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# *o*-PHTHALALDEHYDE AMIDE ADDUCTS—II

## $^1$H AND $^{13}$C NMR STUDIES OF NEW PHTHALANS AND ISOINDOLINES. STEREOCHEMICAL ASSIGNMENTS AND DIFFERENTIATION OF PRODUCTS

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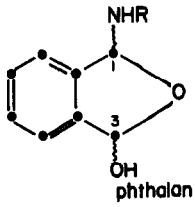
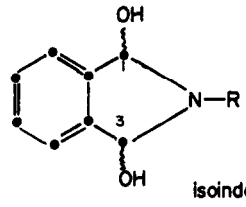
**Abstract**—A study of the $^1$H and $^{13}$C NMR spectra of adducts arising from the condensation of *o*-phthalaldehyde with an amide or a sulfonamide established the stereochemistry and differentiated between phthalan and isoindoline products for this reaction. The steric properties of the 2,6-dichlorobenzamide adduct appear to influence the vicinal H, OH coupling constant associated with the isoindoline ring.

The reaction of *o*-phthalaldehyde with amides leading to phthalans or isoindolines (phthalaldehyde adducts) was described by Reynolds *et al.*[1,2] Often only one product is formed,[1] but mixtures of both are sometimes observed,[3] and product distribution usually depends on steric and electronic properties of the reacting amide.[3] For the isoindoline compounds, the $^1$H NMR data were interpreted in terms of a *cis* configuration for the OH groups at positions 1 and 3. A reaction mechanism was postulated to account for such stereochemistry.[2]



phthalan



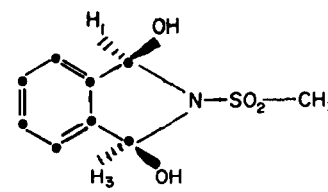
isoindoline

In this paper we report a $^1$H and $^{13}$C NMR study of several new phthalaldehyde adducts.[4] From our $^1$H NMR data we also propose a *cis* arrangement for the OH groups on the isoindoline moiety. Our $^1$H NMR data indicate a mixture of *cis* and *trans* isomers for the phthalan adducts. The assignments of phthalan or isoindoline structures were based on $^{13}$C NMR spectroscopy. We also describe the stereochemical properties and chemical shifts for several sulfonamide adducts.[4]

### RESULTS AND DISCUSSION

*$^{13}$C NMR studies.* The reaction of phthalaldehyde with amides gives either phthalans or isoindolines; sulfonamides form exclusively the isoindoline adduct.[4] For many reactions, $^1$H NMR spectra were used to substantiate our interpretations. However, the $^1$H NMR spectra were sometimes difficult to interpret or ambiguous, and we turned to $^{13}$C NMR for product elucidation. Because of the large chemical-shift differences between the hemiacetal carbons[5] (Table 1) and the aminal (amino alcohol) carbons[6] (Table 2), spectral analysis and structural assignments were straightforward.

The $^{13}$C NMR spectrum of the methylsulfonamide (**1**) adduct is shown in Fig. 1. The plane of symmetry gives rise to three aromatic signals and two alkyl signals. The $\delta$ 83.95 signal is clearly the aminal carbon resonance.[6] This assignment is important for the identification of the aminal resonances in $^{13}$C NMR spectra of isoindolines and phthalans.



**I**

The reaction of acetamide with *o*-phthalaldehyde goes cleanly to the isoindoline adduct (**2**) (Fig. 2). The hindered rotation at the amide bond causes magnetic nonequivalence for C-1, C-3, and C-8, C-9. Accidental degeneracy occurs at C-4, C-7, and C-5, C-6. The similarity in the chemical shifts at $\delta$ 80.64 and

Table 1. $^{13}$C NMR chemical shifts for the hemiacetal carbons of the various *cis*/*trans* phthalaldehyde adducts (phthalans)

| Compound | Chemical Shift (ppm)[a] |
|---|---|
| 3 | 99.37, 99.95 |
| 6 | 101.51, 102.09 |

[a]Relative to internal $Me_4Si$.

Table 2. $^{13}C$ NMR chemical shifts for the aminal carbons for the various isoindolines and phthalans

| Compound | Chemical Shift (ppm)[a] | Adduct Type[b] |
|---|---|---|
| 1 | 83.96 | I |
| 2 | 80.64, 82.59 | I |
| 3 | 81.64, 82.80 | P |
| 4 | 85.84 | I |
| 5 | 81.49, 82.53 | I |
| 6 | 84.56, 85.73 | P |
| 7 | 81.16, 83.18 | I |

[a]Relative to internal $Me_4Si$. [b]I = isoindoline, P = phthalan.

