TRIMETHOXYBENZENE DERIVATIVES FROM INDIGENOUS DRUGS*

By

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Our earlier work on the isolation of active principle from the rhizomes of well known indigenous plant (1, 26) *Acorus calamus Linn.* (Ugragandha, Bach) led us to investigate its volatile (4, 7, 8, 9, 18, 19, 20, 23, 24) which showed considerable pharmacological activity. Subsequent work on the fractionation (2) of the active substance from the volatile oil, by gas phase chromatography showed the presence of at least two components, (3, 6) which were isolated in pure state i.e. α-asarone and β-asarone (Fig 1) which are trans-and cis-isomers, respectively, of 2, 4 , 5—trimethoxy-1-propenyl benzene.

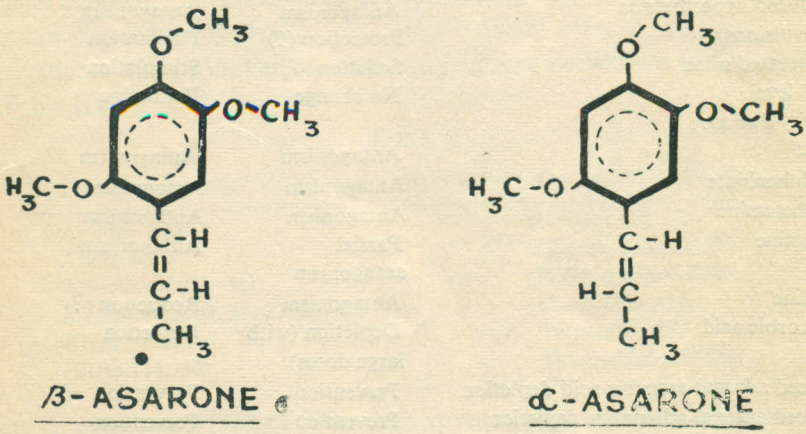

Fig 1

Asarone was found to possess very potent psychotropic properties (13, 15, 16). Asarone possessed a number of actions similar to reserpine and chlorpromazine (Table I). Besides the drug increased the number of shocks accepted by the animals in conflict neurosis (5).

But unlike reserpine it protected animals from electric shock (11) and metrazol induced convulsions and failed to cause release of 5—HT from the brain. The drug also prevented the depletion of adrenal ascorbic acid in rats subjected to cold stress (12).

These findings drew our attention to other naturally occurring drugs having a trimethoxybenzene function in their molecule. Of these at least, two i.e. reserpine and mescaline (Fig 2) are worth mentioning.

An important question that arises out of this study is that two fairly similar chemical structures i.e. asarone and mescaline have not only so different but quite opposite types of

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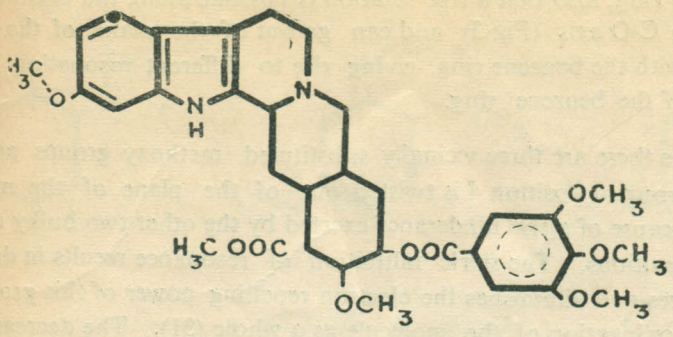
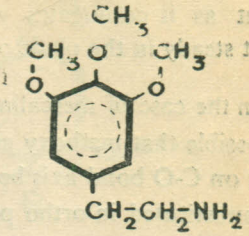
TABLE I

Comparison of pharmacological actions of asarone with reserpine and chlorpromazine.

