STUDIES IN THE HETEROCYCLIC SERIES. XII. THE CHEMISTRY AND APPLICATIONS OF AZA- AND THIA-ANALOGS OF PHENOXAZINE AND RELATED COMPOUNDS*

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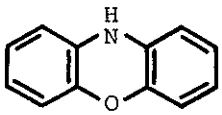
Interest in naturally occurring and synthetic phenoxazine derivatives prompted the synthesis of new rings derived from phenoxazine. Replacement of the benzene rings with pyridine, pyrazine, furan and pyrrole or a combination of them led to novel pyrrolobenzo[1,4]oxazine, furanobenzo[1,4]oxazine, 1,4-diaza- and 1,9-diazaphenoxazines. This article provides a survey of the chemistry and applications of novel heterocyclic ring analogs of phenoxazine and the related dibenzoxazepines and -oxazocines.

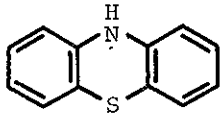
1. INTRODUCTION

Interest in the chemistry of dyes during the last quarter of the last century led to the synthesis of a large number of dyestuffs

derived from phenoxazine[1] ring (I). The parent compound was synthesized for the first time by Bernthsen[2] in 1887 following his successful synthesis of phenothiazine (II), the sulfur analog[3] of phenoxazine.

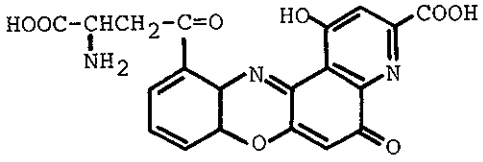


(I)



(II)

The naturally occurring phenoxazine derivatives are also numerous and have been classified as Ommochromes, Fungal Metabolites, Questiomycins and Actinomycins. The ommochromes such as xanthommatin (III) are acidic pigments found in different arthropods and are responsible for the coloration in the wings, cuticle and eyes of insects.[4-8] Some fungal metabolites derived from phenoxazine ring have been isolated from various wood-rotting fungi and from moulds. The coloration in these microorganisms has been attributed to these phenoxazine derivatives of type IV.[9-11]



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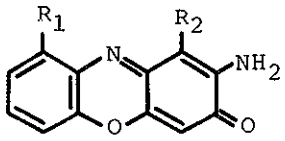
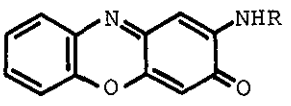


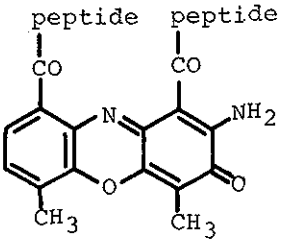
(IV)

Another phenoxazone derivative known as questiomycin A[12] (V, R = H)

was isolated from Streptomyces fungicidicus[13] while the 2-acetyl derivative (V, R = $COCH_3$) was isolated from Waksmania aerata and Pseudosomonas iodinum.[14]



(V)



(VI)

The actinomycins, which are a group of very toxic antibiotics obtained from certain species of the genus, Streptomyces, are complex chromopeptide derivatives[15] of phenoxazine (VI). About eighteen of them have been isolated and they differ mainly in the amino acid sequence in the peptide chain. In small doses, actinomycin antibiotics show anti-tumor activities in laboratory animals but in man they are effective in the treatment of Hodgkin's disease, a cancer-like disease of the lymphatic system.[16-17]

Following repeated reports on the pharmacological activities of phenothiazine[18-20] and phenoxazine, attention was diverted from their dyeing properties to a study of their biological activities. From tests carried out in laboratory animals and in man, it was found that many phenoxazine derivatives showed pronounced pharmacological activities as CNS depressants, sedatives, antiepileptics, herbicides, tranquilizers, antituberculosis, anti-tumor, antibacterial, spasmolytic, anthelminthic and parasiticidal agents.[21-34]

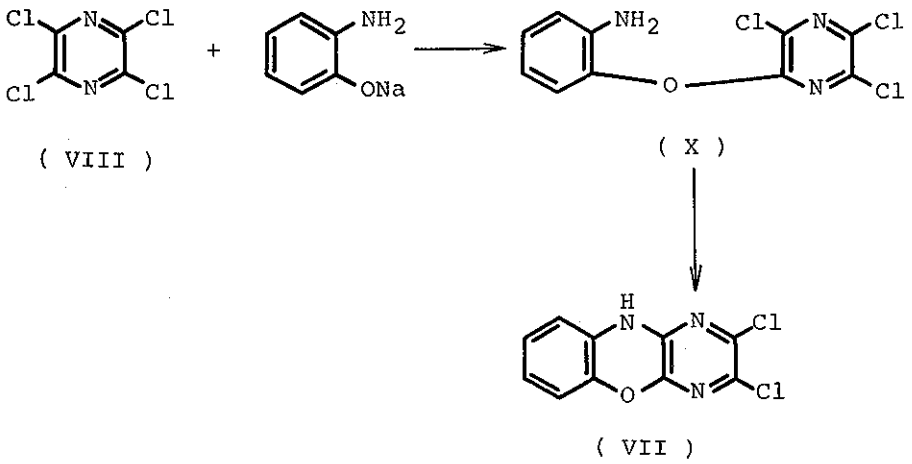
Other applications of phenoxazine derivatives include their use as antioxidants,[35] biological stains,[36] acid-base indicators,[37] and bromometric and stannometric redox indicators.[38-41] Phenoxazine itself has been used as a stabilizer for the polymerization of vinylpyridines,[42] polyethylene and polystyrene.[43] Some derivatives were also reported as having radioprotective and antioxidative actions.[44]

Even though their pharmacological activities appear numerous and impressive, these properties are generally inferior to those of the phenothiazines. Early improvements on the structure of phenoxazine involved changes in the side chain and the 10-alkylaminoalkyl group but nowadays interest is being shown on the modifications of the phenoxazine ring itself through replacements of one or more benzo groups with furan, pyrrole, pyridine and pyrazine rings as the case may be. The modification could also involve expansion of the oxazine ring leading to oxazepines and oxazocines.

A review of the chemistry of phenoxazine has been reported many times by Pearson,[45] Ramage,[46] Rodd, Landquist, McKee,[47] Schaefer,[48] Ionescu and Mantsch.[49] In an earlier paper,[50] it was pointed out that although several azaphenothiazines[51] have been reported, only 1-aza-, 2-aza-, 3-aza-, 4-aza- and 3,4-diaza-phenoxazine rings have been synthesized in the phenoxazine series. In the last few years further advancement has been made in this direction. It is the aim of this paper therefore to spotlight the reports which have been made in recent years on new azaphenoxazines from which some interesting new chemistry and new products of phenoxazine have emerged.

2. 1,4-DIAZAPHENOXAZINE.

Reports on the interesting pharmacological activities of 3,4-diazaphenoxazines[52-57] prompted the synthesis of other isomeric diaza-phenoxazines. The second aza-phenoxazine ring in this series is the 1,4-diazaphenoxazine system (VII) prepared by refluxing a mixture of 2,3,5,6-tetrachloropyrazine (VIII) with the sodium salt of o-amino-phenol (IX) in isopropyl alcohol. The resulting diaryl ether (X) was cyclized with or without rearrangement to the desired compound, VII, by refluxing with sodium hydroxide in isopyropyl alcohol for a half hour period.[58]



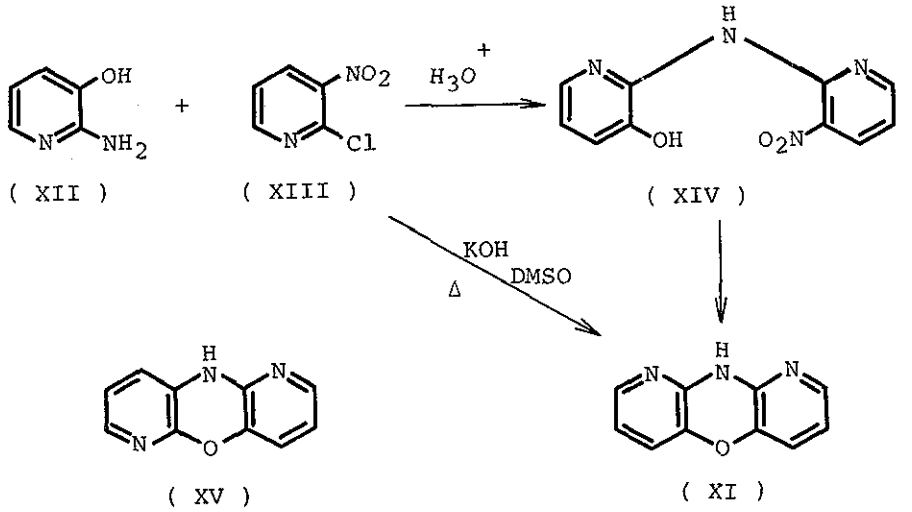
(VIII) (X) (VII)

The same product will be expected if the cyclization proceeded via Smiles rearrangement[51] of diaryl ethers and sulfides.

These 1,4-diazaphenoxazine derivatives showed pesticidal, herbicidal and anthelmintic properties. 2,3-Dichloro-1,4-diazaphenoxazine (VII) gave 100% control of Trichophyton mentagrophytes and Pullularia pullulans at concentrations of only 10 ppm.[58]

3. 1,9-DIAZAPHENOXAZINE.