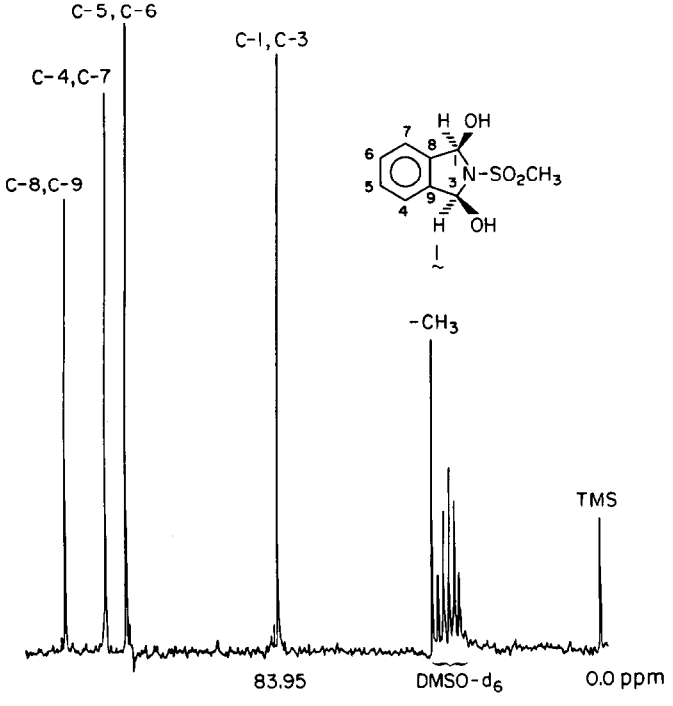
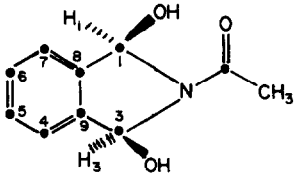


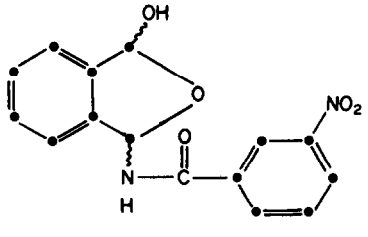

Fig. 1. $^{13}C$ NMR spectrum (15 MHz) of methylsulfonamide/phthalaldehyde adduct. Multiplet at $\delta$ 39.60 is the DMSO-$d_6$ septet.

82.59 to the chemical shift for the aminal C of **1** supports an isoindoline structure for **2**.




**2**

$^{13}C$ NMR spectra of phthalan adducts, such as **3**, are generally more complex because of the lack of symmetry and because of *cis–trans* isomerization. The hemiacetal resonances for C-1 (Fig. 3) are readily identified at $\delta$ 99.95 and 99.37,[5] and the aminal resonances at $\delta$ 82.80 and 81.64 are similar to the aminal resonances previously discussed and tabulated in Table 2. Figure 3(b) shows that the signals are doubled; this is caused by *cis–trans* isomerization at C-1, C-3.




**3**

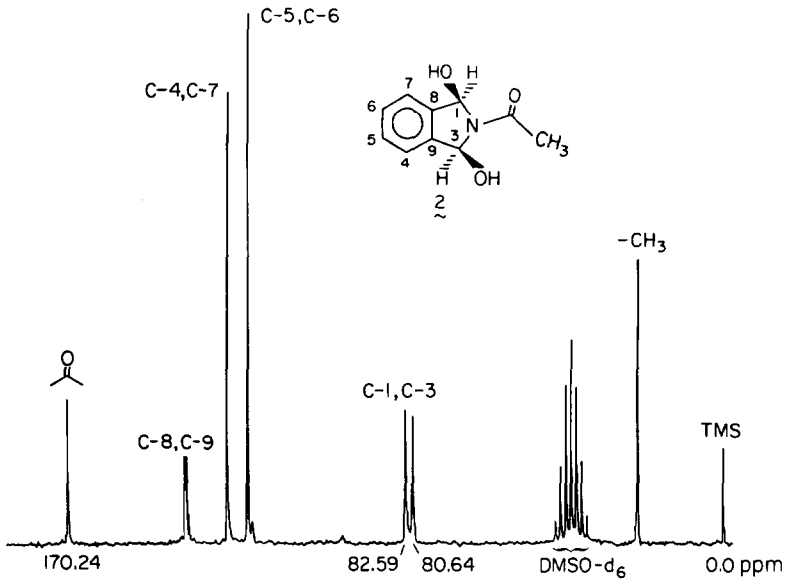
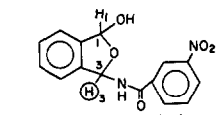