Parameter	*Asarone*	*Reserpine*	*Chlorpromaz*
1. Spontaneous activity in rats, mice and monkeys	Reduction	Reduction	Reduction
2. Barbiturate hypnosis	Potentiation	Potentiation	Potentiation
3. Behaviour of cats, monkeys	Taming	Taming	Taming
4. Fighting behaviour of mice	Suppression	Suppression	Suppression
5. Amphetamine toxicity in aggregated mice	Protection	Protection	Protection
6. Conditioned avoidance response	Specific blockade	Specific blockade	Specific blockade
7. Choice discrimination behaviour	Anxiety reduction	Anxiety reduction	Anxiety reduction
8. Rectal temperature	Hypothermia	Hypothermia	Hypothermia
9. LSD-25 induced hyperthermia	Antagonism	Antagonism	Antagonism
10. Electro-convulsions	Protection (?)	Facilitation	Facilitation(?
11. Iproniazid-treated mice	Sedation	Stimulation	Sedation
12. Brain 5-HT level	No change	Reduction	No change
13. Hyperactivity due to:			
(a) LSD-25	Antagonism	Antagonism	Antagonism
(b) Methylphenidate	Antagonism	Antagonism	Antagonism
(c) d-Amphetamine	Antagonism	Antagonism	Antagonism
(d) Imipramine	Partial antagonism	Antagonism	—
(e) Mescaline	Antagonism	Reduction (?)	Antagonism
14. Adrenal ascorbic acid	Depletion (with large doses)	Depletion	Depletion
15. Stress-induced adrenal ascorbic acid depletion	Prevention	Prevention	Prevention
16. Stress-induced adrenal adrenaline depletion	Prevention	Prevention	Prevention
17. Stress-induced brain neurohormonal changes	Prevention	Prevention	Prevention
18. Tremorine-induced tremors.	Partial protection	Partial protection	Partial protection
19. α-Methyltyrosine treated animals:			
(a) Pentobarbitone hypnosis	Further potentiation	Further potentiation	Further potentiation
(b) Conditioned avoidance response.	-do-	-do-	-do-
(c) Rectal temperature	-do-	-do-	-do-
20. Blood pressure	Hypotension	Hypotension	Hypotension
21. Smooth muscle contractions induced by:			
(a) Acetylcholine	Antagonism	Antagonism	Antagonism
(b) Histamine	Antagonism	—	Antagonism
(c) 5-hydroxytryptamine	Antagonism	Antagonism (?)	Antagonism



RESERPINE



MESCALINE

Fig 2

pharmacological actions. This intriguing phenomenon prompted us to explain the difference on the basis of molecular orbital theory.

To investigate this a number of trimethoxybenzene derivatives were synthesized in our laboratory (Table II).

TABLE II

Trimethoxybenzene derivatives synthesised in the author's laboratory.

Amides (30)	Hydantoins (28)
Anilides (30)	Hydrocarbons (17)
Azlactones (27, 31)	Nitro-styrenes (29)
Benzamides (10, 17, 22, 25, 32)	Oxazolines (27)
Cinnamides (17, 29)	Tetrazoles (27)
Esters (14, 30)	Thiohydantoins (28)

Pharmacological screening of these derivatives revealed that the position of the methoxy group in the benzene ring as well as unsaturation in the side chain played an important role in the manifestation of CNS depressant activity (17).

The recent electron defraction studies and dipole moment data (21) have shown that a methoxy group, attached to the benzene ring is not straight like -O-CH_3 but the methyl group is deviated at an angle of 72° from the axis of the C-O bond between the oxygen of methoxy group

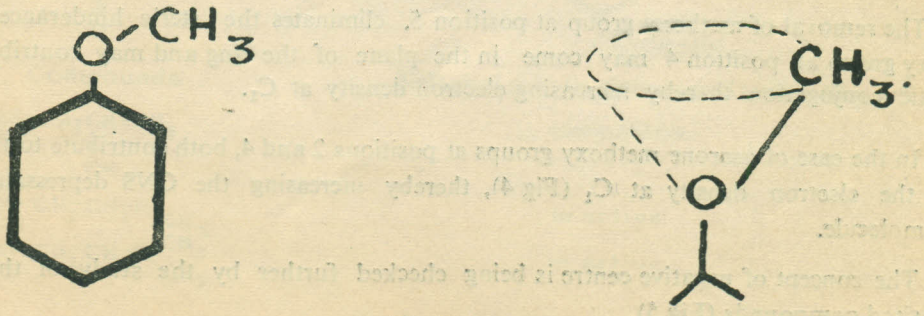


Fig 3

and the carbon of the benzene ring; also that a free rotation is possible along the C-O bond and so methyl group can rotate on C-O axis (Fig 3) and can go out of the plane of the benzene ring, but as it conjugates with the benzene ring, giving rise to different resonating hybrids, it is kept steady in the plane of the benzene ring.

