Steric Considerations on the Chemical Structure and Physiological Activity of Methadone and Related Compounds

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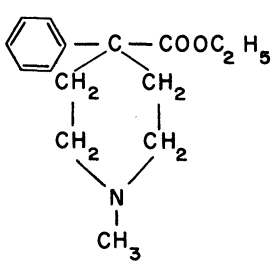
THE DISCOVERY, in 1939, of the morphine-like physiological action (*1*) of meperidine (γ-phenyl-γ-carbethoxy-*N*-methylpiperidine) (I) focused attention on the *N*-methylpiperidine grouping as the essential fragment of the morphine molecule (II), rather than the phenanthrene or dibenzofurane groupings which had been favored earlier. In fact, with one exception, all morphine substitutes in clinical use today are derivatives of γ-phenyl-*N*-methylpiperidine. The exception is methadone (III), which like the other morphine-type analgesics, contains a benzene ring attached to a tertiary nitrogen but, unlike the others, is an open-chain amine rather than a piperidine derivative. This difference in structure has made it impossible to correlate the analgesic activity of these compounds with any definite structural feature.

I



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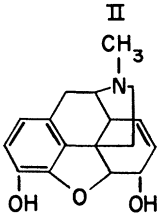

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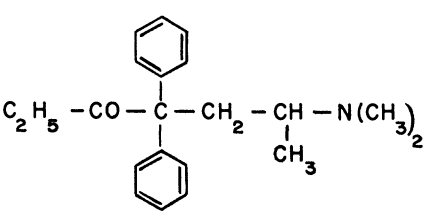

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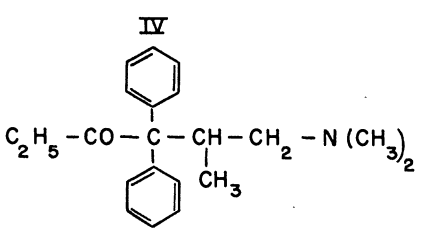
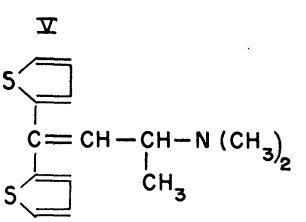
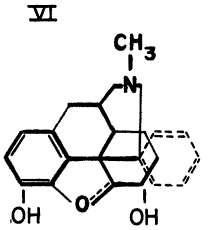


V



VI



Besides methadone itself, many of its analogues and derivatives have been studied, some of which show appreciable analgesic action. Thus isomethadone (IV) is only somewhat less active than methadone (*2*) while the activity is lost when the carbon chain between the quaternary carbon and the nitrogen is lengthened or shortened (*3*) or when one benzene ring is moved to the neighboring carbon atom (*4*) or is replaced by other groups such as benzyl or allyl (*5*). On the other hand, replacement of the carbonyl group of methadone by a sulfo group yields a highly active compound (*6*). Reduction of the carbonyl group to carbinol diminishes the activity but acetylation restores it (*7, 8*). Perhaps the most remarkable observation is that the remotely related compound (V) is highly active; saturation of its double bond reduces but does not abolish its activity (*9*).

There has been some controversy on the question whether methadone and its derivatives should not be classed by themselves rather than be forced into relationship with other morphine-type analgesics. Bergel and Morrison (*10*) state that a model of the methadone molecule shows spatial compactness and similarity to morphinan and the phenylpiperidines, but Eddy (*11*) and Bockmühl and Ehrhart (*5*) fail to see any such similarity. Nor do Adamson and Green (*9*) see any possible structural relationship between their

dithienylbutenyldimethylamine (V) and morphine.

It was hoped that an accurate scale model of the methadone molecule might reveal factors not readily seen in a conventional structural formula, and that it would throw more light on the possible relationship of methadone to morphine than the somewhat cryptic statement of Bergel and Morrison (*10*) about the "compactness" of the methadone molecule. Such a model was constructed from aluminum spheres, precision-ground to the known atomic diameters on the scale 17¼ mm: 1 A and connected by pegs and holes at the correct bond angles.[1]

The model showed that the bulky phenyl, methyl, and propionyl groups impose considerable steric restraints on the methadone molecule, not in the sense of any impossibility of rotation but rather in that parts of the molecule can rotate only if they do so in concert with other parts of it. Such concerted rotation is obviously contrary to randomness and thus represents a decrease in entropy. This does not happen of itself in a physical system, hence such steric impediment is equivalent to a degree of steric hindrance and restrains the methadone molecule to some apparent rigidity.