Fig. 2. $^{13}C$ NMR spectrum of acetamide/phthalaldehyde adduct. Doubling of several peaks arises from hindered rotation of amide bond.



3 cis, trans (1:1)

| Hydrogen | Isomer | Resonance | δ (ppm) |
|---|---|---|---|
| 3 | trans | A ($H_3$) | 7.15 |
| 3 | cis | B ($H_3$) | 6.90 |
| 1 | trans | C ($H_1$) | 6.55 |
| 1 | cis | D ($H_1$) | 6.28 |

| Carbon | Resonance | δ (ppm) |
|---|---|---|
| 1 acetal | I | 99.95 |
| 1 acetal | II | 99.37 |
| 3 aminal | III | 82.80 |
| 3 aminal | IV | 81.64 |

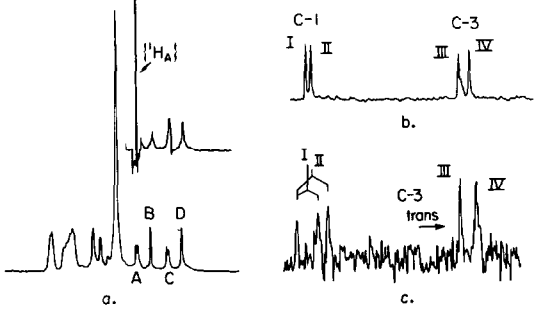
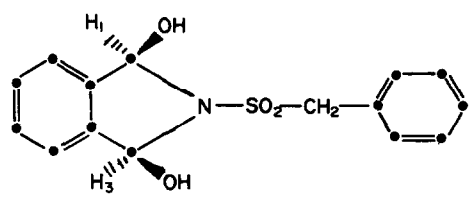



Fig. 3. $^1H$ (60 MHz) and $^{13}C$(15 MHz) NMR spectra of the *m*-nitrobenzamide/phthalaldehyde adduct. Spectrum *a* shows the deuterium-exchanged ($D_2O$) $^1H$ NMR spectrum for the methine and aromatic protons and selective irradiation of $H_A$. Spectrum *b* shows the broadband $^1H$ decoupled $^{13}C$ acetal (C-1) and aminal (C-3) resonances (for assignments see text). Spectrum *c* shows the effect of selective irradiation $\{^1H_A\}$ on resonance III, leaving I, II and IV partly coupled. Chemical shift differences in III and IV between *b* and *c* are attributed to temperature changes.

*$^1H$ NMR studies.* Compounds **1** and **4** are the products of the *o*-phthalaldehyde/sulfonamide condensation reaction (methanesulfonamide and α-toluenesulfonamide). The $^1H$ NMR chemical shifts and multiplicities for each adduct are given in Table 3. Both sulfonamides react to form isoindolines **1** and **4**, based on their $^{13}C$ NMR spectra; no evidence for phthalans has been observed.

The methylene protons in the α-toluenesulfonamide adduct **4** appear as a singlet. If the *trans*-disubstituted isomer (dissymmetric) were present, the methylene protons would be nonequivalent and would appear as an AB quartet in the absence of accidental degeneracy. Conversely, the *cis*-isomer would give rise to a singlet, owing to symmetry considerations. Although we cannot preclude the possibility of accidental degeneracy, our results suggest a *cis* configuration for the OH groups in **4**. The methine protons are coupled to the OH protons with $^3J_{H,OH} = 9$ Hz.




**4**

The methine protons in the sulfonamide adduct **1** appear as a singlet, but the OH resonance is broad, suggesting an intermolecular exhcange with water present in solution. The chemical shifts of protons $H_1$ and $H_3$ in **1** are identical with their shifts in **4**, suggesting equivalent stereochemistries for **1** and **4**.