In addition to the preparation of 3,4-diaza- and 1,4-diazaphenoxazines, the synthesis of 1,9-diazaphenoxazine (XI) was recently reported. This is the only known diazaphenoxazine in which the ring nitrogens are in different rings. The reactions leading to the parent heterocycle involved the base-catalysed condensation of 2-amino-3-hydroxypyridine (XII) with 2-chloro-3-nitropyridine (XIII) in dilute sulfuric acid. The diarylamine, (XIV), obtained in 45% yield, after neutralization with concentrated ammonia, was converted to 1,9-diazaphenoxazine (XI) in 31% yield by refluxing with potassium hydroxide in dimethyl sulfoxide for 10 hours.[59-60]



(XII) (XIII) (XIV)

(XV) (XI)

1,9-Diazaphenoxazine obtained in an overall yield of 14% is the second azaphenoxazine whose parent compound is now known. It is a microcrystalline compound melting at 245-246°. The ultraviolet spectrum had three intense absorption maxima at 338, 217 and 210 nm. Most phenoxazine compound show characteristic absorption maxima between 318 and 338 nm.[49]

The infrared spectrum showed strong bands at 1297 cm^{-1} (aromatic NH), 1250 cm^{-1} (aromatic C-O-C ether linkage), 741 and 772 cm^{-1} (presence of three adjacent free hydrogen atoms of pyridine) (Fig I). The nmr spectrum provided confirmatory evidence of structure. The aromatic protons appeared as a multiplet between 2.70 and 3.50 τ . Owing to the symmetrical nature of the molecule, H_A, representing the protons at C-2 and C-8 appeared as doublet of doublets at 2.76 τ (J_{AB} = 6 Hz, J_{AC} = 1 Hz). H_C representing the protons at C-4 and C-6 appeared in the same pattern at 2.94 τ (J_{AC} = 1 Hz, J_{BC} = 8 Hz). The uppermost field doublet of doublets centred at 3.30τ is due to H_B (3H and 7H), J_{AB} = 6 Hz and J_{BC} = 8 Hz (Fig. II). Thus the nmr spectrum is in agreement with structure XI which was assigned to this compound. The alternative isomeric 1,6-diazaphenoxazine (XV) would be expected to have a more complex spectrum due to absence of symmetry.

The diarylamine intermediate was also obtained but in a much lower yield by refluxing a mixture of compounds (XII) and (XIII) in alcoholic base. If the starting aminohydroxypyridine and chloronitropyridine were refluxed in dimethyl sulfoxide in the presence of potassium hydroxide for nine hours, only an 8% yield of 1,9-diazaphenoxazine (XI) was obtained in this single step reaction compared to an overall 14% yield obtained by the 2-step reaction.[60]

1,9-Diazaphenoxazine and its precursor, (XIV), were tested in mice and rats for their effects on the central nervous system. Both compounds showed both analgesic and CNS-depressant activities. They decreased body temperature by as much as 1.9° compared to 0.8° in chlorpromazine.[61]

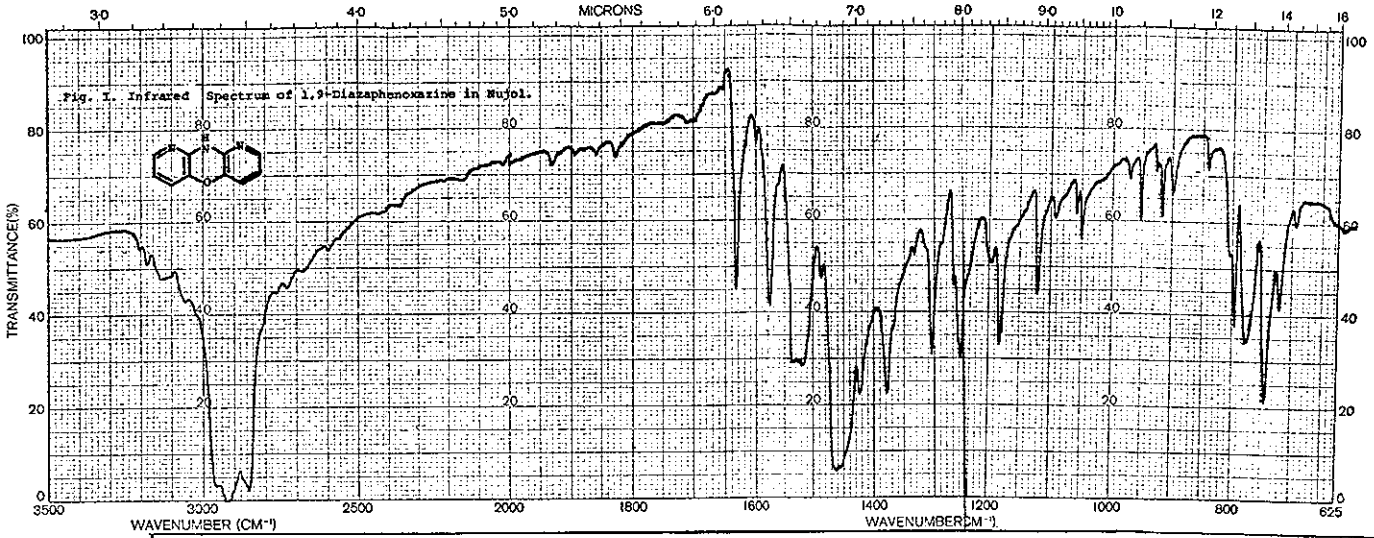


Fig. I. Infrared Spectrum of 1,9-Diazaphenoxazine in Nujol.

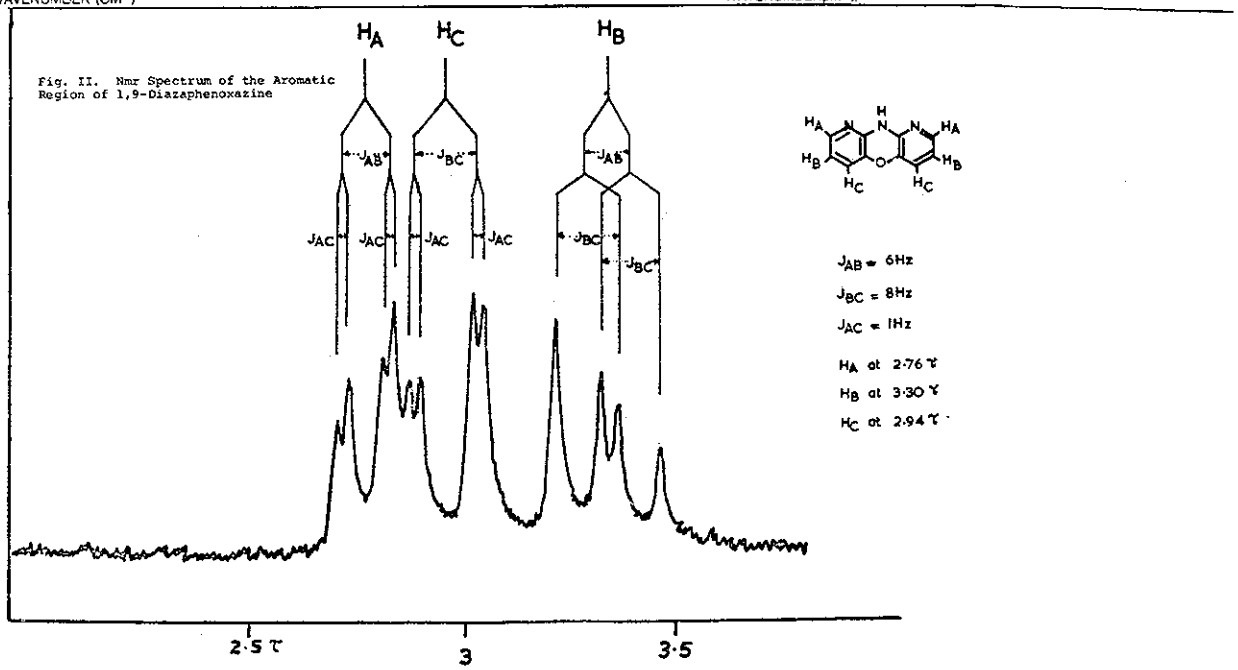


Fig. II. Nmr Spectrum of the Aromatic Region of 1,9-Diazaphenoxazine

J_{AB} = 6Hz

J_{BC} = 8Hz

J_{AC} = 1Hz

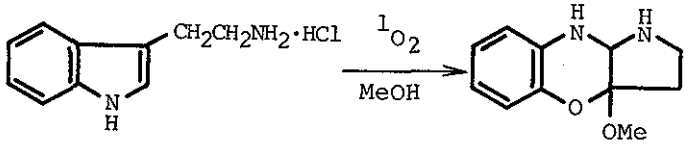
H_A at 2·76 τ

H_B at 3·30 τ

H_C at 2·94 τ

4. PYRROLOBENZO[1,4]OXAZINE.

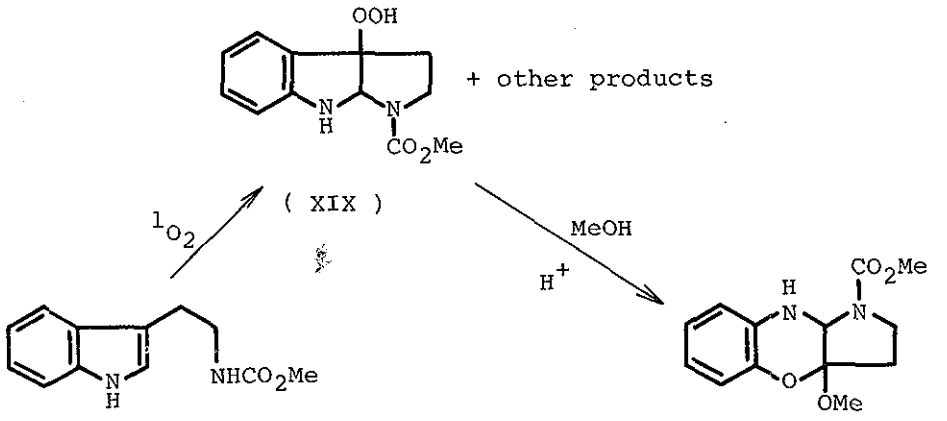
Replacement of one of the benzo groups in phenoxazine with pyrrole leading to pyrrolobenzo[1,4]oxazines (XVI) has been recently achieved by photosensitized oxygenation of 3-substituted indoles. Methylene blue-sensitized photo oxygenation of tryptamine hydrochloride (XVII) yielded the 2,3-dihydro-pyrrolobenzo[1,4]oxazine (XVI) in 89% yield[62] as a colorless oil, bp. 159-160° (1 mm Hg).



(XVII) (XVI)

These photooxygenation reactions were inhibited by the addition of well-known singlet oxygen quenchers such as 1,4-diaza-bicyclo[2,2,0]octane or triethylamine indicating that the reactions involve singlet oxygen.

When a thoroughly O_2-saturated solution of N^b-methoxycarbonyltryptamine (XVIII) was irradiated in 5% pyridine in methanol using a 200-W halogen lamp for three hours in the presence of rose bengal in an ice-cooled bath, a variety of products was obtained after chromatography. However, when the reaction mixture was concentrated and filtered over an alumina column followed by preparative TLC (Al_2O_3), the 3a-hydroperoxy-pyrroloindole (XIX) was isolated in 41% yield as an oil.