Another observation was that the protons of one N-methyl group can actually touch the oxygen of the carbonyl group. This writer has shown that under such circumstances a C—H—O hydrogen bond arises (*12*) which in the present case further confines the methadone molecule to a pseudo-rigid position. This position is shown in Fig. 1, a photograph of the methadone model. It is clearly seen that the steric factors mentioned above force the six atoms, which are marked with a cross in the photograph, into a position closely resembling a piperidine ring. These atoms are C_1 of one of the benzene rings, the quaternary carbon, and the —C—C—N—C— chain of the 2-(dimethylamino-)propane group. The model shows that the gap in the ring is about 2.1 A wide which is only 38% more than the length of a C—C single bond.

Similar model studies on the related compounds listed above seem to show that the same factors operate in all of them to determine whether a compound is analgetically active. When the carbonyl group of methadone is replaced by a sulfo group, the semi-ionic S→O bonds make the oxygen atoms more strongly negative than in C=O so that the N-methyl group is held in position even more rigidly than in methadone itself. Hence the analgesic activity of the sulfone analogue of methadone (*6*). The model of isomethadone also shows the same possibility for the formation of a six-membered pseudo-ring as the methadone model, but obviously no such ring is possible when the chain between the nitrogen and the quaternary carbon is longer or shorter than in methadone. Furthermore, the models reveal far less steric impediment when one or both benzene rings are replaced by benzyl or allyl groups, or when one of the benzene rings is shifted to the adjacent carbon atom. Thus the

[1] The author wishes to express his thanks to E. H. Cox of Swarthmore College for the loan of his molecular models.

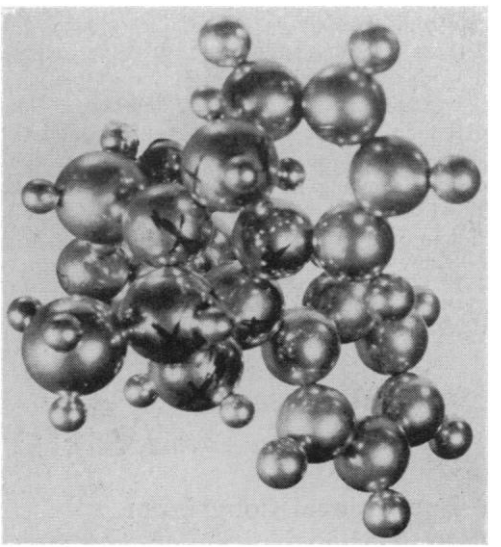
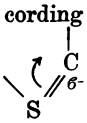


FIG. 1. Photograph of the methadone model.

molecules of these compounds must be more flexible and less prone to force their atoms into the semblance of a piperidine ring.

In methadol, the carbinol corresponding to methadone, the oxygen is more weakly negative than the ketonic oxygen of methadone, hence less able to hold the basic chain in position through a C—H—O hydrogen bond. A more important effect here must be a hydrogen bond between the OH and the nitrogen, which is sterically perfectly possible; but then the gap in the ring is greater than in methadone. The reverse is true of the compound obtained by acetylating the carbinol: the removal of the proton from the oxygen also removes the possibility of an O—H—N hydrogen bond while the newly introduced carbonyl group in the ester restores a C—H—O bond, this time in such a position as to close the gap in the ring almost completely.

As to (V), while it lacks the bulk of the propionyl group and the steric impediment provided by the O—H—C bond, the rigidity of its double bond contributes to the rigidity of the basic chain. If electronic effects are also taken into account, it must be assumed that the two sulfur atoms, positively charged by resonance, will tend to be as far as possible from each other while the CH_3—N group will align itself according to electrostatic attraction alongside the



part of a thiophene ring. The result is, again, a semi-rigid structure imitating a piperidine ring. Saturation of the double bond somewhat diminishes both the rigidity of the structure and the analgesic effect of the compound.

