completely saturated in the aqueous phase. The polyoxyethylene signal from the aqueous phase disappears at about 5% phenol, indicating that little POEPOP remains in the aqueous phase.

The relatively large shifts shown in Fig 2c and d indicate the presence of micelles in POEPOP–phenol–water systems. This is further supported by the magnitude of the shifts of the phenol ring-proton signals (Fig. 2a and b) which compares with that of the corresponding phenol–cetomacrogol systems, whereas in phenol–macrogol systems, where the aromatic rings are essentially in an aqueous environment, a very small shift is observed.

Significant broadening of both polyoxyethylene methylene and the polyoxypropylene methyl peaks upon the addition of phenol to POEPOP in water is also indicative of micelle formation; the polyoxyethylene peaks (but not polyoxypropylene) also split.

These micelles need not necessarily be aggregates of polymer molecules but could consist of one molecule with the polyoxyethylene chains rolled around the polyoxypropylene region.

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Apomorphine and its dopamine-like action

Observations published a few months ago (Pinder, Buxton & Green, 1971) demonstrating the low dopamine-like potency of aporphine, call for some comment on the problem that has arisen in the relation between apomorphine and dopamine effects. From molecular orbital calculations on dopamine using the extended Hückel theory (Kier & Truitt, 1970) it has been concluded that a *trans* conformation is absent and that only the two *gauche* conformers are significantly populated (Fig. 1A). In consequence Kier & Truitt postulated that an important part of the apomorphine molecule in its interaction with dopamine receptors is the tetrahydroisoquinoline moiety (the combination of *N* with phenyl ring *a* in Fig. 1B). Our calculations* and those of Bustard & Egan (1971) using the extended Hückel theory showed that, in contrast to Kier & Truitt's findings, the *trans* conformation was slightly preferred to the *gauche* conformers. Additional evidence was obtained by Bustard & Egan from potential energy functions and nmr spectroscopy.

In our opinion, it may now be readily assumed that Kier & Truitt's view is conformationally incorrect; hence Pinder, Buxton & Green rightly postulate that, when allowance is made for the low potency of aporphine, apomorphine in producing dopamine-like effects acts in a way which intimately involves the dihydroxytetrahydroaminonaphthalene moiety (the combination of *N* with phenyl ring *b* in Fig. 1B). Fig. 2 shows the Newman projections of the three low-energy dopamine conformers.

* To be published. We have found that rotation of 30° about the phenyl — C_1 axis in the $\theta_{c-c-} = 300°$ conformer did not reveal new conformations of low energy.

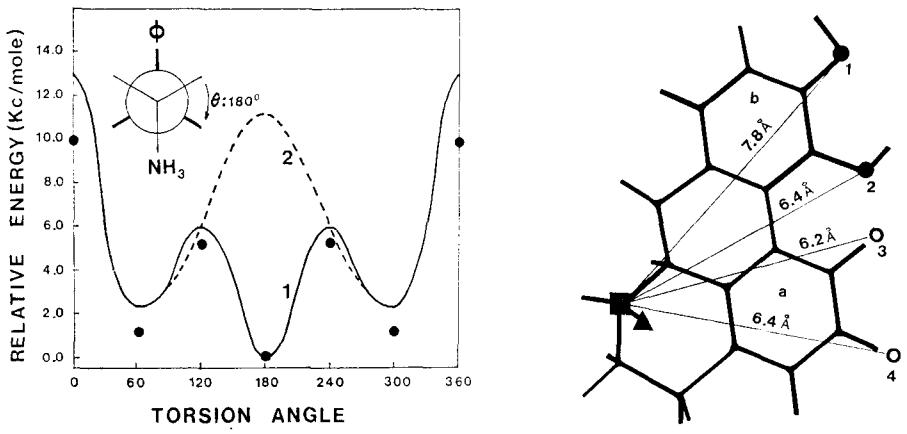

FIG. 1A. Internal energy, calculated by EHT, plotted as a function of torsion angle. Curve 1: Bustard & Egan. Curve 2: Kier & Truitt. Bold-type points represent our energy calculations performed by using extended Hückel theory with slightly differing parameters (details will be published elsewhere). B. Dreiding model projection of apomorphine using the technique described by McEachern & Lehmann (1970). ■: nitrogen ▲: CH_3. (1) and (2): oxygen; (3) and (4): locations of dopamine oxygen atoms if this structure in an almost *gauche* form were projected on top of the apomorphine molecule.

