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The Synthesis of (±), (+) and (−) α-(3-Thiamorpholinyl)-benzhydrol, a New Selective Stimulant of the Central Nervous System

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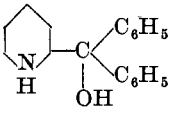
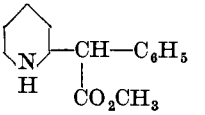
The discovery of the pronounced activity of α-(2-piperidyl)-benzhydrol (I) (pipradrol)* as a central nervous system (CNS) stimulant[1–3] created interest in piperidine derivatives as potential substitutes for the classical 2-phenethylamine drugs such as amphetamine and ephedrine. The cardiovascular effects of the latter class of central stimulants made it highly desirable to design new chemical structures with improved selectivity of action.[4]



(I)



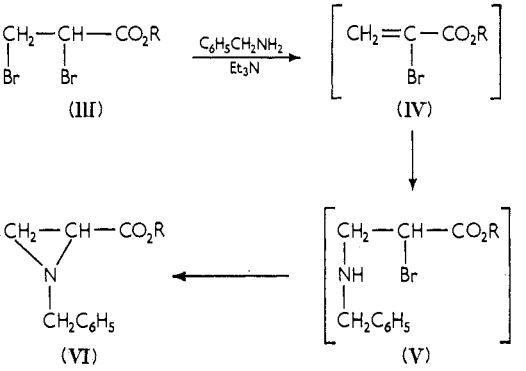
(II)

Along this line of research, methyl α-(2-piperidyl)-phenylacetate (methylphenidate) (II)† has also been recently proposed as a CNS stimulant[5, 6] and would appear to confirm the potentialities of piperidine derivatives in this respect.[7] The pharmacology of these drugs present several points of interest, the most striking being the selectivity of action which serves to establish that the central and peripheral actions of sympathomimetics can be dissociated. This suggested to us that a greater selectivity of action and a narrower spectrum of pharmacological activity might be achieved through appropriate chemical modification of the pipradrol molecule. An attractive modification consists in the introduction of a sulphide moiety in such a position that all of the important conformational properties of the pipradrol molecule are retained. In this manner, stimulant activity should also be retained, while the presence of a sulphide group should tend to

* Meratran ® † Ritalin ®

minimize toxicity by virtue of the marked susceptibility of sulphides to enzymatic attack in detoxification mechanisms. Moreover, the presence of a sulphide linkage in the drug might influence passage across the so-called 'blood–brain barrier' and lead to different distribution patterns at the brain level. On the basis of this reasoning, the title compound (X)* was chosen as a potentially useful CNS drug.

A survey of the chemical literature revealed that virtually no functionally substituted 1,4-thiamorpholines are known. This

