1,4-Cycloaddition Reactions. I. Stereoisomers of 2,3,3a,4,5,9b-Hexahydro-9b-methyl-4-Phenylfuro[3,2-c]quinolines from 2,3-Dihydro-5-methylfuran and *N*-Benzylideneanilines.

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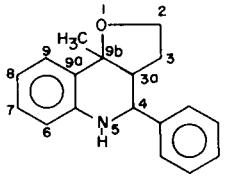
Sir:

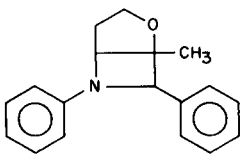
Several years ago Povarov and coworkers reported the preparation of 2,3,3a,4,5,9b-hexahydro-9b-methyl-4-phenylfuro[3,2-c]quinoline (I) in 81% yield from the 1,4-addition of 2,3-dihydro-5-methylfuran to *N*-benzylideneaniline in the presence of catalytic amounts of boron trifluoride etherate (1). Further, the authors indicated that this reaction was remarkably stereospecific and that only one of the possible stereoisomers was obtained (1). No attempt was apparently made to establish the configuration of this product. Repetition of this reaction in our laboratory afforded a crystalline solid, apparently identical with I, in 73% yield. The melting point of this product (141-143°) was close to that previously recorded (139-139.5°) (1), and the material analyzed correctly (C,H,N) for $C_{18}H_{19}NO$. However, TLC (alumina) showed two spots, indicating that this material was not homogeneous. The NMR spectrum showed peaks of approximately equal intensity at δ 1.70 and 1.41, which were tentatively assigned to two different CH_3 groups.

Separation of the two components was readily accomplished with column chromatography, using alumina and eluting with a cyclohexane-benzene mixture (84% recovery). Two pure compounds were obtained, m.p. 162-164° and m.p. 135-137°, in approximately equal amounts. Both showed only one spot on TLC and both gave microanalyses (C,H,N) consistent with a 1:1 adduct. These observations led to a more thorough investigation of the structure of these products.

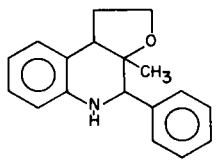
1,2-Cycloaddition products such as II were eliminated on the basis of a strong N-H absorption in the IR



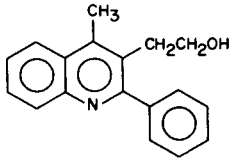
I



II

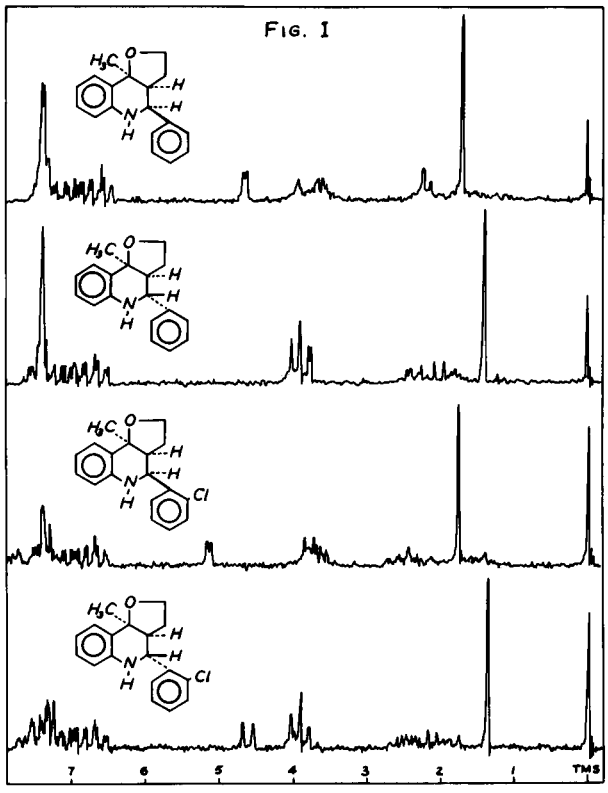


III



IV

spectra (potassium bromide) at 3320 cm^{-1}. It was concluded that neither of the products was III based on previous work (2) which showed that several known 2-phenylquinolines could be generated from various *N*-benzylideneaniline-vinyl ether adducts. Elimination of III was confirmed from the relative integration of the NMR curves which showed a ratio of 6:9 protons in the



δ 1.3-2.6 region *versus* the aromatic region, while III requires a ratio of 5:9.