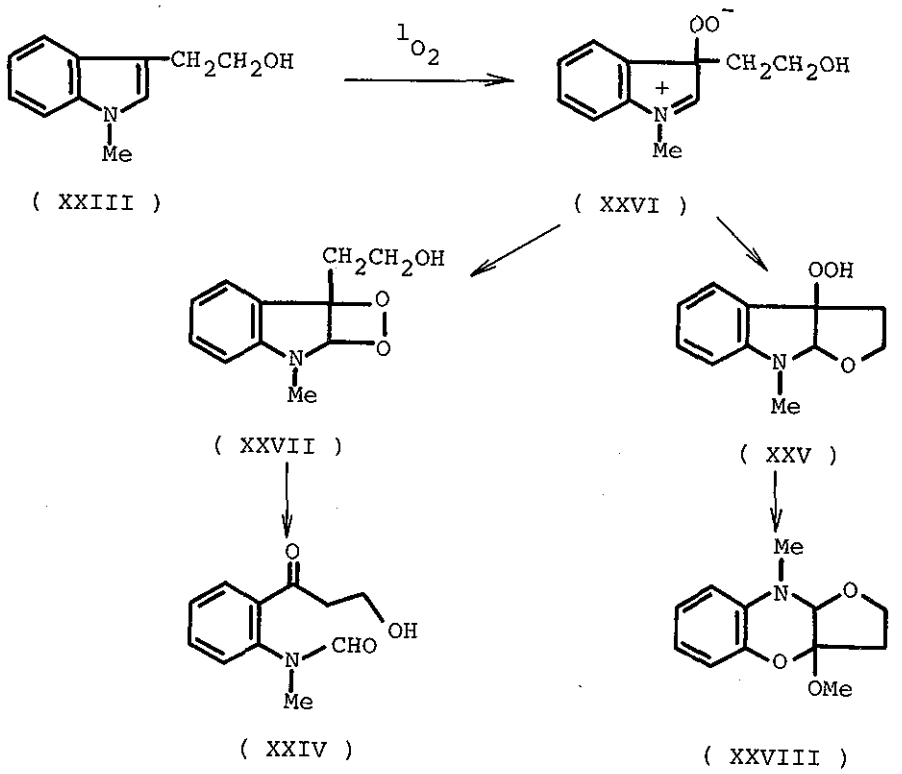
(XVIII) (XX)

In methanol compound (XIX) underwent a facile acid catalysed rearrangement at room temperature to afford 89% yield[63] of the 2,3-dihydropyrrolobenzo[1,4]oxazine (XX). These reactions provide a new method for the oxidative transformation of indoles into pyrrolo[1,4]-benzoxazines. Similar acid-catalysed rearrangements have been observed by other workers.[64]

5. FURANOBENZO[1,4]OXAZINE.

Further variation of phenoxazine structure leading to furanobenzo[1,4]oxazines (XXI) was accomplished by photosensitized oxidation of 3-substituted indoles (XXII). The hydroperoxidic products underwent acid-catalysed rearrangement to 2,3-dihydrobenzo[1,4]oxazines.

The rose bengal-sensitized photooxygenation of N-methyltryptophol (XXIII) (2 mM solution) in methanol at room temperature gave the C_2-C_3 ring cleavage product (XXIV) in 90% yield. If the photooxygenation reaction were however carried out at -70° until one molar equivalent of oxygen was absorbed and the solvent removed under vacuum at 0°, the 3-hydroperoxyindoline (XXV) was obtained in 95% yield.



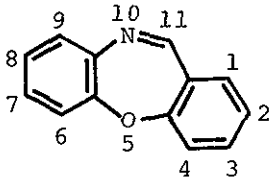
(XXIII) (XXVI) (XXVII) (XXV) (XXIV) (XXVIII)

When compound (XXV) was treated with methanol containing a catalytic amount of hydrochloric acid at room temperature, the 2,3-dihydrofurano-benzo[1,4]oxazine (XXVIII) was obtained in 75% yield as a pale yellow oil,[62] The proposed intermediates (XXVI) and (XXVII) have not been fully established.

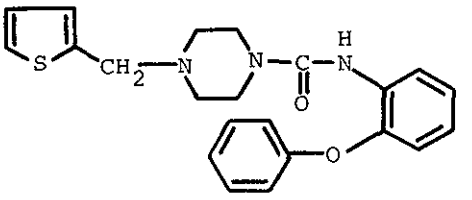
6. DIBENZ[b,f][1,4]OXAZEPINES.

In addition to modifications involving the two benzo groups in phenoxazine, the central oxazine ring can be expanded leading to oxazepine and oxazocine rings. Because of the formal relationship between these structures with phenoxazine, the chemistry of these ring systems is also discussed.

Derivatives of dibenz[b,f][1,4]oxazepine (XXIX), particularly the 11-piperazino derivatives were prepared by cyclization of 4-(2-thenyl)-1-piperazinecarboxylic acid o-phenoxyanilide,[65] (XXX).



(XXIX)



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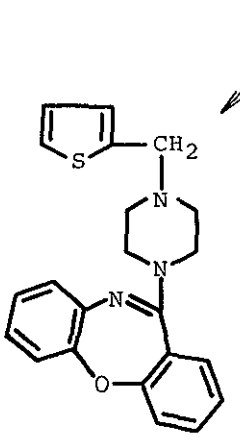
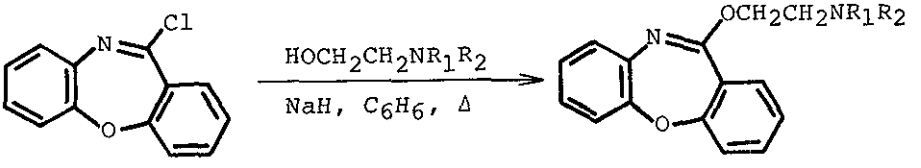


(XXXI)

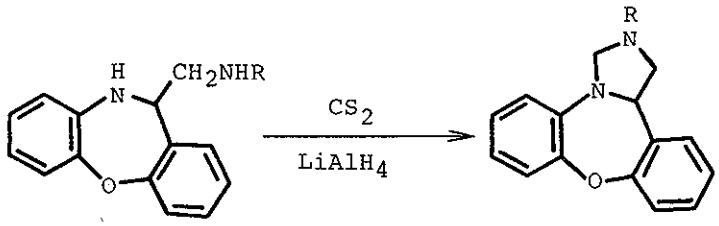
Starting with 11-chlorodibenz[b,f][1,4]oxazepine (XXXII), the 11-alkoxyamino derivative (XXXIII) was obtained by refluxing with 2-dimethylaminoethanol and sodium hydride in benzene.[66]



(XXXII) (XXXIII)

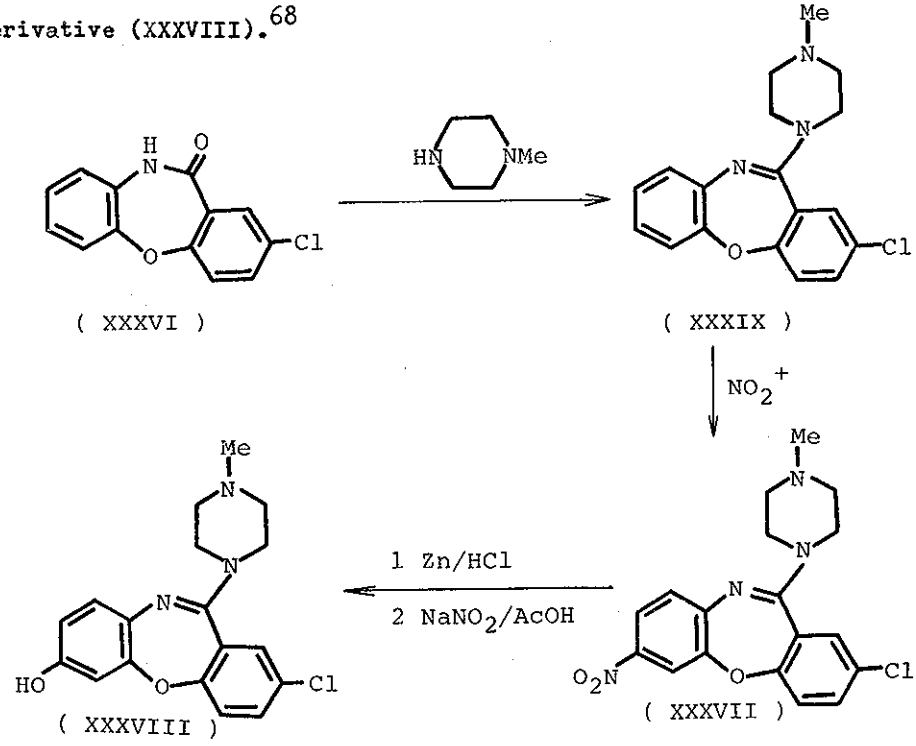
Several derivatives in this series were also reported.[66] The dibenzoxazepine (XXXIV) was converted to the 1,2,3,13b-tetrahydroimidazo-

[3,4-d]dibenz[b,f][1,4]-oxazepines (XXXV) by reaction with carbon disulfide followed by reduction with lithuim aluminium hydride.