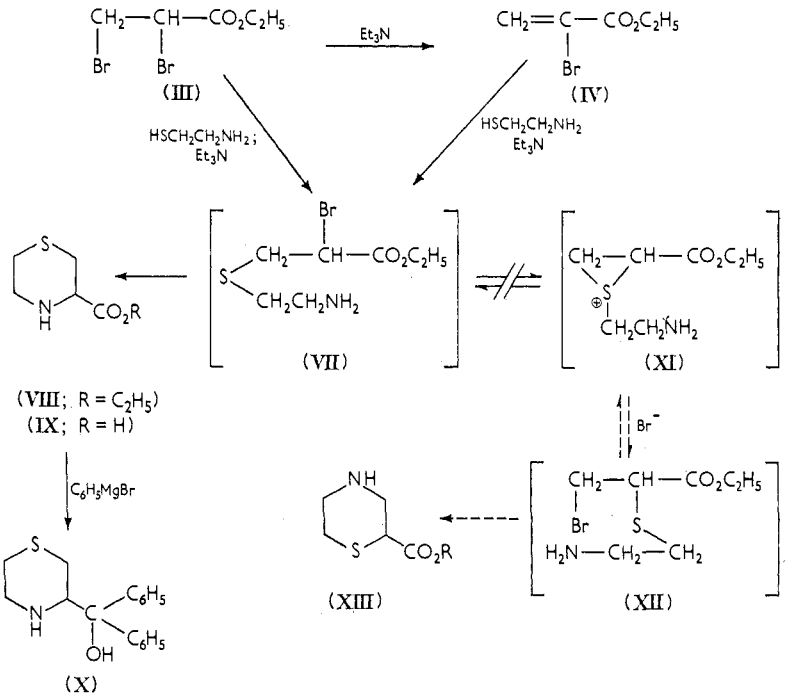


may be ascribed to a lack of practical and economical synthetic methods. The specific key intermediate required for the preparation of the title compound (X) is an ester of 1,4-thiamorpholine-3-carboxylic acid (VIII), a substance which has hitherto not been described. We realized initially that an obvious approach to this compound could use cysteine as a starting material. However, the high cost of the latter made it necessary to devise an alternative approach involving readily accessible and inexpensive materials. The reaction of ethyl 2,3-dibromopropionate (III) with 2-mercaptoethylamine was selected for study, as it appeared theoretically applicable to the preparation of the desired 1,4-thiamorpholine derivatives.

A reaction which has a bearing on the present problem was described by Stolberg, O'Neill and Wagner-Jauregg[8] and consists

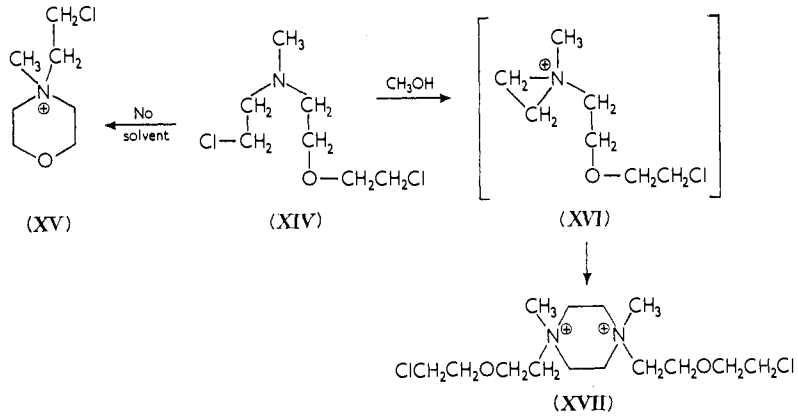
* B. Belleau, U.S. Pat. 2,921,935, Jan. 19, 1960.

in the formation of the aziridine carboxylate ester (VI) from benzylamine and methyl 2,3-dibromopropionate (III). Since the reaction could be carried out in the presence of triethylamine, it would appear that the initial step might involve the formation *in situ* of the corresponding α-bromoacrylic ester (IV) followed by 1,4-addition of benzylamine to give the intermediate (V). However, this possibility was not discussed by Wagner-Jauregg[8] and



it is pertinent to note that under the suggested reaction conditions, but with the omission of benzylamine, we obtained a high yield of ethyl α-bromoacrylate. Should the reaction be carried out in the presence of 2-mercaptoethylamine instead of benzylamine, 1,4-addition of the thiol group rather than the amino group to give the intermediate (VII) would readily be expected. This expectation is in keeping with the greater nucleophilicity of the sulphide anion as compared with that of certain amines[9] and also

agrees with previous observations on the reactivity of α-chloroacrylonitrile towards thiols.[10,11] Subsequent cyclization of the intermediate (VII) to the desired 1,4-thiamorpholine-3-carboxylate ester (VIII) should be straightforward. However, an important alternative path from intermediate (VII) can be discerned if the previous observations of Gundermann and Thomas[11] are



(XV) (XIV) (XVI) (XVII)

taken into consideration. These workers showed that when α-chloro-β-phenylmercaptopropionitrile is treated with ammonia it undergoes a rearrangement to α-phenylmercapto-β-aminopropionitrile. Undoubtedly, an ethylenesulphonium ion must be an intermediate in this rearrangement. Should such a rearrangement occur in the case of adduct (VII), there would result the isomeric 1,4-thiamorpholine-2-carboxylate ester (XIII). This is an interesting case of competing mechanisms where kinetic and thermodynamic factors come into play. The sulphide linkage in (VII) is presumably less nucleophilic than the amino group, thus favouring direct six-membered ring formation (VIII). However, the entropy of activation being much lower for three-membered ring formation,[12,13] the ethylenesulphonium intermediate (XI) should be favoured. This should be reflected in a higher frequency factor[14] for the formation of (XI) but since a three-membered transition state is more strained than a six-membered one,[15] direct formation of (VIII) should predominate.