Treatment of the initial mixture (m.p. 141-143°), or of either of the pure isomers, with sulfur or with palladium on carbon in nitrobenzene, gave high yields of a single compound (IV) of m.p. 131-133°. This was consistent with a sample of IV (m.p. 129-130°) obtained earlier (3) by treatment of I with potassium permanganate in acetone. Using palladium on carbon, where the conversion was relatively slow, it was apparent that the high melting isomer of I was converted to IV more rapidly than the low melting isomer.

It then seemed very likely, despite previous claims (1), that the products were stereoisomers of I, differing in configuration at positions 3a and 4. Inspection of molecular models indicated that both of the isomers shown at the top of Figure I might exist in two stable conformations. However, in the structure where the protons at positions 3a and 4 are *cis*, both conformations show dihedral angles of approximately 60°, while in the case where these protons are *trans*, one conformation shows a dihedral angle of about 60° and the other nearly 180°. Therefore, it seemed probable that a structural assignment could reasonably be made *if* the J-values of the NMR signals from the 4-proton of each isomer differed significantly (4). Inspection of the top curve (high melting isomer) of Figure I shows a 1-proton doublet at δ 4.65 with J = 2, which was assigned to the 4-proton. The low J-value suggests that in this isomer the 3a and 4 protons more frequently have a dihedral angle nearer 60° than 180°. Unfortunately, inspection of the second curve of Figure I (low melting isomer) shows no doublet near δ 4.65. Apparently this signal is lost in the complex absorption at δ 3.6-4.1. This area also contains the N-H absorption, but treatment of the deuteriochloroform solution with deuterium oxide did not afford sufficient simplification to permit assignment of the signal for the 4-proton.

Since the 4-proton from both isomers did not display a signal in an area free from other peaks, a similar set of compounds was prepared with substitution in the *ortho* position of the 4-phenyl group. It was anticipated that the signals would then be shifted downfield into an unencumbered area of the spectra.

The condensation was repeated using *N*-(*o*-chlorobenzylidene)aniline in place of *N*-benzylideneaniline. Again two isomers were formed, m.p. 127-129° and 111-113°, in approximately equal amounts. Fortunately, the signal due to the 4-proton from the higher melting isomer (third curve, Figure I) was at δ 5.11 (J = 2), while that from the lower melting isomer showed clearly at δ 4.62 with J = 8. Structures were assigned as indicated in Figure I for the two isomers of 4-(*o*-chlorophenyl)-2,3,3a,4,5,9b-hexahydro-9b-methylfuro[3,2-*c*]quinoline with the 4-proton of the higher melting *cis* isomer having J = 2, and the lower melting *trans* isomer having J = 8. Structural assignments for the two isomers of I were then made as indicated (Figure I) on the basis of the correspondence of the CH_3 peaks at δ 1.70 and 1.41 with those of the *o*-chlorophenyl analogs, and the small J-value for the δ 4.65 peak shown by the higher melting isomers.

The furo[3,2-*c*]quinolines were tested by drug-diet (six days) against a normal drug-sensitive strain of *Plasmodium berghei* in mice (5). 2,3,3a,4,5,9b-Hexahydro-9b-methyl-4-phenylfuro[3,2-*c*]quinoline (I) exhibited significant antimalarial activity, while the *o*-chlorophenyl analog was inactive. The SD_{90} (daily dose required for 90% suppression of the parasitemia) for I was approximately 245 mg./kg. This stimulated the synthesis of other furo[3,2-*c*]quinoline derivatives which will be described in subsequent communications.

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