In the case of mescaline there are three vicinally substituted methoxy groups and it is quite possible that methoxy group at position 4 is twisted out of the plane of the molecule, rotating on C-O bond axis because of steric hinderance exerted by the other two bulky methoxy groups substituted in ortho positions. The steric inhibition of resonance results in decreased number of resonating structures and diminishes the electron repelling power of this groups and also the degree of aromatic conjugation of the molecule as a whole (31). The decrease in the aromatic coujugation also results in decrease of the electron density at C_1 (10).

The increase in the electron density at C_1 is probably directly proportional to the CNS depressant potency This view is further supported by the fact that removal of methoxy group at position 5 in mescaline results in 50% loss of the stimulant activity (33).

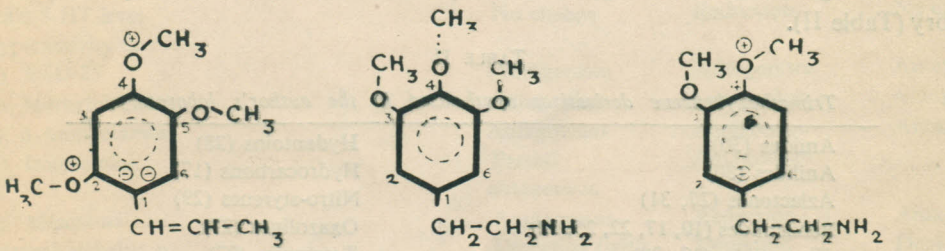


Fig 4

(In Fig 4 two -ve signs only represent comparative increase in the electron density at C_1, they are not true negative charges and the total value of these charges is only a fraction of true electron charge).

The removal of methoxy group at position 5, eliminates the steric hinderance and then methoxy group at position 4 may come in the plane of the ring and may contribute to the aromatic conjugation thereby increasing electron density at C_1.

In the case of asarone methoxy groups at positions 2 and 4, both contribute to the increase in the electron density at C_1 (Fig 4), thereby increasing the CNS depressant activity of the molecule.

The concept of negative centre is being checked further by the study of the recently synthesised compounds (Fig 5).

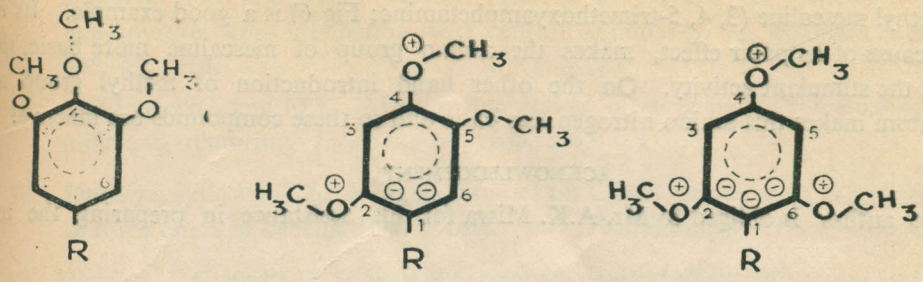


Fig 5

3, 4, 5-*trimenthoxvebnzene derivatives* (*Compannd I*) | 2, 4, 5-*trimenthoxybenzene derivatives* (*Compound II*) | 2, 4, 6-*trimenthoxybenzene derivatives* (*Compouud III*)

If this hypothesis is correct, compound III should possess highest CNS depressant activity, as in this compound all the three methoxy groups contribute to the increase in the electron density at C_1. (This is represented by three negative signs in the figure).

There are certain factors other than conjugation like hyperconjugation due to the double bond and—I effect due to the methyl group in the side chain (in asarone) which might also play some role. But these effects would not be very significant.

Apart from the these considerations, the nature of side chain is also responsible for CNS depressant activity. It was observed in this laboratory (17) that increase in the length of side chain reduces CNS depressant activity whereas branching in the side chain increases CNS depressant activity. This can be explained on the basis of inductomeric effect.

With the increase in the length of side chain the inductomeric effect of certain specific groups goes on decreasing and it cannot conjugate with the trimethoxybenzene nucleus, whereas, branching of the side chain increases the polarity of the molecule, thereby contributing to the inductomeric effect of these groups present in the side chain.