Clearly, the mechanistic pathway might also be solvent dependent. An analogous case of competing mechanisms can be found in the behaviour of the dichloride (XIV) which cyclizes to the morpholinium ion (XV) in the absence of solvent, but to an intermediate ethylenimmonium ion (XVI) which dimerizes to the piperazinium ion (XVII) when dissolved in methanol.[16] It can be seen therefore that no safe prediction of the outcome of the reaction can be made.

When equimolar amounts of ethyl 2,3-dibromopropionate and 2-mercaptoethylamine were reacted in benzene–chloroform in the presence of two molar equivalents of triethylamine, a single carbethoxy-1,4-thiamorpholine was obtained in 60–65 per cent yield. The homogeneity of the product was ascertained by paper chromatography of the corresponding amino acid (IX) obtained by acid hydrolysis. A single sharp spot of R_f 0·60 was observed with the solvent system methanol, water and pyridine, and ninhydrin as the developing reagent. The amino ester reacted readily with phenylisocyanate to give a 90 per cent yield of a crystalline phenylhydantoin which exhibited the two characteristic bands of hydantoins at 1750 cm^{-1} and 1755 cm^{-1} in the infrared. These results conclusively eliminate the alternate structure (XIII) for the homogeneous reaction product, since only an α-amino acid structure can lead to hydantoin formation. It was noted above that the formation of (VII) as an intermediate presupposes the initial generation *in situ* of ethyl α-bromoacrylate (IV). To verify this point, the latter was prepared and reacted with 2-mercaptoethylamine under the same conditions that led to the 1,4-thiamorpholine ester (VIII). In agreement with expectations the same yield of the latter compound resulted, thus establishing the stepwise sequence III → IV. The identity of the material was ascertained by its infrared spectrum which was superimposable on that of authentic (VIII), prepared as described above.

To complete the synthesis of the title compound (X), it remained only to react the ester (VIII) with phenylmagnesium bromide, a reaction which proceeded smoothly in good yield to give an easily crystallizable product (X). In view of the marked difference in pharmacological activity between the enantiomers of a variety of CNS stimulants, it was of interest to resolve the racemate (X).

A convenient separation was achieved by fractional crystallization of the dibenzoyl tartrate salt of the base from acetone. Regeneration of the resolved base gave the (+) isomer, $[\alpha]_D = +75°$. The (−) isomer was obtained by crystallization from isopropyl alcohol.

Pharmacology

The racemic base (X) as well as the optical enantiomers were tested for CNS stimulating activity by Dr. M. Pindell, Director of Pharmacological Research, Bristol Laboratories Inc. A preliminary account of his results has already been published.[17] It will suffice to reproduce here only the pharmacological constants: LD_{50} (mice) (i.p.) 361 mg/kg, 127 mg/kg and 292 mg/kg, for racemic (X), (+) (X) and (−) (X) respectively. The drugs exhibited no convulsant properties even above toxic levels. They produced a marked increase in motor activity (mice) at a minimum dose level (i.p.) of 10 mg/kg, 5 mg/kg, and 30 mg/kg for the racemic (X), the (+) isomer and (−) isomer respectively. They were all administered as aqueous solutions of their crystalline hydrochlorides. The observed high therapeutic index (36) and the virtual absence of undesirable side effects warrants clinical evaluation. Such studies are now under way.

Experimental*

Starting Materials. The ethyl 2,3-dibromopropionate was prepared from ethyl acrylate as described elsewhere.[11] The 2-mercaptoethylamine was purchased from Evans Chemetics Inc., Waterloo, N.Y. It is supplied as the hydrochloride which was converted to the free base by treatment in absolute methanol with an equimolar amount of sodium methoxide. The filtered methanol solution was then evaporated to dryness *in vacuo* under a nitrogen atmosphere. The crystalline residual base was used as such in subsequent operations. All the solvents were redistilled before use.