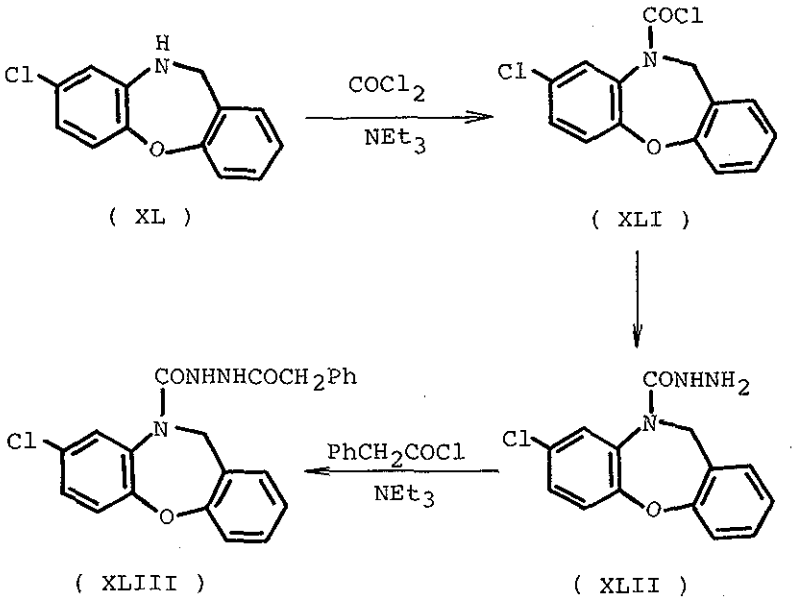
(XXXIV) (XXXV)

Alternatively, the same product was obtained by cyclization with 40% formalin.[67] Treatment of 2-chloro-dibenz[b,f][1,4]oxazepin-11(10H)-one (XXXVI) with N-methyl-piperazine followed by nitration resulted in 2-chloro-7-nitro-dibenz[b,f][1,4]oxazepin-11(10H)-one (XXXVII). Reduction with zinc and concentrated hydrochloric acid followed by diazotization in the presence of acetic acid led to the 7-hydroxy derivative (XXXVIII).[68]



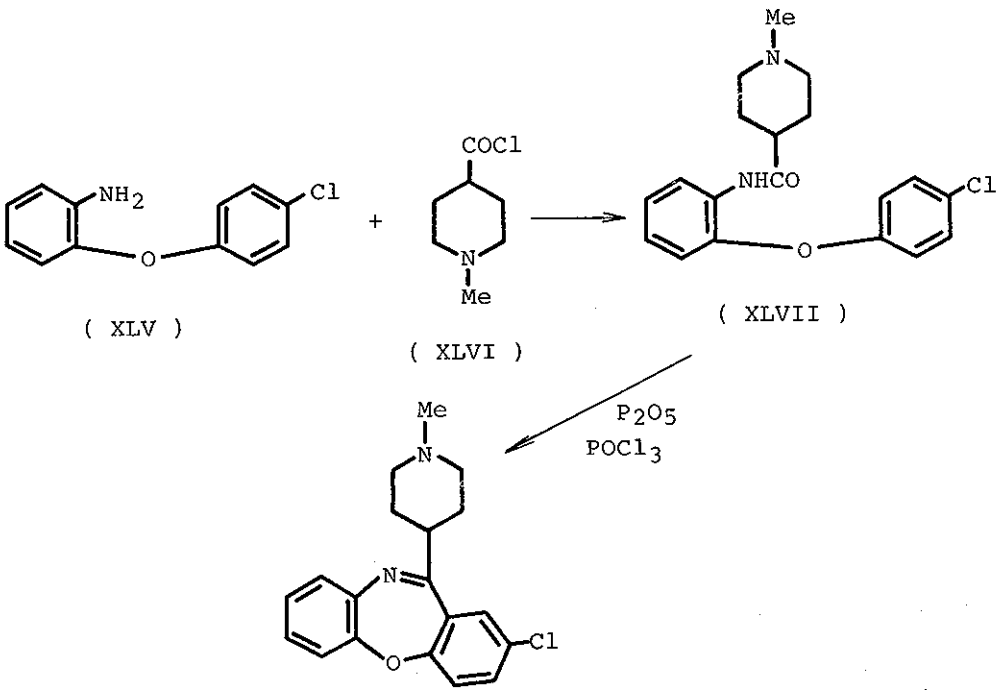
(XXXVI) (XXXIX) (XXXVII) (XXXVIII)

The action of phosgene on 8-chloro-10,11-dihydrodibenz[b,f][1,4]-oxazepine (XL) in mixed toluene and diethyl ether in the presence of triethylamine led to the 10-carbonyl chloride (XLI). Reaction with hydrazine hydrate in ethanol in the presence of methylene chloride and diethyl ether gave the hydrazide (XLII) which was converted to the amide (XLIII) by the action of phenylacetyl chloride in triethylamine.[69]



(XL) (XLI) (XLII) (XLIII)

The 11-nipecotyl derivative (XLIV) was obtained by acylation of o-(4-chlorophenoxy)aniline (XLV) with 1-methylisonipecotinoyl chloride (XLVI). The resulting 2'-(p-chlorophenoxy)-1-methylisonipecotinanilide (XLVII) was cyclized by refluxing with phosphorus oxychloride and phosphorus pentoxide.[70]



(XLV) (XLVI) (XLVII) (XLIV)

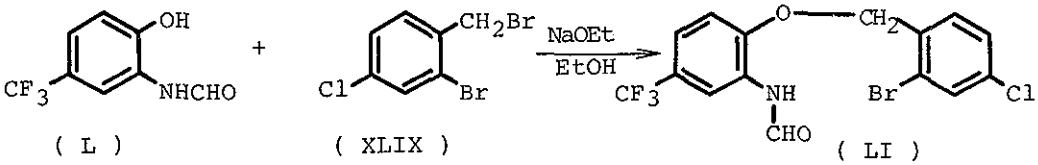
Several other derivatives of dibenzo[b,f][1,4]oxazepine were also described.[71-86]

In a study of the biological properties of these compounds, it was found that they were active antihypercholesterolemic,[69] antihistaminic,[66] antidepressive,[66,72,75] antiasthma,[66] neuroleptic[71,83] and antiemetic agents.[71,83] Some derivatives of this ring system are useful as anti-allergic[72] agents, inflammation inhibitors,[73,80] sebum secretion inhibitors[73] and antagonists to acetylcholine, 5-hydroxytryptamine[73,85] and prostaglandins.[73,85] In 8-chloro 10-carboxylic acid hydrazide derivatives (XLII) prostaglandin E_2-induced diarrhoea in mice was inhibited in 50% of the mice.[85] The 11-piperazinyl derivatives (XXXI)

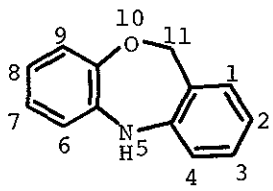
have antiphlogistic[65] and tranquilizing activities.[68,75] The ED_{50} for the depression of motor activity in Rats is 0.24 - 28 mg/kg i.p.[68] The imidazodibenzoxazepines (XXXV) were antidepressants[77] at 0.01 - 1.0 mg/kg. Other pharmacological properties include hypochesteremic,[80] analgesic[80,82] and psychotropic[80] activities. The 11-aminoalkyl esters have CNS activities and their LD_{50} in mice on i.p. or oral application are 75 to 500 mg/kg or 300 to 2000 mg/kg respectively.[86]

7. DIBENZ[b,e][1,4]OXAZEPINES.

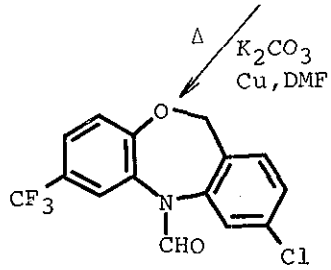
Further variation of the dibenzoxazepine ring involves the preparation of dibenz[b,e][1,4]oxazepines (XLVIII) in which the positions of ring nitrogen and oxygen are exchanged. The trifluoromethyl derivative was obtained by condensing a mixture of 4-chloro-2-bromobenzyl bromide (XLIX) and 5-trifluoromethyl-2-hydroxyformanilide (L) in the presence of ethanolic sodium methoxide. The resulting 2-(4-chloro-2-bromobenzyloxy)-5-trifluoromethylformanilide (LI) was cyclized by refluxing for 3.5 hours in the presence of potassium carbonate and copper bronze in dimethylformamide.



(L) (XLIX) (LI)



(XLVIII)



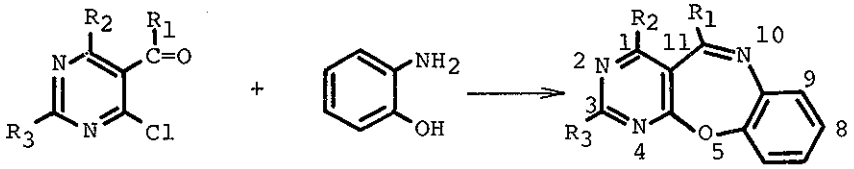
(LII)

The cyclic product, 3-chloro-5,11-dihydro-7-(trifluoro-methyl)dibenz[b,e][1,4]oxazepine-5-carboxaldehyde (LII) was deformylated by refluxing with 25% aqueous sodium hydroxide. 5- Alkylation was achieved by refluxing with alkyl halides for three hours in the presence of sodium hydroxide[87] and gave satisfactory yields of 3-chloro-5-alkylaminoalkyl-5,11-dihydro-7-(trifluoromethyl)dibenz[b,e][1,4]oxazepine (LIII).

Several derivatives were also prepared[86,88-94] and tested for their pharmacological properties. These compounds showed considerable tranquilizing,[87,91] microbicidal,[88] surface disinfectant,[88] CNS stimulant,[90] muscle relaxant,[90] sedative,[91] antibacterial,[92,93] fungicidal,[93] antituberculosis,[92] and antiarrhythmic[94] activities. At concentrations between 0.001 and 0.1% solns, some N-alkylaminoalkyl derivatives eliminated Staphylococcus aureus and Trichophyton mentagrophytes[94] and in doses of 20-200 mg per day, they showed sedative and hypotensive activities.[95]

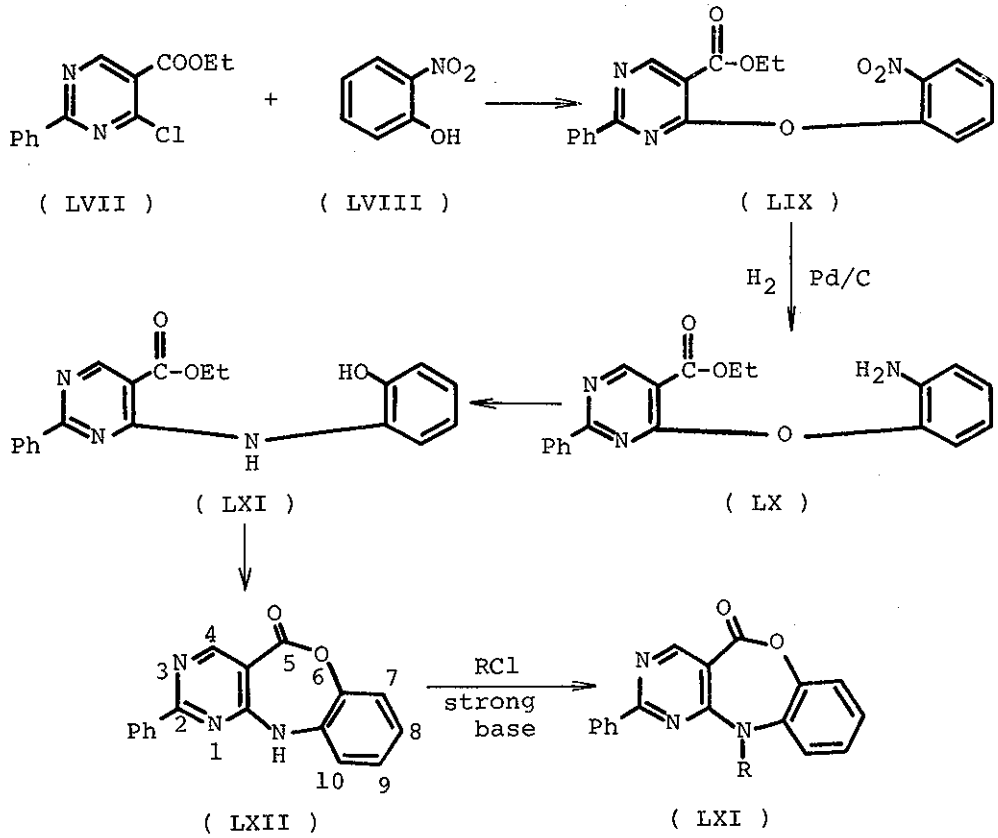
8. PYRIMIDO[4,5-b][1,5]BENZOXAZEPINES.