Carbonamide **5** is derived from the reaction of phthalaldehyde with iodoacetamide. The spectrum of this adduct shows an interesting splitting pattern (Fig. 4). The methine protons are nonequivalent, and coupling is observed to the adjacent OH proton ($^3J_{H,OH} = 10$ Hz). The methylene protons appear as a geminal coupled AB quartet ($^2J_{H_A,H_B} = 12$ Hz). One explanation for the nonequivalence of the methylene protons is dissymmetry resulting from a *trans* arrangement of the OH groups.[7] Another explanation for this effect would be hindered rotation at the amide bond. The nonequivalence of the two methine pro-

Table 3. NMR chemical shifts (ppm) and multiplicity patterns for selected protons in phthalaldehyde adducts

| Compound | $H_1$ | $H_3$ | OH | NH | Other |
|---|---|---|---|---|---|
| 1 | 6.10[a](s)[b] | 6.10(s) | 6.30(b)[c] | -- | $-CH_3$, 3.08(s) |
| 2 | 6.17(s)[d] | 6.17(s)[d] | 6.17(s) | -- | $-CH_3$, 2.20(s) |
| | 6.00(d)[e] | 6.00(d) | 6.31(d) | -- | |
| 3a cis | 6.28(d) | 6.90(d) | 6.66(d) | 9.51(d) | |
| 3b trans | 6.55(d-d)[f] | 7.15(d-d) | ? | 9.68(d) | |
| 4 | 6.10[a](d) | 6.10(d) | 6.64 | -- | $-CH_2-$, 4.50(s) |
| 5 | 6.20(s)[d] | 6.20(s)[d] | 6.20(s) | -- | $-CH_2-$, 4.07 |
| | 6.10(d) | 6.10(d) | 6.67(d) | | AB(q)[g] |
| 6a cis | 6.25(d) | 6.65(d) | 5.90(d) | 8.70 two overlapping doublets | |
| 6b trans | 6.45(d-d) | 6.94(d-d) | 5.90(d) | | |
| 7 (DMSO-$d_6$) | 5.70(d)[d] | 5.70(d)[d] | 6.25(d) | -- | |
| | 6.60(s) | 6.50(s) | 6.50(s) | | |
| 7 ($CDCl_3$) | 5.88(d) | 5.88(d) | 3.30(d) | -- | |
| | 6.66(s) | 6.66(s) | 4.75(s) | | |

[a]All chemical shifts are with respect to internal $Me_4SI$. [b]Singlet. [c]Broad. [d]$H_1$ and $H_3$ are nonequivalent, owing to hindered rotation, and the assignments are interchangeable. [e]Doublet. [f]Doublet of doublets. [g]Quartet.

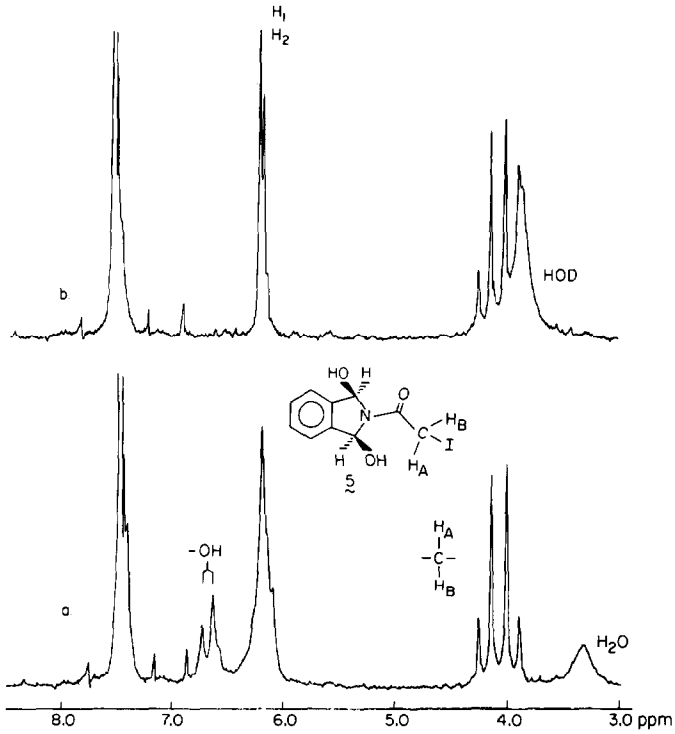
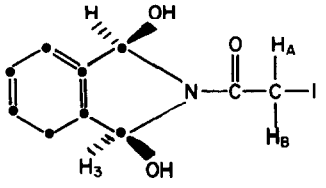



