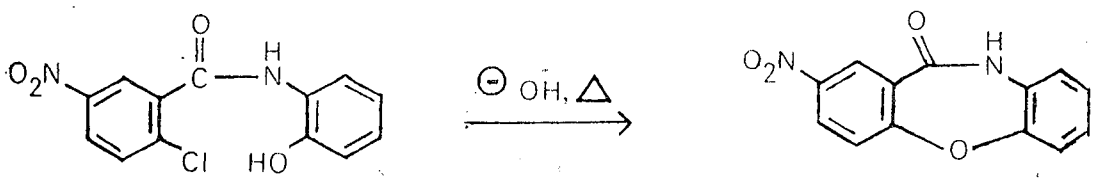
(1) Intramolecular lactamisation of a 2-amino-2′-carboxy-diphenyl ether (MACLAY and HAMILTON, 1932; BREWSTER and STRAIN, 1934; TOMITA and KUMAOKA, 1955; ALLEN and MOIR, 1959) or imine formation from a 2-amino-2′-acyl-diphenyl ether (BRODRIK et al, 1953).

(2) Acid-induced cyclization of a 2-acylamino-diphenyl ether[2] (BRODRIK et al, 1953; HIGGINBOTTOM and SUSCHITZKY, 1962).

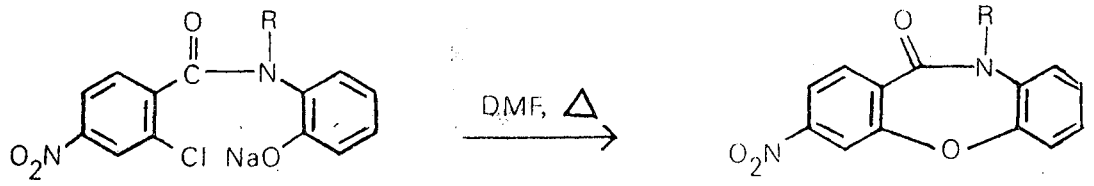
(3) Thermal rearrangement of 9-azido-9-phenyl-xanthene[3] (GALT et al, 1958; COOMBS, 1958).

There exists another possibility—route 4 in which the N-C bond is formed first and the oxygen bridge introduced later, thus reversing the reaction sequence employed in schemes (1) and (2). Our synthesis (Chart 3) which is illustrative of this hitherto unexplored possibility, consists of forming amide XIV from o-aminophenol and 2-chloro-5-nitrobenzoic acid, both commercially readily available. Heating amide XIV with dilute aqueous alkali brought about the desired ring closure to XV by intramolecular nucleophilic displacement of the doubly activated chlorine, by the phenoxide ion. Yields of more than 90% were realized in both steps. Other dibenzoxazepines could be prepared similarly

Chart 3



XIV XV



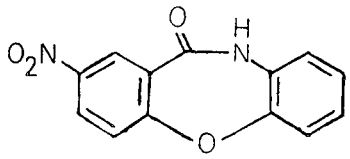
XVI XVII

[2] Cyclization of o-isocyanatodiphenyl ethers reported by SCHMUTZ et al, 1965, belongs to this category.

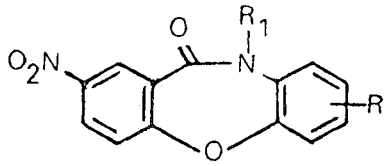
[3] Recent examples of this type are Beckmann rearrangements of xanthone oximes [TROSHCHENKO and LOBANOVA, 1967; NAGARAJAN et al, 1968; Amer. Cyanamide, U.S. 3,412,193 (Chem. Abstracts, 70, P 47509 h (1969)].

by using o-aminophenols carrying substituents like acetyl, chloro, methoxy, methyl and nitro groups. The principle could be extended to less activated o-chlorobenzoyl derivatives of o-aminophenol by a simple modification of the cyclization step, for example XVI→XVII (R = H) (NAGARAJAN et al, 1958).

Chart 4



XV



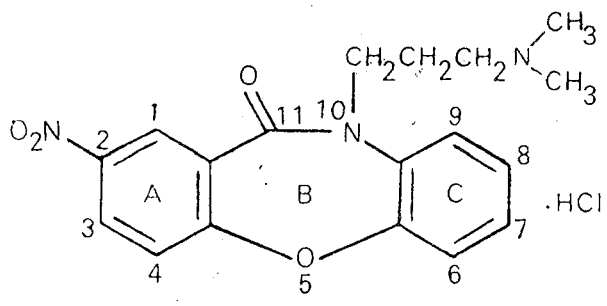
XIX

R = H, $R_1 = CH_3$,

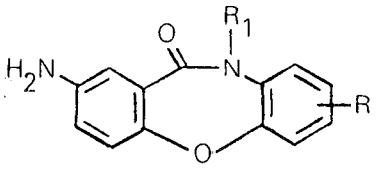
$CH_2C{\equiv}CH$, $(CH_2)_nN$

R = CH_3, Cl, OCH_3;