Attar, Wamhoff and Korte[96] have recently reported the synthesis of one of the diaza-analogs of dibenzo[1,4]oxazepine. In the reactions leading to this ring system, 4-chloro-5-acylpyrimidines (LIV) were condensed with o-aminophenol (IX) and gave good yields of 1,3,11-trisubstituted pyrimido[4,5-b][1,5]benzoxazepines (2,4-diazadibenzoxazepines) (LV).



(LIV) (IX) (LV)

Kim and Santilli[97] have obtained the isomeric pyrimido[5,4-c][1,5]benzoxazepine ring system (LVI) by condensing 4-chloro-5-carbethoxy-2-phenylpyrimidine (LVII) with o-nitrophenol (LVIII). The resulting diaryl ether (LIX) was reduced with palladium on carbon. During this reaction, the o-amino diaryl ether (LX) thus formed rearranged to the corresponding o-hydroxy diarylamine (LXI) followed by cyclization to the product, 2-phenylpyrimido[5,4-c][1,5]benzoxazepin-5(11H)-one (LXII).

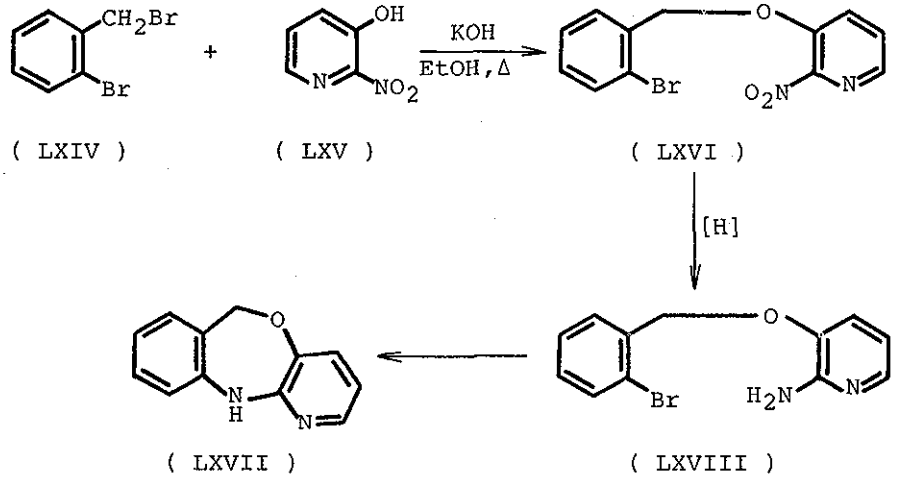


(LVII) (LVIII) (LIX) (LX) (LXI) (LXII) (LXI)

The pyrimidobenzoxazepines,(LXIII), as well as their intermediates (LIX) and (LXI) were CNS-depressants.[97]

9. PYRIDOBENZOXAZEPINES.

Pyridobenzoxazepine was obtained by refluxing a mixture of o-bromobenzyl bromide (LXIV) and 3-hydroxy-2-nitropyridine (LXV) with ethanolic potassium hydroxide. The resulting diaryl ether (LXVI), obtained in 60% yield was reduced and cyclized probably by refluxing with potassium carbonate in the presence of copper bronze to yield pyrido[1,4]benzoxazepine (LXVII).[98]



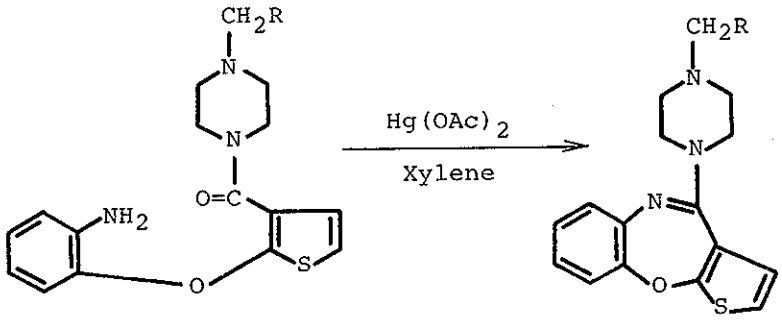
(LXIV) (LXV) (LXVI)

(LXVII) (LXVIII)

10. THIENOBENZO[1,4]OXAZEPINE.

The thieno analog of dibenzoxazepine was recently reported by Nakanishi and his co-worker.[99] By refluxing suitably o-substituted thienyl-(2-aminophenyl) ether (LXIX) with mercuric acetate in xylene

for a period of 24 hours, the corresponding thienobenzoxazepine (LXX) was obtained.



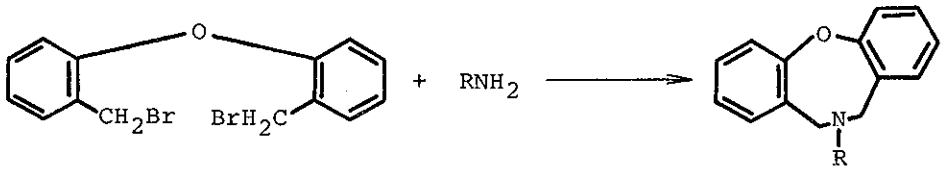
(LXIX) (LXX)

Several derivatives[76,99] were also prepared but the biological evaluation has not been reported.

11. DIBENZ[b,g][1,5]OXAZOCINE.

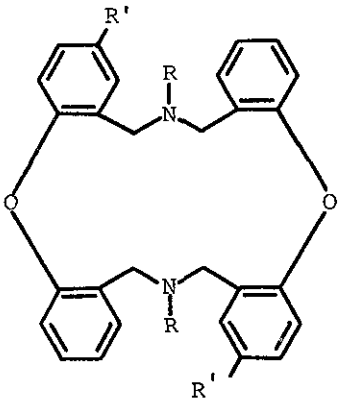
Further variation of the phenoxazine ring involves the expansion of the oxazine ring by two carbon atoms leading to dibenzoxazocines.

In one method 2,2′-di(bromomethyl)diphenyl ether (LXXI) was reacted with primary amines at 80° in an autoclave for 5 hours. N-substituted dibenzoxazocines (LXXII) were obtained. The N-methyl derivative was collected in 68% yield.[100]



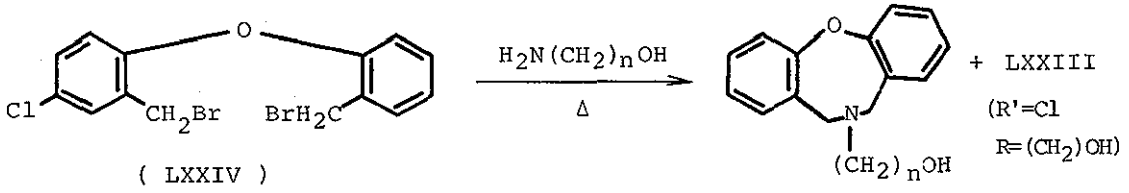
(LXXII)

The polycyclic azocine derivatives LXXIII , (R′ = H) were also obtained from these reactions.[101]



(LXXIII)

When the same workers[102] condensed 4-chloro-2,2′-di(bromomethyl) diphenyl ether (LXXIV) with w-amino-alcohols, the expected 3-chloro-6-(w-hydroxyalkyl)-6,7-dihydro-5H-dibenz[b,g][1,5]oxazocine (LXXV) was obtained along with the 16-membered ring dimer (LXXIII)(R′ = Cl, R = $(CH_2)_nOH$) as a by-product.



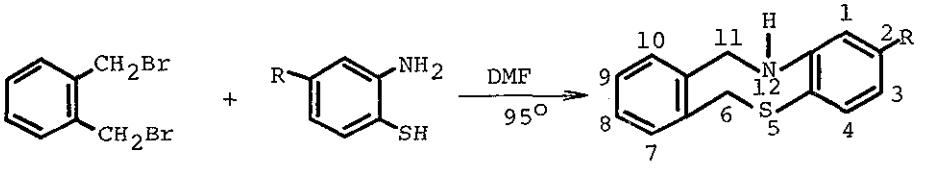
(LXXIV) (LXXV)

The formation ratio of these products varied with the reaction conditions. From the original reaction of 2,2′-di(bromomethyl)diphenyl ether (LXXI) with a primary amine, the two products - the dibenz[b,g][1,5]-oxazocine (LXXII) and the 16-membered ring dimer LXXIII (R′ = H) were both isolated.[103] Again the formation ratio varied with the reaction conditions.

Many derivatives of this ring system were also reported[100-104] and found to possess antiinflammatory,[100,101] analgesic,[100] antidepressant,[100,104] antiedema[101] and psychotropic[101] activities.

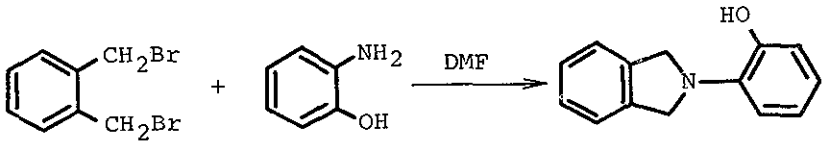
12. DIBENZ[b,f][1,4]OXAZOCINE.