* All melting points and boiling points are uncorrected. Microanalyses by Midwest Microlab Inc. The infrared spectra were recorded with a Perkin-Elmer Infracord instrument.

Ethyl α-bromoacrylate. To a solution of ethyl 2,3-dibromopropionate (0·44 mole) in benzene (500 ml) was added 44 g (0·44 mole) of triethylamine. The mixture was allowed to stand for 1 h and then heated under reflux for 1 h. The salt was filtered off and the filtrate distilled *in vacuo* over a trace of hydroquinone to give 70 g of ethyl α-bromoacrylate, b.p. 52°/14 mm (reported:[18] 55–65°/12 mm).

Ethyl 1,4-thiamorpholine-3-carboxylate (VIII). A warm solution of 2-mecaptoethylamine (69 g) and triethylamine (180 g) in chloroform (500 ml) was added portionwise as rapidly as possible to a stirred solution of ethyl 2,3-dibromopropionate (234 g) in a 5 : 3 mixture of benzene and chloroform (800 ml). The rate of addition was such that vigorous reflux of the solvent was maintained. After the addition was completed, the mixture was stirred for 5–6 h at room temperature, then the precipitated salt removed by filtration. The filtrate was evaporated *in vacuo* and the residue distilled at 114–118°/8 mm to give 100 g of colourless ethyl 1,4-thiamorpholine-3-carboxylate (VIII).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: N, 8·00; S, 18·2. Found: N, 7·91; S, 18·3.

1,4-Thiamorpholine-3-carboxylic acid hydrochloride (IX). Five grams of the preceding ester (VIII) were dissolved in conc. hydrochloric acid (50 ml) and the mixture heated under reflux for 4 h. The solution was evaporated *in vacuo* to give a crystalline mass which when crystallized from ethanol melted at 201–203° (d.).

Anal. Calcd. for $C_5H_{10}ClNO_2S$: C, 65·39; H, 5·45; N, 7·62. Found: C, 65·60; H, 5·55; N, 7·44.

A sample of the crude crystalline mass was subjected to descending chromatography on paper using the solvent system 80 methanol, 20 water and 4 pyridine. A single sharp purple spot of R_f 0·60 was revealed with the usual ninhydrin reagent.

Phenyl hydantoin. Equimolar amounts of the above ester (VIII) and phenylisocyanate were heated briefly on the steam-bath and boiled with 15 per cent hydrochloric acid for 30 min. The crystalline mass that separated on cooling was recrystallized from ethanol to give colourless needles, m.p. 119–120°. Yield, 90 per cent.

Anal. Calcd. for $C_{12}H_{12}NO_2S$: C, 58·06; H, 4·84. Found: C, 58·20; H, 4·80.

The infrared spectrum, determined in chloroform, exhibited two strong bands at 1700 cm^{-1} and 1755 cm^{-1}.

Ethyl 1,4-thiamorpholine-3-carboxylate (VIII) from ethyl α-bromoacrylate. Using the proportions of reagents and solvents as described above for the preparation of (VIII) but reducing by half the amount of triethylamine and substituting ethyl α-bromoacrylate for ethyl 2,3-dibromopropionate, the same thiamorpholine ester (VIII) was produced in a similar yield; their infrared spectra were superimposable.

(±) *α-(3-Thiamorpholinyl)-benzhydrol* (*X*). A solution of phenylmagnesium bromide in dry ether (1500 ml) was prepared from bromobenzene (283 g) and magnesium turnings (43 g). While stirring and cooling, a solution of ethyl 1,4-thiamorpholine-3-carboxylate (VIII) (90 g) in dry ether (100 ml) was added dropwise over a period of 1–2 h. The mixture was heated under reflux for 15 h, cooled in ice and carefully decomposed with a solution of 250 g of ammonium chloride in one litre of water. Prolonged vigorous stirring was required to decompose the insoluble gum. The precipitated solid was collected by filtration, and the ether layer separated and evaporated *in vacuo* to yield a crystalline residue. The solid fractions were combined, dissolved in chloroform and the solution was washed with dilute ammonium chloride solution. The chloroform was dried and evaporated to incipient crystallization. One volume of ether was added, the mixture chilled and the crystals were collected. The product was pure and had m.p. 164–165°, unchanged by crystallization from chloroform–ether. The yield amounted to 87 g (60 per cent).

