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STEREOCHEMICAL STUDIES OF SOME 1,3-DISUBSTITUTED PHTHALANS (1)

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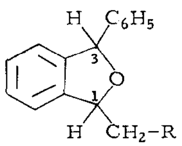
No systematic studies appear to have been reported on the synthesis or methods of assigning the stereochemistry of 1,3-disubstituted phthalans such as 1 - 4. As part of pharmacological studies (3) on the separated cis-trans isomers of 1-(N,N-dimethylaminomethyl)-3-phenylphthalan (3) prepared sequentially from 1 and 2, it was desirable to establish the stereochemical configurations of the cis-trans isomers of 1 - 4. We report here nonstereospecific syntheses of 1 - 4, proton and ^{13}C nmr studies which are somewhat indicative of the configurations, stereoselective syntheses of the cis isomers of 2 - 4 from *o*-benzoylbenzaldehyde and confirmation of the nmr assignments by X-ray diffraction determination of the crystal structure of trans-1.



1, R = $-NO_2$
2, R = $-NH_2$; 2a, R = $-\overset{\oplus}{N}H_3\overset{\ominus}{O}_2CCH_3$
3, R = $-N(CH_3)_2$; 3a, R = $-\overset{\oplus}{N}(CH_3)_2H\overset{\ominus}{Cl}$
4, R = $-\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{Cl}$

The reaction of 1-hydroxy-3-phenylphthalan with nitromethane in the presence of trimethylammonium acetate affords 1-(nitromethyl)-3-phenylphthalan (1) which, on fractional crystallization from a benzene/petroleum ether mixture (30 - 60°) could be separated into the pure cis and trans isomers. Reduction with hydrogen over PtO_2 in methanol containing excess acetic acid and methylation of the separate isomers of 1 gave no epimerization and afforded the pure isomers of 2, 3, and the ammonium salt (4).

A very tentative assignment of the sterochemistry of 1 - 4 was made on the basis of the pmr chemical shifts for the various isomers as shown in Table I. The argument is based on the fact that the protons on C-1 and C-3 of 1 - 4 in one isomer are uniformly 6 - 13 Hz downfield from the corresponding protons in the other isomer. This effect with the protons on C-1 is less easily seen than at C-3 because of the splitting of the C-1 proton resonances by the adjacent protons in the $-CH_2R$ group. The downfield shifts of the C-1 protons can be rationalized by a deshielding effect arising from the 3-phenyl group which should be greater with the trans-configuration (phenyl cis to the 1-proton) than with the cis configuration (phenyl trans to the 1-proton). The observed magnitude of the chemical-shift difference of the C-1 protons is quite in accord with a predicted shift difference of 6.6 Hz arising from the ring current of the 3-phenyl as calculated by the procedure of Johnson and Bovey (5) when the phenyl group is perpendicular to the plane of the phthalan nucleus (6). The shift differences found for the 3-hydrogens of about the same order of magnitude are substantially less explicable. The ring-current effect of the phenyl group is expected to be substantially the same for each, and the observed differences may in fact be due to some differential distortions of the phthalan ring for the *cis* and *trans* compounds. Because of the uncertainties associated with rationalization of the chemical-shift differences of the C-3 protons, it seemed advisable to seek other indicators of which isomer is *cis* and which *trans*.

Table I

Melting-Point and Chemical-Shift Data for Disubstituted Phthalans

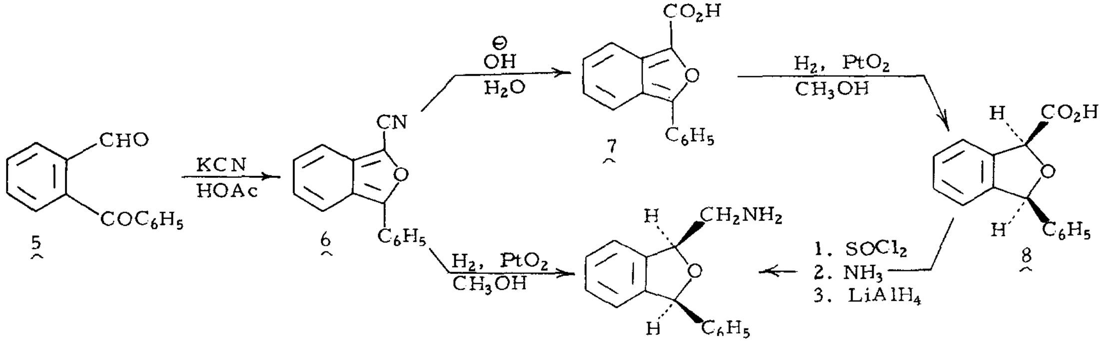
Phthalan	mp, °C		δ(3H), Hz[a]		δ(1H), Hz[a]	
	cis	*trans*	*cis*	*trans*	*cis*	*trans*
1	83-86	93-95	371	377	357	364
2	b	b	367	374	317	329
2a	107-109	84-86	369	377[c]	319[c]	330[c]
3	b	b	366	374	324	336
3a	240-241	186-189	372[d]	385	346[d]	359[d]
4	250-260d.	180-184d.	376[c]	385[c]	357[c]	372[c]

[a] Measured with a Varian A60A spectrometer, downfield from internal tetramethylsilane in $CDCl_3$, unless otherwise noted. [b] The free bases were usually obtained as oils or low-melting solids. [c] In dimethyl sulfoxide-*d*$_6$. [d] In methanol-*d*$_4$.

A substantial four-bond coupling (H-C-O-C-H) is observed between the 1- and 3-protons across the oxygen bridge of both the *cis* and *trans* isomers but is of little diagnostic value because it is about 2 Hz for either the *cis* or the *trans* configuration.