Thus we can now correlate the structure of methadone and its derivatives with that of morphine, meperidine, and other related analgesics and state that the

common and (probably) essential structural feature of all these compounds is an actual or virtual γ-aryl-(mostly phenyl-)-N-methylpiperidine system.

The relationship between morphine and methadone, postulated in the foregoing, is brought out in structure (VI), a composite structure of morphine and methadone, showing in thin lines structural features peculiar to morphine, in broken lines those peculiar to methadone, and in heavy lines those common to both.

References

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News and Notes

XIV International Congress of Zoology, 1953

THE second post-war International Congress of Zoology was held in Copenhagen, Denmark, Aug. 5–12. Forty-six countries were represented, with a delegate from the United Nations in addition, with a total of 562 delegates and members. The largest delegation was that of Denmark (104), followed by Germany with 70, the United States 59, the United Kingdom (without the Dominions) 57, Sweden 30, Italy 24, Netherlands 19, Norway 13, Finland 4, and others. The Russian delegation of 6 members took an active part in the meetings, speaking in other languages as well as in Russian, and in general exhibiting a much greater degree of freedom and of willingness to cooperate in scientific matters with the western nations than had been the case in Paris in 1948. A gift of some 150 bound volumes of recent Russian zoological publications was made to the University of Copenhagen.

Fifteen papers were presented by the members at general meetings, and about 265 to the sixteen sectional meetings. These were arranged for Nomenclature (7); Paleozoology (6); Zoogeography (10); Evolution and Genetics of Populations (12); Cytology (13); Morphogenesis (41); Animal Psychology (8); Comparative Physiology (43); Serology and Paper Chromatography (6); Parasitology (11); Nematology (10); Terrestrial Ecology (14); Hydrobiology (25); Terrestrial Arthropods (21); Invertebrates (11); and Vertebrates (17); the figures in parenthesis are the number of papers offered for each section. There were in addition two major Colloquia, one, with 13 invited papers, on the Deep Sea Bottom Fauna, and one on the problems of zoological nomenclature.

The Colloquium on Zoological Nomenclature was called by the International Trust for Zoological Nomenclature to meet July 29–Aug. 4, in advance of the Congress proper. Nearly fifty representatives of societies and institutions interested in these problems convened, and their long and arduous meetings continued throughout the week scheduled, often until midnight. The proceedings of the Colloquium made it possible to present 142 specific recommendations to the Section for Nomenclature of the Congress, all of which had been exhaustively discussed by the members of the Congress attending the Colloquium. With this previous discussion, it was possible to take action on the numbered proposals, with active discussion only of certain controversial items. Among these was the modification of the so-called Law of Priority in the interest of nomenclatural stability. Strong support for such modification came from the zoologists in general, and was opposed mainly by those who seek to divorce zoological nomenclature, as an independent activity, from zoology. (See "Zoological Nomenclature: Decisions taken by the Fourteenth International Congress of Zoology," by Francis Hemming, in this issue, p. 131.)

The results of the action of the Colloquium and of the Section for Nomenclature were ratified by the Congress as a whole and accepted by the International Commission on Zoological Nomenclature which met concurrently. Certain actions of the previous Congress in Paris (1948) were reversed, and various problems, postponed by the Paris congress for further study and for action in 1953, were dealt with. Comprehensive revision and rewriting of the rules, as of 1953, was thus made necessary, and this was placed in the hands of J. Chester Bradley, Cornell University, President of the Commission. The resignation of Francis Hemming, secretary to the Commission, was accepted, to take effect in 1955, with division of the duties of that office by the establishment of a separate post for the editor of the *Bulletin for Zoological Nomenclature*. Mr. Hemming received a special vote of thanks for his efforts throughout his tenure of office and especially for his conduct of the Colloquium preceding the Congress.

The meetings of the scientific sessions and especially the discussions following individual papers were extremely stimulating, and of course scarcely less so were the continuing informal discussions that went on in the corridors of the lecture halls, over luncheon