It was shown by Yale, Sowinskii and Spitzmiller[105] that the reaction of α,α'-dibromo-o-xylene (LXXVI) with an o-aminothiophenol (LXXVII) in DMF at 95° led to the corresponding 10,11-dihydrodibenzo[b,f][1,4]thiazepines (LXXVIII).



(LXXVI) (LXXVII) (LXXVIII)

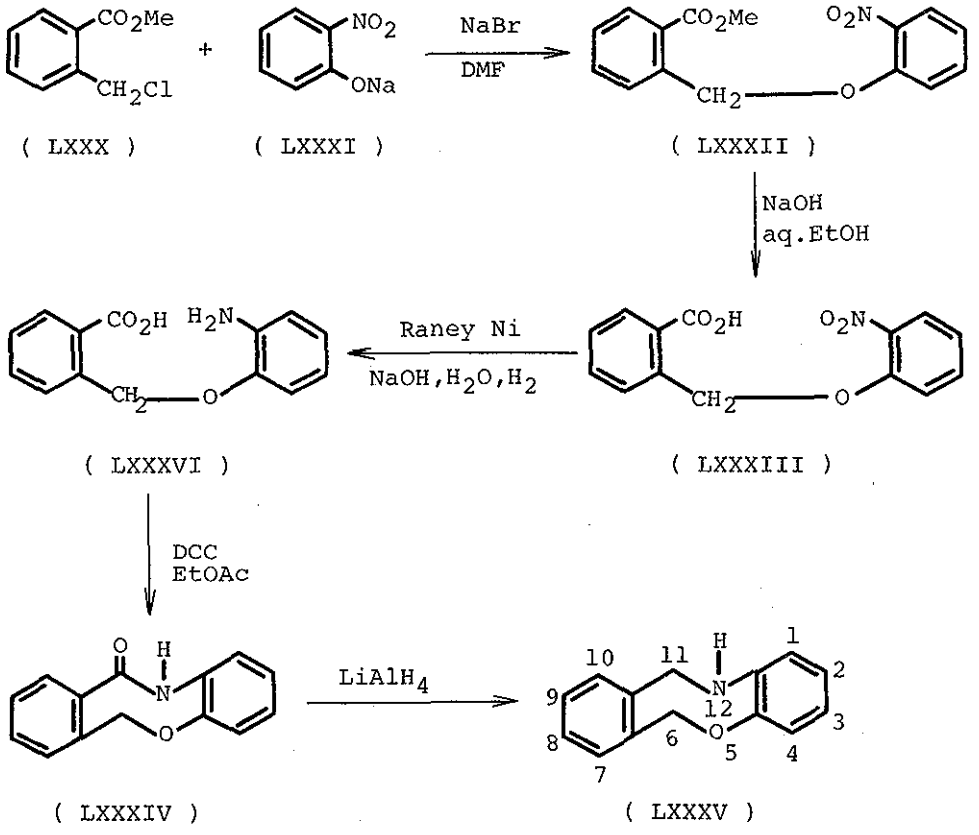
Replacement of the o-aminothiophenol with o-aminophenol (IX) did not give the expected dibenzoxazocine but instead the product, (LXXIX), was isolated.[106]



(LXXVI) (IX) (LXXIX)

A successful route to this ring system involved the condensation of α-chloro-o-toluate (LXXX) with the sodium o-nitrophenoxide (LXXXI) in ethanol-DMF mixture. The resulting α,α'-bis(o-nitrophenoxy)-o-xylene (LXXXII) was hydrolysed with sodium hydroxide in aqueous ethanol. The product α-(o-nitrophenoxy)-o-toluic acid (LXXXIII) was then reduced with Raney nickel. An intramolecular cyclization was induced by the

addition of dicyclohexylcarbodiimide (DCC) in ethyl acetate. Dibenz-[b,f][1,4]oxazocin-11 (12H)-one (LXXXIV) was obtained in 39% yield. Lithuim aluminium hydride reduction converted compound (LXXXIII) to the parent compound, dibenz[b,f][1,4]oxazocine (LXXXV) in 79% yield. Compound (LXXXV) is a solid melting at 133 - 135°. In the nmr spectrum, the eight aromatic protons appeared as a multiplet between τ 3.58 and 2.65. The two protons on C-6 appeared as a singlet at 4.67 τ while those on C-11 appeared at 5.42 τ as a singlet too. The 12-NH proton appeared as a broad peak at 6.10 τ .



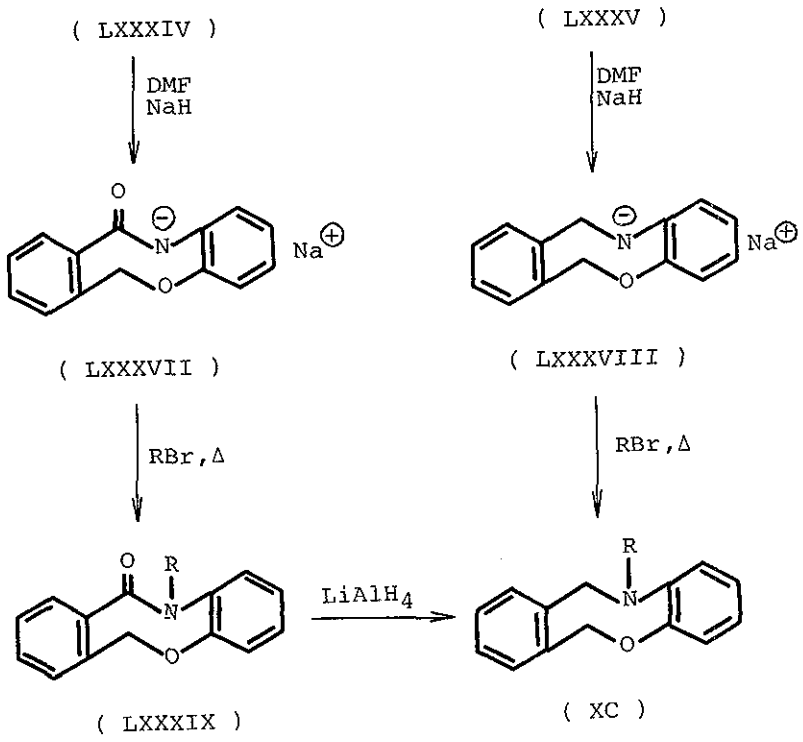
(LXXX) (LXXXI) (LXXXII)

(LXXXVI) (LXXXIII)

(LXXXIV) (LXXXV)

N-Alkylation was accomplished via two routes which involve the

generation of the anions (LXXXVII) and (LXXXVIII) followed by the action of the alkyl halide.



The 12-alkyl-dibenzoxazocin 11-one (LXXXIX) was also converted to 12-alkyl dibenz[b,f][1,4]oxazocine (XC) by lithium aluminium hydride reduction.[106] A number of other derivatives and mainly the 12-alkylaminoalkyl-, the 12-acylamino- and 12-aralkyl derivatives were also reported.[106]

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13. REFERENCES.

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1 R. Meldola, Ber. Deut. Chem. Ges., 1879, 12, 2065. Ein Wirkung von Nitrosodimethylanilin auf Phenole, welche nicht die Methylgruppe enthalten.

2 A. Bernthsen, Ber Deut. Chem. Ges., 1887, 20, 942.

3 A. Bernthsen, Ber. Deut. Chem. Ges., 1883, 16, 2896. Zur Kenntniss des Methylenblau und verwandter Farbstoffe.

4 A. Butenandt, E. Biekert, H. Kubler and B. Linsen, Hoppe-Seyler's Z. Physiol. Chem., 1960, 319, 238. Ommochromes. XX. Distribution of Ommatin in Animals - New Method for Their Identification and Quantitative Determination.

5 M. Nakagaki, N. Koya and S. Iwata, Yakugaku Zasshi, 1962, 82, 1134. Biophysicochemical Studies on Phenoxazine Compounds. I. Diffusion Constant and Degree of Association.

6 A. Butenandt and G. Neubert, Hoppe- Seyler's Z. Physiol. Chem., 1955, 301, 109, Ommochromes. V. Xanthommatin, an ocular pigment found in blowflies (Calliphora erythrocephala).

7 A. Butenandt and R. Beckmann, Hoppe-Seyler's Z. Physiol. Chem., 1955,

301, 115. Ommochromes. VI. Origin of Rhodommatin and Ommatin C.

8 L. R. Morgan, Jr, D. M. Weimorts and C. C. Aubert, Biochim. Biophys. Acta, 1965, 100, 393. Oxidation of 3-Hydroxyanthranilic acid by a Soluble Liver Fraction from Poikilothermic Vertebrates.

9 R. Lemberg, Aust. J. Exp. Biol. Med. Sci., 1952, 30, 271. Nitrogenous Pigment from the Fungus, Coriolus sanguineus (Polystictus cinnabarinus).

10 J. Gripenberg, Acta Chem. Scand, 1951, 5, 590. Fungus Pigments. I. Cinnabarine, A Coloring Matter from Trametes cinnabarina.

11 G. W. K. Cavill, B. J. Ralph, J. R. Tetaz and R. L. Werner, J. Chem. Soc., 1953, 525. The Chemistry of Mold Metabolites. I. Isolation and Characterization of a Red Pigment from Coriolus sanguineus.

12 K. Anzai, K. Isono, K. Okuma and S. Suzuki, Rika Gaku Kenkyusho Hokoku, 1960, 36, 577. [Chem. Abstr., 1960, 55, 25150].

13 M. Matsuoka, J. Antibiotics (Tokyo) Ser, 1960, A13, 121. [Chem. Abstr., 1962, 56, 9365e] Biological Studies on Antifungal Substances produced by Streptomyces fungicidicus.

14 N. N. Gerber and M. P. Lechevalier, Biochem, 1964, 3, 598. Phenazines and Phenoxazines from Waksmania aerata and Pseudomonas iodinum.

15 H. Brockmann in "The Chemistry of Natural Products, International Union of Pure and Applied Chemistry, Section of Organic Chemistry," Butterworths Publishers and Co, Ltd, London, 1961, pp. 405 - 424. Chemistry of the Actinomycins.

16 C. Hackmann, Z. Krebsforsch, 1952, 58, 607. Effect of Actinomycin C on Malignant Tumors.

17 S. Farber in "CIBA Foundation Symposium on Amino Acids and Peptides with Antimetabolite Activity," CIBA Foundation, London, 1958, p. 138.

