cis- and *trans*-3-Methylamino-2-phenyltetrahydropyran

D. R. GALPIN[▲], S. R. BOBBINK, and T. E. ARY

Abstract □ The syntheses of *cis*- and *trans*-3-methylamino-2-phenyltetrahydropyran are described and their configurations are established by NMR. The stereochemistry of previously reported 3-bromo-2-phenyltetrahydropyran was also ascertained.

Keyphrases □ 3-Methylamino-2-phenyltetrahydropyran, *cis* and *trans*—synthesis, configuration established by NMR □ 3-Bromo-2-phenyltetrahydropyran—stereochemistry determined □ NMR spectroscopy—configuration confirmation of *cis*- and *trans*-3-methylamino-2-phenyltetrahydropyran

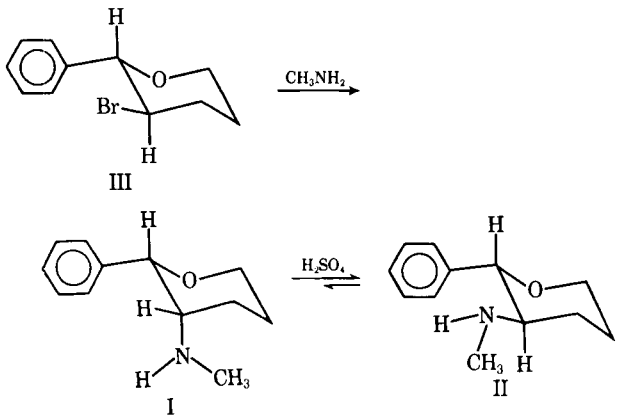
As part of a series of studies on the configurational and conformational preferences for compounds involved in various biological processes utilizing adrenergic amines, it was necessary to synthesize *cis*- and *trans*-3-methylamino-2-phenyltetrahydropyran (I and II, respectively). These compounds are configurationally related to pseudoephedrine and ephedrine, respectively; in their predominant conformations, they represent single rotameric forms of their corresponding open-chain analogs. Subsequent to the synthesis of I, it was learned that this compound had been prepared by Jenkins (1) *via* an almost identical route. However, he did not stipulate the stereochemistry of his product. We now wish to report the synthesis of the *trans*-isomer II and to make configurational assignments to the products of the reaction sequence leading to I and II (Scheme I).

DISCUSSION

The *cis*-isomer I was prepared by displacement of halide with methylamine from *trans*-3-bromo-2-phenyltetrahydropyran (III). Isomerization of I in sulfuric acid yielded a mixture of I and II consisting of 80–85% II, from which the *trans*-isomer II was isolated by column chromatography over silica gel. The synthesis of III was effected by the condensation of phenylmagnesium bromide with dibromotetrahydropyran according to Paul (2).

Apparently the geometry of III obtained by this synthesis was not previously determined (1, 2). We established its configuration by NMR. Since the benzylic hydrogen is coupled significantly with only one other hydrogen, its signal is uncomplicated and quite diagnostic for determining configuration. In carbon tetrachloride, the signal of this hydrogen appears as a doublet at 4.23δ, exhibiting an apparent coupling constant of 9.5 Hz. and indicating axial–axial coupling to the vicinal hydrogen at C-3. This result is consistent with the tetrahydropyran ring predominantly in a chair form, the aromatic group equatorially oriented, and a *trans*-configuration of the substituents (*vide infra*).

The pertinent portions of the NMR spectra of the free bases of I and II in deuteriochloroform appear in Fig. 1. The spectrum of I shows a doublet for the signal of the benzylic hydrogen at 4.57δ with a coupling constant of 1.9 Hz. The signal for the hydrogen at C-3 appears as an unresolved multiplet at 2.83δ with a $W_{1/2}$ of ~7 Hz., indicating that this hydrogen occupies predominantly an equatorial position. The assignment of this signal was confirmed by decoupling experiments in which irradiation of C-3 at 2.83δ resulted in the collapse of the doublet for the benzylic hydrogen into a singlet. The signals appearing between 4.57 and 2.83δ are those of the axial and equatorial hydrogens at C-6. The signals of the remaining hydrogens appear as a series of overlapping unresolved peaks from about 2.4 to 1.0δ. The low intensity peak just downfield from the signal for the C-3 hydrogen is a rotational side band from the *N*-methyl group. The coupling constant of 1.9 Hz. between the C-2 and C-3 hydrogens is consistent with values observed for axial–equatorial coupling (3, 4); this fact, in conjunction with the equatorial orientation of the C-3 hydrogen, shows the product to be *cis*