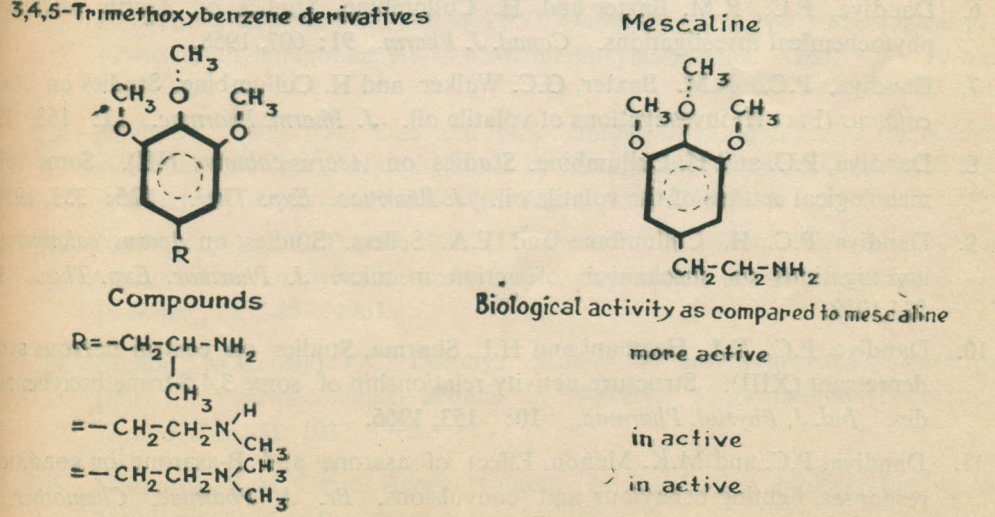


Fig 6

Methyl mescaline (3, 4, 5-trimethoxyamphetamine; Fig 6) is a good example. Its meth group, because of its polar effect, makes the amino group of mescaline more basic, there increasing the stimulant activity. On the other hand introduction of methyl group at t nitrogen atom makes this amino nitrogen less basic and so these compounds are inactive.

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REFERENCES

1. Agarwal, S.L., P.C. Dandiya, K.P. Singh and R.B. Arora. A note on the prelim nary studies of certain pharmacological actions of *Acorus calamus Linn.* *J. A Pharm. Ass.*, **45**: 655, 1956.
2. Baxter, R.M., P.C. Dandiya, S.I. Kandel, A. Okany and G.C. Walker. Separatio of hypnotic potentiating principles from the essential oil of *Acorus calamus Lin* of *Indian origin* by *liquid-gas chromatography.* *Nature* (*London*), **185**: 466, 1960.
3. Baxter, R.M., M.C. Fan and S.I. Kandel. Cis-trans isomers of asarone, their liquid gas chromatographic behaviour and that of certain other propenyl phenolether *Canad. J. Chem.*, **40**: 154. 1962.
4. Bose, B.C., R. Vijayvargia, A.Q. Saifi and S.K. Sharma. Some aspects of chemica and pharmacological studies of *Acorus calamus Linn.* *J. Am. Pharm. Ass.*, 49 32, 1960.
5. Chak, I.M. and J.N. Sharma. Effect of asarone on experimentally induced conflic neurosis in rats. *Ind. J. Exp. Biol.*, **3**: 252, 1965.
6. Dandiya, P.C., R.M. Baxter and H. Cullumbine. Studies on *Acorus calamus* (I phytochemical investigations. *Canad. J. Pharm.*, **91**: 607, 1958.
7. Dandiya, P.C., R.M. Baxter, G.C. Walker and H. Cullumbine. Studies on *Acoru calamus* (Part II) investigations of volatile oil. *J. Pharm. Pharmac.*, **11**: 163, 195
8. Dandiya, P.C. and H. Cullumbine. Studies on *Acorus calnmus* (III). Some phar macological actions of the volatile oil. *J. Pharmac. Exp. Ther.*, **125**: 353, 1959.
9. Dandiya, P.C., H. Cullumbine and E.A. Sellers. Studies on *Acorus calamus* (IV investigations on mechanism of action in mice. *J. Pharmac. Exp. Ther.*, 126 334,1959.
10. Dandiya, P.C., K.L. Hemnani and H.L. Sharma, Studies on central nervous syste depressant (XIII). Structure activity relationship of some 3,4,5-trimethoxybenzami des. *Ind. J. Physiol. Pharmac.*, **10**: 153, 1966.
11. Dandiya, P.C.,and M.K. Menon. Effect of asarone and B-asarone on conditioned responses, fighting behaviour and convulsions. *Br. J. Pharmac. Chemother.*, 20 436, 1963.

12. Dandiya, P.C. and M.K. Menon. Actions of asarone on behaviour stress and hyperpyrexia and interaction with central stimulants. *J. Pharmac. Exp. Ther.*, **145**: 42, 1964.