18 S. P. Massie, Chem. Rev., 1954, 54, 791. The Chemistry of Phenothiazine.

19 C. Bodea and I. Silberg in "Advances in Heterocyclic Chemistry," Vol. 9, A. R. Katritzky and A. J. Boulton. Eds, Academic Press Inc, New York, N.Y., 1968, pp 321 - 460. Recent Advances in the Chemistry of Phenothiazines.

20 E. von Schenker and H. Herbst, "Progress in Drug Research," Vol 5, E. Jucker, Ed, Birkhauser Verlag, Basel, 1963, pp 269 - 627. Phenothiazine und Azaphenothiazine als Arzneimittel.

21 B. Boothroyd and E. R. Clark, J. Chem., Soc., 1953, 1499. Aminophenoxazines as Possible Antitubercular Agents. I. Method for the synthesis of 3-Aminophenoxazine.

22 T. Yuasa, Ann. Rept. Res. Inst. Tuberc. Kanazawa Univ., 1953, 11, 265. In Vitro Bacteriostatic Activity of Phenoxazone Compounds upon Various Kinds of Bacteria.

23 M. Gordon, P. N. Craig and C. L. Zirkle, "Molecular Modification in Drug Design," R. F. Gould, Ed, American Chemical Society, Washington D.C., 1964, pp 140 - 147. Molecular Modification in the Development of Phenothiazine Drugs.

24 C. F. Boehringer, (G.m.b.H. Soehne), Belgian Patents 631,122 (4th November, 1963). /Chem. Abstr. 1964, 60, 14514/ New Basic Derivatives of Phenoxazine.

25 Smith, Kline and French Labs., British Patent 897,158 (23rd May, 1962). [Chem. Abstr., 1962, 57, 12506]. Therapeutic Cyanophenoxazine Derivatives.

26 M. P. Olmsted (Smith, Kline and French Labs.), U.S. Patent 2,947,746 (2nd August, 1960); [Chem. Abstr., 1961, 55, 11443]. Phenoxazine Intermediates.

27 Societes des Usines Chimiques Rhone-Poulenc, French Patent 1,169,518 (29th December, 1958), [Chem. Abstr., 1961, 55, 3628]. Phenoxazines.

28 P. N. Craig (Smith, Kline and French Labs.), U.S. Patent 2,947,747 (2nd August, 1960) [Chem. Abstr., 1961, 55, 580]. Trifluoromethyl-substituted Phenoxazines.

29 P. N. Craig (Smith, Kline and French Labs.), U.S. Patent 2,947,745 (2nd August, 1960) [Chem. Abstr., 1961, 55, 582] Substituted Phenoxazine Sedative Agents.

30 A. Ribbentrop and W. Schaumann, Arch. Intern. Pharmacodyn. 1964, 149, 374. [Chem. Abstr., 1964, 61, 9924]. Intensity and duration of Central Nervous Action of 2-Acetylated Phenothiazines and Phenoxazines.

31 A. Sekera, J. Mondial Pharm., 1962, 5, 5. [Chem., Abstr., 1963, 58, 4421]. Syntheses and Pharmacological Studies of a Series of Basic Esters of Substituted Carbamic Acids.

32 A. Girard (Russel - UCLAF, SA.), U.S. Patent 3,048,586 (7th August, 1962) [Chem. Abstr. 1963, 58, 1471]. Novel Derivatives of Phenoxazine.

33 W. P. Rogers, J. Cymerman-Craig and G. P. Warwick, Brit. J. Pharmacol., 1955, 10, 340. Chemical Constitution and Anthelminthic Activity of Cyclic Analogs of Phenothiazine.

34 H. B. Rickert and W. M. Geiger (Dow Chem. Co) U.S. Patent 2,945,856 (19th July, 1960). 2,4,6,8-Tetra-Tert-butylphenoxazine.

35 C. M. Murphy, H. Ravner and N. L. Smith, Ind. Eng. Chem., 1950, 42, 2479. Action of Phenothiazine-type Antioxidants.

36 (a) W. C. Holmes and A. R. Peterson, Stain Tech., 1931, 6, 79. Atmospheric dealkylation of aqueous solutions of cresyl blue.
(b) W. C. Holmes, Amer. Dyestuff Rept., 17, 626 (1928). /Chem. Abstr. 1929, 23, 1767 Certified Biological Stains.

37 G. Mannelli and E. Martini, Ann. Chim. (Rome), 1951, 41, 68. A New Neutralization Indicator.

38. (a) E. Ruzicka, Collection Czech. Chem. Commun, 1959, 24, 930. 7-Amino-4-Methyl-2-phenoxazone as an analytical Reagent.
(b) E. Ruzicka, Z. Anal. Chem., 1959, 168, 414. Ascorbinometric Determination of Resazurin, Resorufin and Derivatives.

39 E. Ruzicka, Collection Czech. Chem. Commun, 1964, 29, 2244. Some oxazones as Bromatometric Indicators.

40 S. Musha and T. Kitagawa, Nippon Kagaku Zasshi, 1955, 76, 1289 /Chem. Abstr. 1957, 51, 12737/. Phenoxazone, a New Oxidation-Reduction Indicator.

41 E. Ruzicka, Chem. Listy, 1957, 51, 969. /Chem. Abstr., 1957, 51, 11936/. Microdetermination of 2-Aminothiophenol.

42 A. M. Schnitzer and R. E. Reusser (Phillips Petroleum Co),U.S. Patent 2,857,389 (21st October, 1958). /Chem. Abstr., 1959, 53, 5296/. Stabilization of vinylpyridines.

43 K. Peterlein and K. Schmitz (Gelsenberg Benzin Akt.-Ges), German Patent 1,103,577 (30th March, 1961). /Chem. Abstr., 1961, 55, 27980/. Stabilization of solid polyolefins.

44 V. N. Benevolenskii and A. I. Zhuravlev, Radiobiologiya, 1963, 3, 745. /Chem. Abstr., 1964, 60, 836/. Radioprotective Action of Phenoxazine Derivatives.

45 D. E. Pearson in "Heterocyclic Compounds," Vol 6, R. C. Elderfield, Ed, John Wiley and Sons, Inc, New York, N.Y., 1957, Ch. 14, pp 624 - 726. Phenazines, Phenoxazines and Phenothiazines.

46 G. R. Ramage, E. H. Rodd and J. K. Landqiust in "The Chemistry of Carbon Compounds," Vol IV, Part C, "Heterocyclic Compounds," E. H. Rodd, Ed, Elsevier Publishers Inc, London, 1960, pp. 1491 - 1502. Compounds Containing two Heteroatoms: Oxazines, Thiazines, Dioxans and their Analogs.

47 R. C. McKee in "The Chemistry of Heterocyclic Compounds," Vol 17, R. H. Wiley, Ed, A. Weissberger, Consulting Ed, Interscience Publishers, Inc, New York, N.Y., 1962, Ch. XV, pp. 377 - 444. The 1,4-oxazines.

48 W. Schaefer in "Progress in Organic Chemistry," Vol 6, J. Cook and W.Carruthers, Eds, Butterworth Publishers and Co, Ltd., London, 1964, pp 135 - 163. The Chemistry of Phenoxazones.

49 M. Ionescu and H. Mantsch in "Advances in Heterocyclic Series", Vol 8, A. R. Katritzky and A. J. Boulton, Eds, Academic Press Inc, New York, N.Y., 1967, pp. 83 - 113. Phenoxazines.

50 C. O. Okafor, Int. J. Sulfur Chem., B, 1971, 6, 345. Studies in the Heterocyclic Series. IV. Azaphenoxazines and related Naturally occurring Compounds.

51 C. O. Okafor, Int. J. Sulfur Chem., B, 1971, 6, 237. Studies in the Heterocyclic Series. III. The Chemistry of Azaphenothiazine Compounds.

52 M. D. Mashkovskii, L. F. Roshchina, Farmakol. Toksikol (Moscow), 1971, 34, 144. Action of Azaphen (a New Antidepressant) on the bioelectric activity of the Brain.

53 M. R. Bagreeva, Khim. Farm. Zh., 1971, 5, 59. Thin-Layer Chromatography of Azaphen (2-(4-methyl-1-piperazinyl)-10-methyl-3,4-diazaphenoxazine-dihydrochloride).

54 T. V. Gortinskaya, M. N. Shchukina, N.Y. Savitskaya, V. G. Nyrkova, M. D. Mashkovskii, A. I. Polezhaeva, L. N. Bondar and T. F. Andryushina, French Patent M. 7441 (2 January, 1970). [Chem. Abstr., 1972, 77, 5501p]. Psychotropic 3,4-Diazaphenoxazines.

55 T. V. Gortinskaya, V. G. Nyrkova, N. V. Savitskaya, M. N. Shchukina, Z. M. Klimonova, V. G. Potapova, L. Sh. Gorodetskii, O. N. Volzhina, Khim. Farm. Zh., 1973, 7, 21. Azaphen preparation Method.

56 T. V. Gortinskaya, V. G. Nyrrkova, G. N. Litova, L. N. Bondar, T. F. Andryushina, N. V. Savitskaya, O. A. Fedotova, I. N. Fedorova, M. N. Shchukina (Ordzhonikidze, S, All-Union Scientific Res. Chem.

Pharm. Inst.), German Offen,2,432,394 (23rd January, 1975). 3,4-Diazaphenoxazines.

57 N. V. Savitskaya, T. V. Gortinskaya, V. G. Nyrkova, I. N. Fedorova T. F. Andryushina, L. N. Bondar, M. N. Shchukina, U.S.S.R. Patent 418,035 (5th October, 1975). Nitro-3,4-diazaphenoxazine.

58 A. H. Gulbenk, D. J. Horne and H. Johnston (Dow Chem. Co), U. S. Patent 3,663,543 (16th May, 1972). Pesticidal 2,3-dichloro-5,10-dihydropyrazino[2,3-b]quinoxaline and Related Compounds.

59 C. O. Okafor, J. Chem. Soc. Chem. Commun., 1974, 878. Synthesis of Dipyrido[3,2-b:2',3'-e][1,4]oxazine (1,9-Diazaphenoxazine).

60 C. O. Okafor, J. Heterocyclic Chem., 1976, 13, 107. Studies in the Heterocyclic Series. XI. Reactions of 2-Amino-3-hydroxypyridine with 2-chloro-3-nitropyridine.