$R_1 = (CH_2)_3N(CH_3)_2$

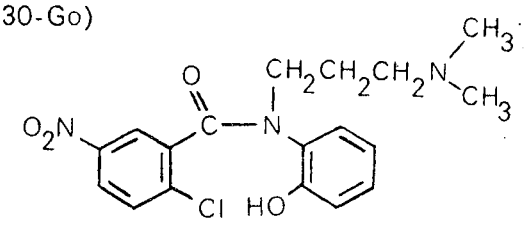


XX Sintamil. (CIBA 2330-Go)



XVIII R = H, Cl, CH_3, OCH_3;

R_1 = H



XXI

XXII R = H, OCH_3;

$R_1 = CH_3, (CH_2)_3N(CH_3)_2$

The nitrolactam XV and analogues carrying other substituents on ring C such as chloro, methyl, methoxyl, etc. were reduced to amines of the type XVIII[4]. Compound XV formed a water-soluble sodium salt which could be alkylated in aqueous alkaline medium with alkyl and aminoalkyl halides (used as their hydrochloride salts) to give in high yields derivatives of general structure XIX[5]. Sintamil® (XX) { CIBA 2330-Go; 10-[3-(dimethylamino)propyl]-2-nitrodibenz [b, f] [1, 4] oxazepin-11(10H)-one hydrochloride } was prepared thus by treatment of XV with dimethylaminopropyl chloride in aqueous alkaline solution and subsequent transformation of the free base into the hydrochloride. Base-induced ring closure of N-(2-chloro-5-nitrobenzoyl)-N-(γ-dimethylamino-propyl)-o-aminophenol (XXI) also afforded Sintamil thus establishing that the alkylation of XV took place on nitrogen and not on oxygen. The alkylated nitro derivatives XIX were further reduced to XXII (Chart 4).

In other experiments, aminoalkylated derivatives of type XIX were prepared wherein either the nitro group had been moved from position 2 to 3, 7 or 8 or additionally one or more nitro groups were introduced in various other positions.

Several other types of dibenzoxazepine derivatives were also synthesized as follows for biological evaluation (Chart 5). Alkali treatment of N-(2-chloro-5-nitrobenzoyl)-8-hydroxy-1, 2, 3, 4 tetrahydroquinoline afforded the tetracyclic system XXIII. Conversion of lactam XV to the iminochloride, followed by reaction with N-methylpiperazine gave XXIV[6]. Aluminium chloride-induced cyclization of 2-isothiocyanato-4'-chlorodiphenyl ether served as a convenient route for the dibenzoxazepinethione XXV, which was transformed into XXVI[7]. Reaction of the iminochloride from XV with sodium azide gave tetrazole XXVII; while with 3-aminopropanol, a product was obtained which was converted to pyrimidine XXIX. The 2-chlorobenzoxazepinone analogue of XXV was transformed similarly to XXVIII. Compound XXX wherein the central ring in Sintamil had been cleaved with sodium methoxide was also prepared for biological evaluation.

In all, one hundred and twentyfive compounds belonging to the various types mentioned above were examined for their effects on the central nervous system. In particular were studied: reversal of reserpine-induced hypothermia (test 1), potentiation of DOPA-induced response (test 2), inhibition of acetic acid-induced writhing (test 3), antagonism to mescaline-induced stereotypy (test 4)

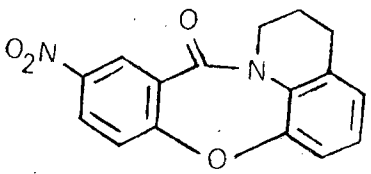
[4] These compounds have been since then claimed in patents; Karl Thomae, S. Afr. 68,04,436 [Chem. Abstracts, **71**, P 50016 w (1969)]; Boehringer, U.S. 3,546,214 [Chem. Abstracts, **74**, P 141907 r (1971)].

[5] Alkylations of tricyclic lactams are generally carried out under anhydrous conditions using dimethyl formamide or dioxane as solvent, sodium hydride or amide and the aminoalkyl chloride free base; for example, Wander, Neth., 302, 836 [Chem. Abstracts, **64**, P 9750 g (1966)].