An attempt to determine the configurations of the isomers of 3 by 15.1-MHz natural-abundance ^{13}C spectroscopy (7) was similarly uninformative. Steric hindrance between the phenyl group and the methylene side chain might be expected to shift the methylene carbon resonance to higher fields for the *cis* isomer (8). However, the difference in shift between the methylene carbons was found to be only 0.6 ppm (9 Hz) and in the wrong direction. This could be due to a ring-current effect overbalancing the steric effect. The only other difference of more than 0.5 ppm between the carbon resonances of the two isomers was an 0.75 ppm greater upfield shift of C-3 in the *cis* isomer compared to the *trans*. This is in the right direction for a steric hindrance effect but is hardly compelling.

Much more definite was the chemical evidence provided by a stereoselective synthesis of the *cis* isomer. The reaction between *o*-benzoylbenzaldehyde (5) (9) with potassium cyanide in glacial acetic acid gave 1-cyano-3-phenylisobenzofuran (yellow needles, m. p. 63 - 64°) (6) as the major product (75%). The corresponding acid 7 is obtained by basic hydrolysis of the nitrile 6. Hydrogenation of 6 or 7 over platinum oxide in methanol is expected to occur in the 1, 3 *cis* manner, and indeed there was formed *cis*-2 in 50% yield and 1-carboxy-3-phenylphthalan (8), respectively. The nmr spectra of *cis*-2 and 8 prepared in this way indicated that none of the *trans* isomers had been formed. The acid 8 was converted by conventional methods to *cis*-2.



Final proof of the stereochemistry of these substances was obtained by an X-ray diffraction analysis on trans-1, using procedures described elsewhere (10). Crystals of trans-1 were found to belong to the monoclinic space group $P2_1/c$ with four molecules per unit cell of dimensions: *a* = 11.885, *b* = 8.342, *c* = 13.621A and β = 113.0°. Independent reflections from 1307 planes were collected with a General Electric-Datex diffractometer using Ni-filtered Cu radiation. Phase information was obtained by iterative application of Sayre's equations (11). The trial structure was revealed in the first E-map and was refined (least squares) to an R index of 4.6%. The final refinement cycles contained the following parameters: coordinates, anisotropic temperature factor and scale factor. The hydrogen positions were calculated and added to the structure factor calculation but were not included in the refinement cycles.

The stereoprojection in Figure 1 shows unquestionably that the crystals are of the trans isomer.

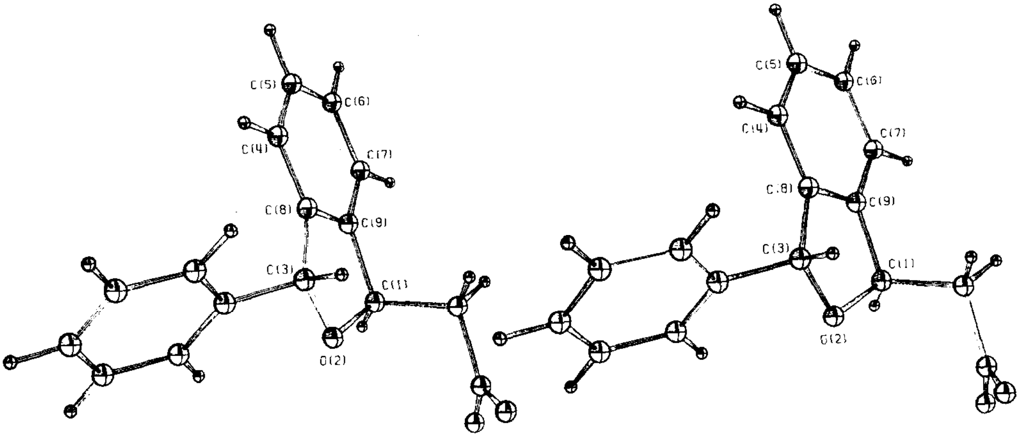


Figure 1. - Stereoprojection of the trans isomer of 1 as determined by X-ray diffraction.

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4. A crystalline 1 : 1 mixture of *cis-trans* isomers of 1-hydroxy-3-phenylphthalan was obtained in 70% yield from the reaction of *o*-phthalaldehyde with phenylmagnesium bromide in ether at 0°. Satisfactory elemental analyses have been obtained for all of the new compounds reported here.
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6. Rather extensive use has been made of pmr shift correlations for establishing configurations in 1,2-diphenyl substituted cyclic compounds by D.Y. Curtin, H. Gruen, and B.A. Shoulders, *Chemistry & Industry*, 1205 (1958), and D.Y. Curtin, H. Gruen, Y.G. Hendrickson, and H.E. Knipmeyer, *J. Am. Chem. Soc.*, **83**, 4838 (1961). It is clear that 1,3-diphenyl substituted cyclic compounds cannot be treated in the same way without other supporting evidence. In this connection, L.A. Carpino, *J. Am. Chem. Soc.*, **84**, 2196 (1961), reversed a previously assigned configuration to one of the geometrical isomers of 1,3-diphenyldihydroisoindole through application of Curtin's rule of upfield α proton shifts for 1,2-diphenyl substituted rings. This assignment which was later abandoned on other grounds, L.A. Carpino, *Chem. Comm.*, 494, 858 (1966), is opposite to the correlation we observed between pmr shifts and configuration.

   A 6-Hz downfield shift of the 1,3-protons in the *trans* relative to the *cis* isomer of 1,3-diphenyl-2-indanone which agreed with the results reported here has very recently been published by G. Quinkert, H.P. Lorenz, and W.W. Wiersdorff, *Chem. Ber.*, **102**, 1597 (1969).
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