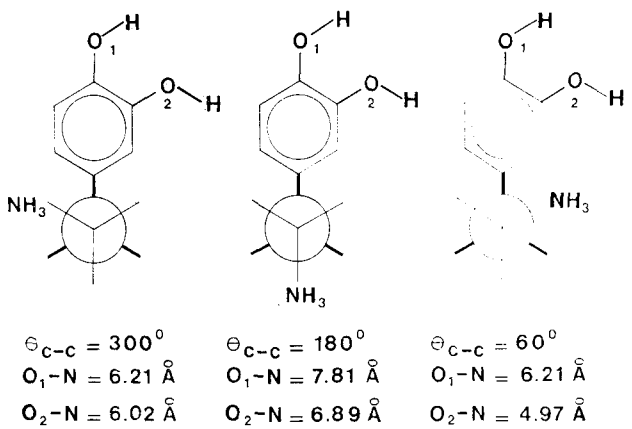

FIG. 2. Newman projections of three dopamine conformers: left and right *gauche*, middle *trans*.

In the *trans* conformation ($\theta_{C-C} = 180°$) the $O_1 - N$ distance (7·81 Å) is identical to the $O_1 - N$ distance in apomorphine (7·8 Å). Bearing in mind that in the extended Hückel theory repulsion interactions are strongly exaggerated and that the energy barrier as calculated by Bustard & Egan (van der Waals repulsion interaction) is low (3·3 Kcal/mol; c. f. 2·7 Kcal/mol for ethane) we are inclined to conclude that an O_2-N distance in the rigid apomorphine molecule can be simulated by both *gauche* conformers of dopamine.

Until now the general idea has been that an interaction of the two dopamine-like structures—apomorphine and dopamine—with the same receptor is unlikely for conformational reasons. Our conclusion is that this idea has to be rejected. The striking agreement between the two key-distances in either structure justifies the hypothesis that these OH-groups represent necessary charge-centres.

Supporting evidence for the necessity of these OH-groups is provided by the ob-

servations that 11-hydroxy aporphine is a weaker dopamine-like agent than is apomorphine (Granchelli, Neumeyer & others, 1971) and that 10-hydroxy-11-methoxyaporphine and 11-hydroxy-10-methoxyaporphine have little dopamine-like activity (Cannon, Smith & others, 1972).

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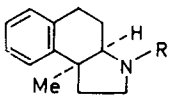
The synthesis and analgesic and cns-suppressant activities of 2-amino-, 2-methylamino-, and 2-dimethylamino-1,1-dimethyltetralin hydrochlorides

Recently a series of 3-amino-1,1-dimethyltetralins (Martin, Parulkar & others, 1969) and three compounds having structures (I, R=H, Me and CH_2—CH=CMe_2) (Harper & Raines, 1969) have been synthesized as potential analgesic agents. Although analgesic evaluation of the latter three compounds was not reported [subsequent to the completion of this present work, it has been brought to our attention by Dr. D. C. Bishop that these compounds do not possess analgesic activity], 1,1-dimethyl-3-dimethylaminotetralin (II, R = H, R′ = NMe_2) possessed an analgesic activity 2·5 times that of codeine (Martin & others, 1969). In view of this, and since compounds of type I possess a 2-aminotetralin moiety with a quarternary carbon atom at position 1, we have synthesized and pharmacologically evaluated the title compounds.



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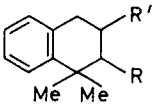

II

1,1-Dimethyl-2-tetralone, prepared from 2-tetralone (Soffer, Bellis & others, 1963) using two successive 1-methylations (Stork, Brizzolara & others, 1963; Harper & Raines, 1969) was converted into the oxime, colourless prisms from ethanol, m.p. 99–100°, by reaction with hydroxylamine hydrochloride in the presence of dry pyridine. Upon reduction with lithium aluminium hydride in ethereal solution the oxime afforded 2-amino-1,1-dimethyltetralin (II, R=NH_2, R′=H), a yellow oil. This was *N*-formylated by reaction with methyl formate at 100° for 24 h and the product (II, R=NH—CHO, R′=H) was reduced with lithium aluminium hydride in ethereal solution to give 1,1-dimethyl-2-methylaminotetralin (II, R=NHMe, R′=H), a brown oil. This monomethylamino derivative was also prepared directly from 1,1-dimethyl-2-tetralone by reaction with *N*-methylformamide in the presence of formic acid (for an analogous reaction with 3-tetralones see Martin & others, 1969). *N*-Methylation with formaldehyde-formic acid (Clark, Gillespie & others, 1933)