13. Dandiya, P.C. and M.K. Menon. Interaction of asarone with mescaline, amphetamine and tremorine. *Life Sci.*, **4**: 1635, 1965.

14. Dandiya, P.C. and S.S. Rungta. Studies on C.N.S. depressant (VI): C.N.S. actions of three esters of benzilic acid. *Arch. Int. Pharmacodyn. Ther.*, **149**: 493, 1964.

15. Dandiya, P.C. and J.D. Sharma. Pharmacodynamical effects of *asarone* and *B-asarone*. *Nature (London)*, **192**: 1299, 1961.

16. Dandiya, P.C. and J.D. Sharma. Studies on Acorus calamus (V): pharmacological actions of asarone and B-asarone on C.N.S. *Ind. J. Med. Res.*, **50**: 46, 1962.

17. Dandiya, P.C., P.K. Sharma and M.K. Menon. Studies on central nervous system depressants (IV). Structure activity relationship of some locally synthesised trimethoxybenzene derivatives. *Ind. J. Med. Res.*, **50**: 750, 1962.

18. Das, P,K., C.L. Malhotra and N.S. Dhalla. Spasmolytic activity of asarone and essential oil of *Acorus calamus Linn. Arch. Int. Pharmacodyn. Ther.*, **135**: 167, 1962.

19. Dhalla, N.S. and I.C. Bhattacharya. Further studies on neuro-pharmacological action of Acorus oil. *Arch. Int. Pharmacodyn. Ther.*, **172**: 356, 1968.

20 Dhalla, N.S., C.L. Malhotra and M.S. Sastry. Effect of Acorus oil *in vitro* on the respiration of rat brain. *J. Pharm. Sci.*, **50**: 580, 1961.

21. Ferguson, L.N. The modern structural theory of organic chemistry. *Prentice-Hall of India (Private) Ltd. New Delhi*, 1966, p. 204.

22. Hemnani, K.L., M.K. Menon and P.C. Dandiya. Some pharmacological actions of N'—(4'diethylaminophenyl)—3,4,5-trimethoxybenzamide. *Ind. J. Pharm.*, **28**: 292, 1966.

23. Malhotra, C.L., P.K. Das and N.S. Dhalla. Investigations on the mechanism of potentiation of barbiturate hypnosis by hersaponin, Acorus oil, reserpine and chlorpromazine. *Arch. Int. Phrmacodyn. Ther.*, **138**: 537, 1962.

24. Malhotra, C.L., K. Prasad, N.S. Dhalla and P. K. Das. Effect of hersaponin and Acorus oil on noradrenaline and-5 hydroxytryptamine content of rat brain. *J. Pharm. Pharmac.*, **13**: 447, 1961.

25. Menon, M.K. and P.C. Dandiya. Studies on central nervous system depressants (Part V): Pharmacological actions of N-acetyl 3,4,5-trimethoxybenzamide. *Ind. J. Med. Res.*, **51**: 1037, 1963.

26. Nadkarni, K.M. Use of Acorus calamus in the Indian Materia Medica. ed. A.K. Nadkarni, *Popular Book Depot, Bombay* 1954.

27. Satish Chandra. Thesis submitted for Ph. D. Rajasthan University (1969).

28. Satish Chandra and P.C. Dandiya. Central nervous system depressants (XVI Some newer hydantoins and thiohydantoins. *Canad. J. Chem.*, **47** : 3704, 196

29. Satish Chandra, P.K. Sharma, R.R. Varma and P.C. Dandiya. Studies on N.S. depressants (XIV) : Structure activity relationship of some 2, 4, 5-trimet oxy styrene and cinnamic acid derivatives. *Ind. J. Pharm.*, **31** : 91, 1969.

30. Sharma, P.K., P.C. Dandiya, B.C. Bose and R. Vijayvargiya. Studies on centr nervous system depressants (XI) : Structure activity relationship of some trimeth xybenzene amides, esters, anilides and tetrazoles. *Ind. J. Med. Res.*, **53** : 119 1965.

31. Sharma, P.K., M.K. Menon and P.C. Dandiya. Central nervous system depres ants (VIII) : Structure activity relationship of some new azlactones. *J. Pharm Sci.*, **53**: 1055, 1964.

32. Sogani, S.K. and P.C. Dandiya. Some 3, 4, 5-trimethoxy substituted benzamide *J. Med Chem.*, **8**: 139, 1965.

33. Smythies, J.R. and C.K. Levy. The comparative psychopharmacology of some me scaline analogues *J. Ment. Sci.*, **106**: 531, 1960.