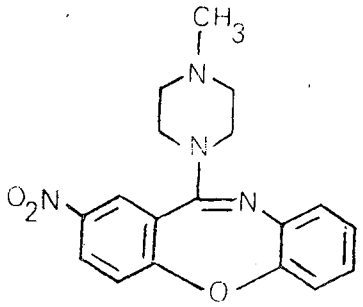
[6] These compounds have been since then claimed in patents: Amer. Cyanamide, Fr. 1,508,536 [Chem. Abstracts, **70**, P 57923 c (1969)]; Wander, S. Afr. 68,01370 [Chem. Abstracts, **70**, P 96835 v (1969)].

[7] A patent covering these compounds has been reported recently; Yoshitomi, Jap. 71,43786 [Chem. Abstracts, **76**, 127030 j (1972)].

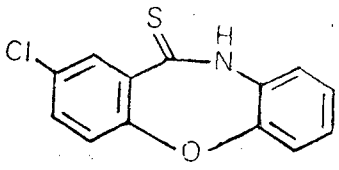
Chart 5



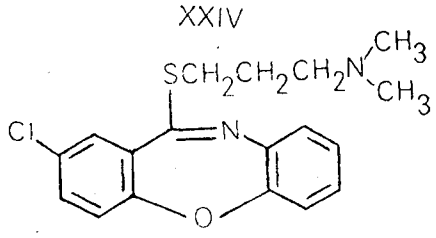
XXIII



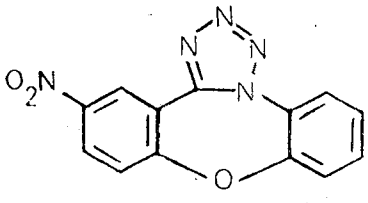
XXIV



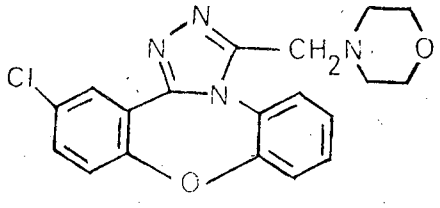
XXV



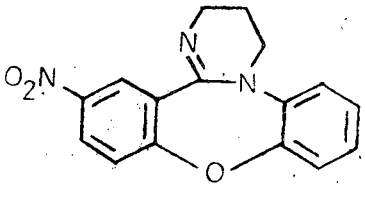
XXVI



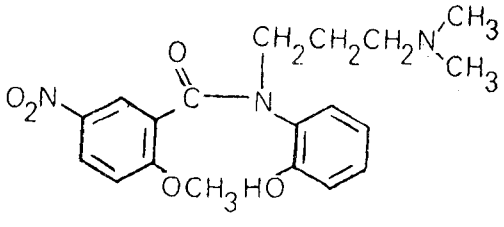
XXVII



XXVIII



XXIX



XXX

and decrease in spontaneous motor activity (test 5) (DAVID and GREWAL). All the tests were carried out on mice. Results of selected examples are presented in Tables I and II.

It is seen from Table I that nitrolactam XV has moderate activity in the 'DOPA' test and marginal or negligible activity in the other tests whereas the corresponding amine XVIII has significant sedative activity[4]. Introducing a non-basic (propargyl) side chain on the amide nitrogen in lactam XV (XIX: R = H;

R_1 = propargyl) did not result in an active compound. XXIII which may be considered to have arisen from XV by linking a N-propyl group on to ring C had moderate 'DOPA' activity but was not potent in other tests. In contrast, Sintamil (XX) resulting from tagging a γ-dimethylaminopropyl side chain to the amide nitrogen of lactam XV, strongly reversed reserpine-induced hypothermia and markedly potentiated the 'DOPA' response in mice. It had marked antimescaline activity and also sedative and antinociceptive properties. Reduction of the nitro group in Sintamil led to XXII [R = H; R_1 = $(CH_2)_3$ NMe_2], which had reduced activity in tests 1, 2, 3 and 5 but still had good antimescaline activity. The piperazinodibenzoxazepine XXIV was negligibly active in tests 1 and 2, but had potent central depressant properties[6-8], while the dimethylaminopropylmercapto derivative XXVI was moderately active in tests 1 and 3-5[7]. The novel tetracyclic compounds XXVII, XXVIII and XXIX obtained by annealing a fourth ring to ring B of the dibenzoxazepine nucleus had only weak to moderate activities in the tests. Compound XXX wherein the central ring of Sintamil had been cleaved, had a low degree of activity in all the tests, thus highlighting the role of the tricyclic template for biological activity.