Fig. 4. $^1H$ NMR spectrum in DMSO-$d_6$ of iodoacetamide/phthalaldehyde adduct, resulting in AB quartet pattern for the methylene protons $H_A$ and $H_B$. Upper trace shows deuterium-exchanged ($D_2O$) sample at 90 MHz.

tons gives rise to two singlets in the $D_2O$-exchanged spectrum (Fig. 4) and can be understood in terms of hindered rotation. Although equal populations are expected for each rotamer, we do not observe equal peak heights. A spectrum of the $D_2O$-exchanged sample at 270 MHz showed a well-resolved singlet for each methine proton. Integration established equal areas for the two signals, consistent with the hindered-rotation hypothesis.



**5**

The solution of carboamide **5** was heated to determine if the nonequivalence of $H_A$ and $H_B$ was due to hindered rotation or *trans* stereochemistry. Unfortunately, the sample decomposed before a determination could be made. However, a variable-temperature study was made with the chloro derivative, and this showed an AB quartet collapsing to a singlet at around 55° ($\Delta G_c^{\neq} \approx 16.6$ kcal mol$^{-1}$). This lends strong support to the *cis* configuration for the carbonamide isoindoline adducts.[8]

Carbonamide **2** is derived from the reaction of phthalaldehyde with acetamide. One methine proton is observed as a doublet ($^3J_{H,OH} = 9$ Hz), showing coupling to the adjacent OH proton. The second methine proton and its adjacent OH proton have the same shielding and appear as superimposed singlets. The nonequivalence of the methine protons, $H_1$ and $H_3$, is due to hindered rotation at the amide bond (N–C=O). The stereochemistry for structure **2** is shown as *cis*. We favor this structure because the NMR data for compound **5** support *cis* stereochemistry (see above); there is no evidence to suggest that the formation of **2** does not follow the same mechanism as **5**.

The isomeric *m*-nitrobenzamide adducts **3a** and **3b** and the trichloroacetamide adducts **6a** and **6b** were

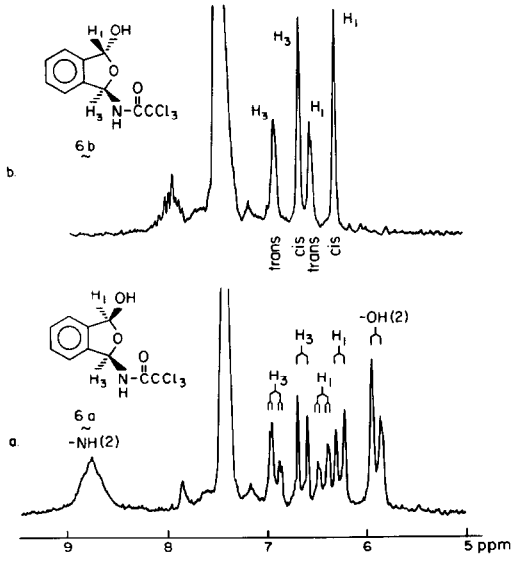
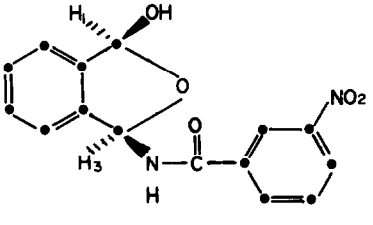


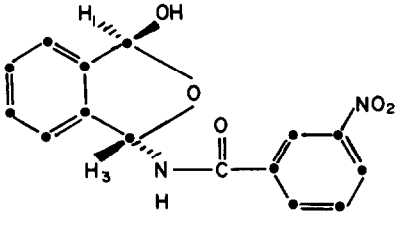

Fig. 5. $^1$H NMR spectrum in THF-$D_8$ of trichloroacetamide/phthalaldehyde adduct, resulting in phthalan product. Upper trace (b) shows deuterium ($D_2O$) exchanged sample at 90 MHz; multiplet at $\sim\delta$ 7.90 represents an unknown impurity.

readily identified by $^{13}$C NMR as phthalans. The $^1$H NMR spectra of both adducts are considerably more complex than the isoindoline spectra, because of the presence of *cis–trans* isomers and long-range coupling. The *cis–trans* mixture gives rise to two chemical shifts for both $H_1$ and $H_3$. For example, $H_1$ is seen as a doublet (*cis*: $^3J_{H_1,OH} > 0$, $^5J_{H_1,H_3} = 0$) and a doublet of doublets (*trans*: $^3J_{H_1,OH} > 0$, $^5J_{H_1,H_3} > 0$) in Fig. 5(a) ($H_1$ is shown as *cis*; in Fig. 5(b) it is *trans*). The assignment of $H_1$ and $H_3$ and *cis* vs *trans* follows from the discussion below.