Scheme I

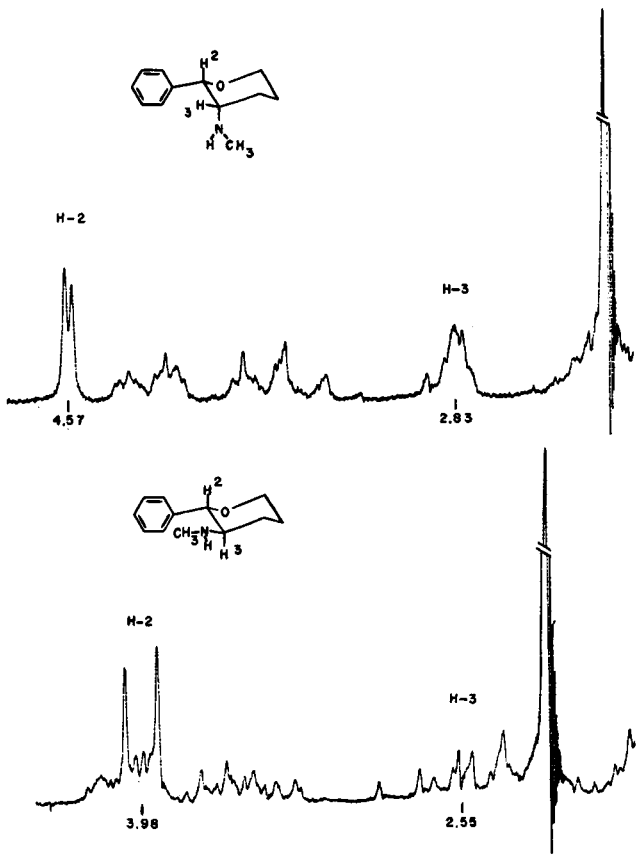


Figure 1—*Portions of the 60-MHz. NMR spectra of I (upper) and II (lower) measured in about 1 M solutions of deuteriochloroform. Chemical shifts are expressed in δ units.*

Figure 2—*The 60-MHz. NMR signal of the C-3 hydrogen of II at the 100-Hz. sweep measured in about a 1 M solution of deuteriochloroform, showing a first-order analysis for apparent coupling constants.*

in configuration. While a coupling constant of 1.9 Hz. could also be indicative of equatorial–equatorial coupling for these hydrogens (3–5), making the product *trans*, such a configuration would require a preferred conformation having the aromatic ring axial, which is highly unlikely due to 1,3-diaxial interactions. An equatorial orientation of the aromatic ring has been established for similar 2-phenylmorpholines (4), 2-aryl cyclohexylamines (6), and 2-aryl cyclohexanols (7).

In the NMR spectrum of II in deuteriochloroform, the signal for the benzylic hydrogen at C-2 appears as a doublet at 3.98δ superimposed on another signal exhibiting a coupling constant of 8.8 Hz. which is consistent with axial–axial coupling. The vicinal hydrogen at C-3 is a multiplet centered at 2.55δ, which is partially overlapped with the signal of another ring hydrogen. The breadth of this signal indicates that this hydrogen is also axially oriented and coupled with two adjacent axial and one equatorial hydrogens. These observations establish the predominant conformation of the tetrahydropyran ring as a chair, with the phenyl ring equatorial, and a *trans*-configuration for the compound.