61 C. O. Okafor, M. L. Steenberg and J. P. Buckley, Europ. J. Med. Chem., 1976, 10, In Press. New CNS-depressants derived from 1,9-Diazaphenoxazine and two Isomeric Triazaphenothiazine Ring Systems.

62 I. Saito, M. Imuta, S. Matsugo and T. Matsuura, J. Amer. Chem. Soc. 1975, 97, 7191. Indole-Singlet Oxygen Reactions. A Novel Rearrangement of the Peroxidic Intermediates to 2,3-Dihydro-1,4-benzoxazines.

63 M. Nakagawa, H. Okajima and T. Hino, J. Amer. Chem. Soc., 1976, 98, 635. Photosensitized Oxygenation of N^b-Methoxycarbonyltryptophan Methyl Ester and N^b-Methoxycarbonyltryptamine. Isolation and Novel Transformations of a 3a-Hydroperoxypyrroloindole.

64 B. Witkop and J. B. Patrick, J. Amer. Chem. Soc., 1952, 74, 3861. Acid-and Base-catalysed rearrangements of a Ring-Chain Tautomeric Ozonide.

65 M. Nakanishi, T. Munekata, T. Tsumagari and N. Setoguchi, Japanese Patent 34,718 (1st September, 1972). Piperazine Derivatives.

66 M. Nakanishi, H. Yugi, A. Nakanishi, Y. Takigawa (Yoshitomi Pharm. Ind. Ltd.,) Japanese Patent 43,786 (25th December, 1971). Heterocyclic Compounds.

67 W. J. Van der Burg (AKZO N. V), German Offen 2,311,019 (20th September, 1973). 1,2,3,13b-Tetrahydrotmidazo[3,4-d]dibenz[b,f]-[1,4]oxazepines, -dibenzothiazepines and -dibenzodiazepines.

68 C. F. Howell (American Cyanamid Co) U.S. Patent 3,773,768 (20th November, 1973). 7-Amino-2-chloro-11-(4-methyl-1-piperazinyl) dibenz[b,f][1,4]oxazepine and its salts.

69 J. W. Cusic, W. E. Coyne (Searle G-D & Co), U.S. Patent 3,624,104 (30th November, 1971). Aralkanoyl derivatives of dibenzoxazepine N-carboxylic acid hydrazide.

70 C. F. Howell, P. Ramirez and R. A. Hardy,Jr, French Patent 1,602,883 (19th March, 1971). 11-Substituted Dibenz[b,f][1,4]-oxazepines and Dibenzo[b,f][1,4]thiazepines.

71 J. Schmutz, F. Hunziker and M. F. Fuenzle, German Offen 2,139,016 (10th February, 1972). Neuroleptic and Antiemetic 2-(Trifluoro-methylsulfonyl)dibenz(b,f)(1,4)-oxazepine Derivatives.

72 M. Nakanishi and T. Oe, Japanese Patent 30,715 (9th August, 1972) Cyclic Hydroxamic Acid Derivatives.

73 R. A. Mueller (Searle G-D & Co), German Offen 2,213,809 (12th October, 1972) 1-Acyl-2-(10,11-Dihydrodibenz[b,f][1,4]oxazepine-10-carbonyl)hydrazines.

74 G. Orzalesi, R. Selleri and O. Caldini, Farmaco Ed. Sci., 1972, 27, 1071. New Derivatives of Dibenz[b,f][1,4]oxazepine with Possible CNS Activity.

75 C. F. Howell and E. N. Greenblatt (American Cyanamid Co), U.S. Patent 3,705,245 (5th December, 1972). 7-Amino-2-chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxazepines acting on CNS.

76 J. Schneider (Wander A.G.), German Offen 2,316,438 (11th October, 1973). Piperazinyl-substituted Dibenzoazepines and Similar Compounds.

77 AKZO N. V., Netherland Appl. 02,963 (11th September, 1973) Imidazolidine Derivatives.

78 J. Schmutz, F. Hunziker and F. M. Kuenzle, Swiss Patent 544,768 (15th January, 1974). Dibenzoxazepines.

79 J. Schmutz, F. Hunziker and M. Franz (Wander, Dr. A, A-G), Swiss Patent 544,767 (15th January, 1974). Dibenzoxazepines.

80 M. Nakanishi, T. Munakata, H. Maruyama and N. Setoguchi (Yoshitomi Pharm Ind Ltd), Japanese Patent 35,272 (26th October, 1973). Piperazine Derivatives.

81 H. L. Yale, and J. Bernstein, British Patent 1,343,922 (16th January, 1974). Dibenzothiazocinyl ethanols.

82 M. Nakanishi, T. Munakata, H. Maruyama and N. Setoguchi, Japanese Patent 43,512 (19th December, 1973). Piperazine Derivatives.

83 J. Schmutz, F. Hunziker and F. M. Kuenzle (Wander, Dr. A, A-G), French Demande 2,187,338 (12th February, 1974). Neuroleptic and Antiemetic Dibenzo[b,f][1,4]oxazepine Derivatives.

84 K. Nagarajan, A. Venkateswarlu, C. L. Kulkarni, N. A. Goud and R. H. Shah, Indian J. Chem., 1974, 12, 236. Condensed Heterotricycles. Amino- and aminoalkyl dibenz[b,f][1,4]oxazepin-11(10H)-ones.

85 R. A. Mueller (Searle G.D & Co), U.S. Patent 3,917,649 (4th November, 1975). Dibenzoxazepine N-carboxylic Acid Hydrazides and Derivatives.

86 C. F. Malen, M. Desnos and J. C. Poignant (Science Union et Cie-Societe Francaise de Recherche Medicale), German Offen 2,030,714 (4th February, 1971). w-(Dibenzoxasepinylamino)alkanoic Acids and w-(dihydrodibenzocycloheptenylamino)alkanoic Acids and Their Esters.

87 H. L. Yale (Squibb E. R. and Sons, Inc), U.S. Patent 3,631,052 (28th December, 1971). 5,11-Dihydrodibenz[b,e][1,4]oxazepine Derivatives.

88 H. L. Yale and R. Petigara (Squibb E. R. & Sons, Inc), German Offen 2,153,589 (4th May, 1972). 1,2-Dihydro-3H,8H-quino[1,8-ab][4,1]benzoxazepin-3-ones, their [8,1-cd][1,5]-isomers, the thioanalogs and Oximes.

89 H. L. Yale and J. Bernstein (Squibb E. R. & Sons Inc), German Offen 2,107,669 (31st August, 1972). Guanidine derivatives of Condensed Heterocycles.

90 H. L. Yale and R. B. Petigara (Squibb E. R. & Sons, Inc) U.S. Patent 3,793,345 (19th February, 1974). 5,11-Dihydrodibenz[b,e][1,4]-oxazepine-5-alkylamidoximes.

91 H. L. Yale and J. Bernstein (Squibb E. R. & Sons, Inc). U.S. Patent 3,780,059 (18th December, 1973). Dibenzoxazepines and Dibenzothiazepines.

92 H. L. Yale (Squibb E. R. & Sons, Inc) U.S. Patent 3,780,044 (18th December, 1973). 1-[3-(5,11-Dihydrodibenz[b,e][1,4]oxazepin-5-yl)propyl]phenylpiperidinols.

93 H. L. Yale and R. B. Petigara (Squibb E. R. & Sons, Inc) U.S. Patent 3,813,396 (28th May, 1974). 1,2-Dihydroquinobenzoxazepine[piperazinylalkyl]oximes.

94 H. L. Yale and J. Bernstein (Squibb E. R. & Sons, Inc.) U.S. Patent 3,796,725 (12th March, 1974). N-Oxides of 5-(aminoalkyl)-5,11-dihydrodibenzoxazepines and 5,11-dihydrodibenzothiazepines.

95 H. L. Yale and J. Bernstein (Squibb E. R. & Sons, Inc), U.S. Patent 3,723,463 (27th March, 1973). Dibenzoxazepines and dibenzothiazepines.

96 A. Attar, H. Wamhoff and F. Korte, Chem. Ber, 1973, 106, 3524. Heterocyclic Compounds from lactones, lactams and thiollactones. 16. Synthesis of heterocondensed pyrimidines from 4-chloro-5-acyl-pyrimidines.

97 D. H. Kim and A. A. Santilli (American Home Products Corporation), U.S. Patent 3,759,922 (18th September, 1973). Pyrimidino[5,4-c][1,5]benzoxazepin-5(11H)-ones and Intermediates.

98 H. L. Yale and J. Pluscec (Squibb. E. R. & Sons. Inc), German Offen 2,029,497 (28th January, 1971). Formamido[benzyloxy]- and -[benzylthio]-pyridines.

99 M. Nakanishi, T. Munakata, S. Setoguchi, S. Fukunari (Yoshitomi Pharm. Ind, Ltd), Japan Kokai 52,798 (24th July, 1973). Piperazine Derivatives.

100 S. Tanaka and K. Hashimoto (Eisai Co, Ltd), Japanese Patent 41,552 (8th December, 1971) Eight-membered Ring Compounds.

101 S. Tanaka, K. Hashimoto and H. Watanabe (Eisai Co. Ltd), Japan Kokai 52,789 (24th July, 1973). Polycyclic azocine Compounds.

102 S. Tanaka, and Y. Ogata, Yakugaku Zasshi, 1973, 93, 1003. Diphenyl ether Derivatives. VII. Synthesis of 3-chloro-dibenz(b,g)(1,5) oxazocine Derivatives.

103 S. Tanaka, K. Hashimoto, Yakugaku Zasshi, 1973, 93, 982. Diphenyl ether Derivatives. IV. Synthesis of Dibenz[b,g][1,5]oxazocines.

104 S. Tanaka and K. Hashimoto (Eisai Co. Ltd, Tokyo), Japanese Patent 11,108 (10th April, 1973). Oxazocine and thiazocine Derivatives.

105 H. L. Yale, F. Sowinskii and E. R. Spitzmiller, J. Heterocyclic Chem., 1972, 9, 899. Novel Polycyclic Heterocycles. VIII. 6,11-Dihydro-12H-dibenzo[b,f][1,4]thiazocines and their Derivatives.

106 H. L. Yale and E. R. Spitzmiller, J. Heterocyclic Chem., 1972, 9, 911. Novel Polycyclic Heterocycles. IX. Dibenz[b,f][1,4]oxazocin-11 (12H)-one, 6,11-dihydro-12H-dibenz[b,f][1,4]oxazocine and their Derivatives.

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