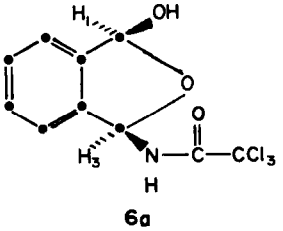
Analysis of the splitting patterns and chemical shifts for adducts **3a,b** and **6a,b** required several lines of evidence. Although the D-exchanged spectra for both mixtures are similar, enough differences exist between the nonexchanged spectra that other assignment strategies were needed; however, spectral similarities permitted facile correlation of the data. For example, we observed that the –NH resonances of



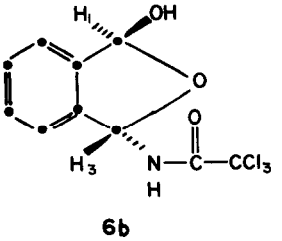
**3a**



**3b**



**6a**

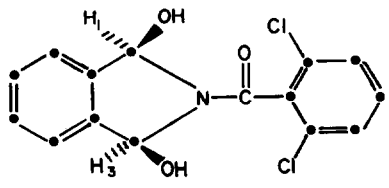


**6b**

**3a,b** separate into two doublets in dimethyl sulfoxide, but those of **6a,b** overlap (Fig. 5a) in tetrahydrofuran.[9] The –NH resonances of **3a,b** were decoupled, permitting the assignment of the adjacent coupled proton $H_3$ (see structures **3a,b**). The assignment of $H_3$ was confirmed by additional NMR experiments.

The methine resonances of **6a,b** collapsed with D-exchange of the NH and OH protons into singlets and doublets (Fig. 5b). For **3a,b** the four methine resonances are similarly resolved (Fig. 3a); such separation (~20 Hz) facilitates selective heteronuclear decoupling. Irradiation of $H_A$ (Fig. 3a) fully decouples the aminal C-3 resonance (III) (Fig. 3c). Carbon signals I, II and IV remain partly coupled (for a discussion of the $^{13}C$ assignments see Ref. 3); the attachment of $H_3$ ($H_A$) to an aminal C is thus confirmed. It is noteworthy that resonance IV is almost totally collapsed,[10] supporting the assignment that $H_B$ (6.9 ppm) is the second aminal methine proton; signals C and D at $\delta$ 6.28 and 6.55 are thus associated with the acetal protons. Differentiation of *cis* from *trans* follows: The doublets at $\delta$ 6.55 and 7.15 (Fig. 3a) were assigned to the *trans* methine protons, since it has been shown[11] that $^5J_{H_1,H_3}$ (*trans*) is greater than $^5J_{H_1,H_3}$ (*cis*).[12] The signals at $\delta$ 6.28 and 6.90 were assigned to the *cis* isomer; the methine proton data are shown in Fig. 3. The complete assignments for **3a,b** and **6a,b** are listed in Table 3. The results of the splitting-pattern analysis are shown in Table 4.

$^1H$ NMR spectra of the 2,6-dichlorobenzamide/phthalaldehyde[13] adduct **7** were obtained in DMSO-$d_6$ and $CDCl_3$. In DMSO-$d_6$ (Fig. 6a) the region between $\delta$ 5.5 and 6.6 shows four protons, two methine and two OH protons, not unlike adduct **2**. Figure 6(a) shows that the methine doublet centered at $\delta$ 5.80 is coupled ($^3J_{H,OH}$ = 10 Hz) to the OH proton at $\delta$ 6.25. The second methine proton at $\delta$ 6.45 is coincident with its adjacent OH proton.