Anal. Calcd. for $C_{17}H_{19}NOS$: N, 4·91; S, 11·2. Found: N, 5·04; S, 11·0.

The *hydrochloride* was prepared in quantitative yield by treating a warm chloroform solution of the base with a methanolic solution of hydrogen chloride. On cooling, colourless needles separated, m.p. 248–250° (d.).

Anal. Calcd. for $C_{17}H_{20}ClNOS$: Cl, 11·0; N, 4·35. Found: Cl, 11·0; N, 4·48.

Resolution of α-(3-thiamorpholinyl)-benzhydrol (*X*). A solution of the racemic base (18·3 g) in a minimum volume of hot chloroform was treated with dibenzoyl tartaric acid (23 g). The solvent was removed *in vacuo* and the residue digested with acetone (200

ml) until crystallization began. The mixture was refrigerated for 24 h and the crystalline mass collected: yield, 11 g. An analytical sample of the salt was obtained after three recrystallizations from acetone. It was obtained as fine colourless needles, m.p. 154–156°, not altered by further recrystallizations.

Anal. Calcd. for $C_{35}H_{33}NO_9S$: N, 2·17; S, 4·97. Found: N, 2·02; S, 4·83.

The preceding 11 g of crude crystalline salt was decomposed with dilute alkali. There was obtained 5·30 g of colourless rods of (−) (X), m.p. 95–96°. Recrystallization from hexane raised the m.p. to 97–98°; $[\alpha]_D^{22}$ −75° ($c = 2$, $CHCl_3$).

Anal. Calcd. for $C_{17}H_{19}NOS$: N, 4·91; S, 11·2. Found: N, 5·04; S, 11·4.

The mother liquor from the first acetone filtrate above was concentrated *in vacuo* and some more crystalline material removed by filtration. The filtrate was diluted with isopropyl alcohol whereupon crystallization commenced. The mixture was chilled for 24 h and the crystals were collected. On crystallization from isopropyl alcohol, colourless needles, m.p. 135–140°, were obtained; yield, 17 g. This crude salt which was enriched in the *dextro*-isomer was decomposed with aqueous base as in the case of the *laevo*-isomer. This gave a crystalline mass which was digested with hot hexane, and the mixture was filtered while hot. The hexane-insoluble crystals proved to be racemic α-(3-thiamorpholinyl)-benzhydrol, m.p. 164–165°. On cooling, the filtrate deposited 3·0 g of crystals, m.p. 96–98°. Recrystallization from hexane gave colourless rods, m.p. 97–98°; $[\alpha]_D^{23}$ +75° ($c = 2$, $CHCl_3$).

Anal. Calcd. for $C_{17}H_{19}NOS$: N, 4·91; S, 11·2. Found: N, 4·97; S, 11·3.

A 50 : 50 mixture of the two enantiomers had m.p. 164–165°, undepressed by further admixture with racemic (X) of m.p. 164–165°.

The *hydrochlorides* of both optical isomers were prepared by the above procedure. Both had m.p. 245° (d.).

Summary. A new convenient synthesis of a functionally substituted 1,4-thiamorpholine is described. The latter heterocycle is suggested as an advantageous substitute for the piperidine ring of certain central nervous system stimulants. The reaction of 2-mercaptoethylamine with ethyl

2,3-dibromopropionate gave ethyl 1,4-thiamorpholine-3-carboxylate in good yield. The mechanism of the reactions involved is discussed. Treatment of the latter ester with phenylmagnesium bromide gave the corresponding benzhydrol derivative which was resolved into its optically active components by crystallization as the dibenzoyl tartrate salt. The racemic α-(3-thiamorpholinyl)-benzydrol as well as its enantiomers proved to be effective CNS stimulants of low toxicity and devoid of convulsant properties.

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