Compound	Reversal of reserpine induced hypothermia at 25 mg/kg p.o.	Potentiation of DOPA response at 25 mg/kg p.o.	Inhibition of AcOH-induced writhing at 100 mg/kg p.o.	Antagonism to mescaline-induced stereotypy	Decrease in spontaneous motor activity at 200 mg/ kg p.o.
XV	±	−	+ ±	±	±
XVIII (R=R_1=H)	±	−	+ ±	−	+ + + (at 50 mg/kg p.o.)
XIX (R=H; R_1=propargyl)	+	−	+ ±	−	
XXIII	±	−	+ ±	±	±
Sintamil (XX)	+ + +	+	+ + + ±	+	+
XXII [R=H; R_1=$(CH_2)_3NMe_2$]	−	−	+ + +	−	−
XXIV	± (at 10 mg/kg p.o.)	± (at 5 mg/kg p.o.)	+ (at 5 mg/kg p.o.)	+ [b]	+ (at 5 mg/kg p.o.)
XXVI	+ ±	−	+	−	+ [d] (at 50 mg/kg p.o.)
XXVII	+ + ±	+	+	−	±
XXVIII	+	+	+ +	±	+
XXIX	±	−	+ ±	±	[e]
XXX	−	±	+	+	−

Table I. Results of various pharmacological tests

[a] Molecular models show that the ring planes of the tricyclic nucleus in Sintamil (XX) are relatively more angled and twisted than those in XXIV. That the former has more antidepressant properties and the latter is more central depressant (typical of neuroleptics) is consistent with correlations in the literature between molecular geometry and biological properties of tricyclics (WILHELM and KUHN, 1970; KAISER and ZIRKLE, 1970).

From a study of Table I, it is thus seen that marked activity in test systems used for the characterization of antidepressants is elicited from nitrolactam XV when an aminoalkyl side chain is introduced on the nitrogen atom. Table II reveals the role of the aminoalkyl side chain, the effect of additional nuclear substituents and the consequence of shifting the nitro group from position 2 to other aromatic positions.

Compound	Reversal of reserpine induced hypothermia at 25 mg/kg p.o.	Potentiation of DOPA response at 25 mg/kg p.o.	Inhibition of AcOH-induced writhing at 100 mg/kg p.o.	Antagonism to mescaline-induced stereotypy	Decrease in spontaneous motor activity at 200 mg/kg p.o.
Sintamil (XX)					
N-oxide of XX					
Desmethyl-XX [XIX: R = H; $R_1 = (CH_2)_3NHMe$]					
XIX (R = H; R_1 = pyrrolidinopropyl)					
XIX [R = H; $R_1 = (CH_2)_2NMe_2$]					
XIX [R = 7—OMe; $R_1 = (CH_2)_3NMe_2$]					
XVII [$R = (CH_2)_3NMe_2$]					

Table II. Results of various pharmacological tests

a The following scoring systems were used for the various tests referred in Table I & II
Test 1: % reversal—0 - 25 = +; 26 - 50 = ++; 51 - 75 = +++; 76 - 100 = ++++ (± indicates half the activity of +).
Test 2: % potentiation—scoring system as for test 1.
Test 3: % inhibition—scoring system as for test 1.
Test 4: ED_{50} between 0.01 - 5 mg/kg p.o. = ++++; 6 - 10 = +++; 11 - 20 = ++; 21 - 50 = +; above 50 = ±.
Test 5: % decrease—scoring system as for test 1.

b $ED_{50} < 0.025$ mg/kg p.o.

c Convulsions at 50-100 mg/kg p.o.; lethal at 200 mg/kg p.o.

d Convulsions at 250 mg/kg p.o.

e Slight stimulation at 200 mg/kg p.o.; toxic at 500 mg/kg p.o.

f Toxic at 200 mg/kg p.o.

The N-oxide of XX retained the 'DOPA' and antimescaline activity of the parent compound, but exhibited a lower order of activity in other tests. Desmethyl XX [XIX: R = H; $R_1 = (CH_2)_3NHMe$] was almost as active as Sintamil. Substitution of pyrrolidine for dimethylamine in Sintamil gave XIX (R = H; R_1 = pyrrolidinopropyl) which had good antimescaline activity but the activity in the other tests was reduced. Shortening the aminoalkyl side

chain [XIX: R = H; R_1 = $(CH_2)_2NMe_2$] led to decreased activity in tests 1 and 2, but increased the antinociceptive and antimescaline properties, whereas substituting a pyrrolidine for dimethylamine in the above compound (XIX: R = H; R_1 = pyrrolidinoethyl) resulted in some decrease in activity. In general, introduction of substitutents such as chlorine, methyl or methoxyl in ring C of Sintamil did not enhance its activity; for example, XIX (R = 7-OMe; R_1 = dimethylaminopropyl); nor was a more active compound than Sintamil obtained, when the nitro group was shifted to position 3, 7 or 8; for example, XVII (R = dimethylaminopropyl).

It was thus seen that among all the compounds studied, Sintamil was the most promising one as a potential antidepressant and was accordingly chosen for detailed studies, the results of which are presented in the following paper by David and Grewal.

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