**7**

The spectrum of **7** in $CDCl_3$ is shown in Fig. 6(c). The influence of solvent is substantial for this compound. Both OH protons are further upfield in $CDCl_3$ than in DMSO, suggesting a weaker intermolecular H-bonding ability of $CDCl_3$ relative to DMSO. An interesting feature of this spectrum is that one of the methine protons ($\delta$ 5.88) is a doublet ($^3J_{H,OH}$ = 13 Hz), but the second shows no resolvable coupling. Irradiation of the doublet at $\delta$ 3.25 (Fig. 6(d)) collapsed the doublet at $\delta$ 5.88 and reduced the OH peak at $\delta$ 4.75, owing to saturation.[14] The difference between the two methine, OH coupling constants is difficult to explain, however. One explanation would be a difference in the exchange rate of the OH protons. A series of variable-temperature spectra were taken, and at – 50°, when the exchange rate was slowed, a coupling of 5 Hz was seen (Fig. 6(e)). Further reduction in temperature did not increase this coupling constant. The intrusion of the Cl atoms, resulting from amide bond rotation (Fig. 7), may force the OH proton $H'_B$ into a different conformation, thereby influencing the magnitude of the average $^3J_{H,OH}$ value.

Table 4. Coupling constants for the isomeric phthalan compounds **3a** and **3b**, **6a** and **6b**

| Compd/Position | Coupling Constant, J (Hz) | |
|---|---|---|
| **3a** (cis) | | |
| $H_1$ | $^3J_{H_1,OH} = 9$ | $^5J_{H_1,H_3} = 0$ |
| $H_3$ | $^3J_{H_3,NH} = 9$ | $^5J_{H_3,H_1} = 0$ |
| **3b** (trans) | | |
| $H_1$ | $^3J_{H_1,OH} = 0$ | $^5J_{H_1,H_3} = 2$ |
| $H_3$ | $^3J_{H_3,NH} = 10$ | $^5J_{H_3,H_1} = 2$ |
| **6a** (cis) | | |
| $H_1$ | $^3J_{H_1,OH} = 8$ | $^5J_{H_1,H_3} = 0$ |
| $H_3$ | $^3J_{H_3,NH} = 9$ | $^5J_{H_3,H_1} = 0$ |
| **6b** (trans) | | |
| $H_1$ | $^3J_{H_1,OH} = 9$ | $^5J_{H_1,H_3} = 3$ |
| $H_3$ | $^3J_{H_3,NH} = 9$ | $^5J_{H_3,H_1} = 3$ |

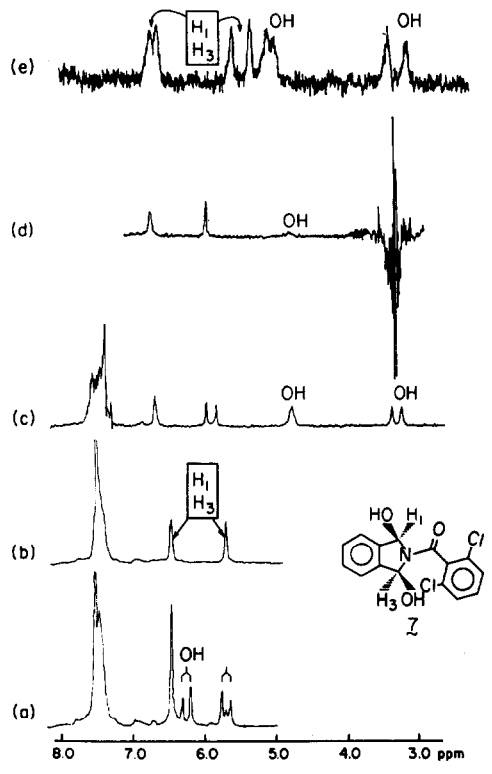



Fig. 6. (a) $^1$H NMR spectrum in DMSO-$d_6$ of 2,6-dichlorobenzamide/phthalaldehyde adduct. (b) Deuterium-exchanged sample. (c) In $CDCl_3$. (d) Saturation experiment. (e) Spectrum in $CDCl_3$ at 223 K. The change in OH chemical shifts is probably due to stronger intermolecular hydrogen bonding at lower temperature.

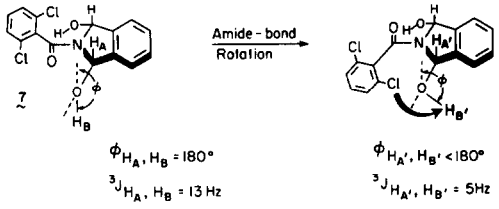



Fig. 7. Rotation of benzylic amide bond allows intrusion of a chlorine atom and compresses the average dihedral angle $\phi$, changing the $J$ value.