An expanded spectrum of the signal for the C-3 hydrogen of II is shown in Fig. 2. Because C-2 is bonded to an electronegative oxygen atom whereas C-4 is not, it might be anticipated that the coupling constants of the C-3 hydrogen with the adjacent axial hydrogens at C-2 and C-4 would differ. By a first-order analysis, this unequal coupling, in conjunction with that of the equatorial hydrogen at C-4, should give rise to an eight-peak multiplet for the C-3 hydrogen, since it is being split by three nonequivalent hydrogens with different coupling constants. That this is the case can be seen in Fig. 2, where seven of the eight peaks are visible; the last is obscured by a portion of another signal. Analysis of this signal gives apparent coupling constants of $J_{a,a}$ (2,3) = 8.8 Hz., $J_{a,a}$ (3,4) = 10.6 Hz., and $J_{a,e}$ (3,4) = 4.0 Hz.

The Grignard synthesis of III and the displacement of bromide from III to form I appear to yield stereochemically pure products. The other geometric isomer of each could not be detected at any stage of the workup of these reactions by NMR analysis, indicating a composition of at least 95% one isomer. These results strongly suggest that the Grignard reaction proceeds with complete retention of configuration and that the displacement of bromide is exclusively by an S_N2 process. The results also show that the product reported by Jenkins (1) was the *cis*-isomer I.

EXPERIMENTAL[1]

***trans*-3-Bromo-2-phenyltetrahydropyran (III)**—This compound was prepared according to Paul (2). Following distillation, it was recrystallized from methanol–water, m.p. 40.5–41.5° [lit. (1) m.p. 41.5–42.5°].

***cis*-3-Methylamino-2-phenyltetrahydropyran (I)**—This compound was prepared in an almost identical process as that described by Jenkins (1), differing only in that no solvent other than methylamine was employed and the temperature was 100° for 40 hr. Yields were comparable. The hydrochloride salt melted at 216–217.5° [lit. (1) m.p. 216.5–218.5°].

***trans*-3-Methylamino-2-phenyltetrahydropyran (II)**—This compound was obtained by isomerization of I in sulfuric acid in a procedure similar to that outlined by Dvornik and Schilling (8) for the isomerization of phendimetrazine diastereoisomers. Five grams of I was dissolved in 20 ml. of sulfuric acid and allowed to stand overnight. The solution was then diluted to about 10 times its volume with water, made alkaline with solid sodium carbonate, and extracted three times with small portions of ether. The combined ether extracts were washed twice with water and dried over anhydrous sodium sulfate. Following filtration and removal of solvent, the mixture of isomers, estimated to be 80–85% II from integration of the NMR spectrum, was chromatographed over silicic acid[2] using chloroform–ethanol, 80:20, as the eluent; II eluted first. Fractions were analyzed by NMR. The combined fractions containing II were distilled (60–66° at 0.04–0.07 mm. Hg). The hydrochloride salt was prepared in ether and recrystallized from ethyl acetate–chloroform, m.p. 147–148.5°.

Anal.—Calc. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.35; H, 8.04; N, 5.93.

REFERENCES

(1) H. Jenkins, U. S. pat. 3,419,555; through *Chem. Abstr.*, **71,** 3276w(1969).

(2) R. Paul, *Bull. Soc. Chim.*, **2,** 311(1935).

(3) H. Booth and G. C. Gidley, *Tetrahedron*, **21,** 3429(1965).

(4) P. S. Portoghese, *J. Med. Chem.*, **10,** 1057(1967).

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, New York, N. Y., 1959, p. 86.

(6) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, **54,** 1552 (1965).

(7) A. C. Huitric and J. B. Carr, *J. Org. Chem.*, **26,** 2648(1961).

(8) D. Dvornik and G. Schilling, *J. Med. Chem.*, **8,** 466(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 15, 1971, from the *College of Pharmacy, Washington State University, Pullman, WA 99163*

Accepted for publication February 9, 1972.

Supported in part by Grant GM-16838 from the National Institutes of Health, U. S. Public Health Service, and by funds provided for medical and biological research by State of Washington Initiative Measure No. 171.

▲ To whom inquiries should be directed.

[1] The NMR spectra were obtained on a Varian T-60 spectrometer at 37° using tetramethylsilane as the reference. Melting points were determined on a Kofler micro hot stage and are corrected. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

[2] Merck.