## CONCLUSIONS

The $^1$H NMR data show that the OH groups in isoindolines are *cis*. In the phthalan compounds, mixtures of *cis* and *trans* are observed. $^{13}$C NMR spectroscopy is a useful technique to distinguish between phthalan and isoindoline.

## EXPERIMENTAL

The $^{13}$C NMR and low-field $^1$H NMR spectra were obtained on a JEOL JNM-FX60Q Fourier-transform spectrometer and a 90-MHz Perkin–Elmer R-32 spectrometer, respectively. The high-field $^1$H NMR spectrum was run on a Bruker WH-270 spectrometer. The $^{13}$C spectra were obtained with broadband $^1$H decoupling unless otherwise noted. All carbon and proton chemical shifts are reported with respect to internal $Me_4Si$; $^{13}$C chemical shifts are accurate to $\pm 0.07$ ppm; the samples were run at ambient temp (30–35°) in DMSO-$d_6$ (sample **6** in THF-$d_8$) unless otherwise specified.

The syntheses of the compounds investigated here have been reported.[3]

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## REFERENCES

[1]R. D. Reynolds, D. L. Arendsen, D. F. Guanci and R. F. Wickman, *J. Org. Chem.* **35**, 3940 (1970) and refs therein.
[2]R. D. Reynolds, D. F. Guanci, C. B. Neynaber and R. J. Conboy, *Ibid.* **43**, 3838 (1978).
[3]T. DoMinh, M. H. Stern, D. D. Giannini and L. W. Kelts, *Tetrahedron* **39**, 1667 (1983).
[4]Syntheses of the compounds discussed in this work, except **1** and **4**, are described in Ref. 3. Adduct **1**: m.p. 114–116°, yield 58%; adduct **4**: m.p. 123–125°, yield 40%.
[5]K. Bowden, F. A. El-Kaissi and N. S. Nadvi, *J. Chem. Soc. Perkin Trans.* 2, 642 (1979).
[6]Carbons of this type have been reported with chemical shifts of ~81 ppm: F. Knoll and R. Appel, *Chem. Ber.* **110**, 3950 (1977).
[7]For an excellent discussion of this subject, see: R. K. Hill and T.-H. Chan, *Tetrahedron* **21**, 2015 (1965).
[8]We acknowledge a reviewer's suggestion to perform a VT experiment.
[9]Compound **6a,b** decomposed rapidly in dimethyl sulfoxide but was stable for several hr in THF. These products often exist as a slowly equilibrating mixture of reactants and adducts, but we have not determined which factors most influence the equilibrium. The position of equilibrium appears to depend on the solvent and the structure of the adduct.
[10]The residual coupling constant $J_r$ has been shown to be directly proportional to the difference $\Delta\omega$ between the Larmor frequency $\omega_x$ of $^1H_x$ and the coherent radio frequency $\omega_{rf}$: R. R. Ernst, *J. Chem. Phys.* **45**, 3840 (1966). Thus, the $^{13}$C nucleus attached to $H_B$ (Fig. 3(a)) will show the smallest $J_r$ in Fig. 3(c), and $J_r$ for C-1 will be proportionally larger.
[11][a]L. F. Johnson, A. V. Robertson, W. R. J. Simpson and B. Winthrop, *Austral. J. Chem.* **19**, 115 (1966); [b]K. C. Cole and D. F. R. Gilson, *Can. J. Chem.* **52**, 281 (1974); [c]M. Barfield, R. J. Spear and S. Sternhell, *J. Am. Chem. Soc.* **93**, 5322 (1971); [d]M. Barfield, R. J. Spear and S. Sternhell, *Ibid.* **97**, 5160 (1975).
[12]A variable-temp. experiment was done on a phthalan compound similar to **6** (with a *t*-Bu group instead of the trichloro group). Heating to 100° showed no coalescing of peaks, thus showing that if hindered rotation was present $\Delta G_c^{\ddagger} > 18.7$ kcal mol$^{-1}$, which is unlikely.
[13]The stereochemistry for structure **7** is shown as *trans*. See discussion regarding structures **2** and **5**.
[14]Two mechanisms are possible to explain the effect. One, intramolecular, involves the interchange of OH protons due to amide slow rotation. The other, intermolecular, is spin saturation due to the replacement of an unsaturated proton by one that is partly saturated from another molecule.