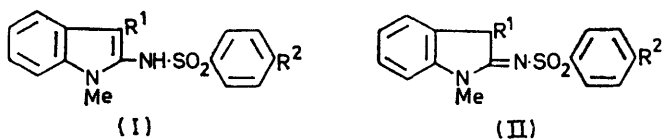


Reactions of Some 1,3-Disubstituted Indoles and of 3-Methylindole with Arylsulphonyl Azides

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1,3-Dimethylindole reacts with arylsulphonyl azides forming 1,3-dimethyl-2-arylsulphonylaminoindoles. The compounds exist in solution as both the aminoindole and iminoindoline forms. The reaction of 1-benzyl-3-methylindole is similar but 1-methyl-3-phenylindole is less reactive and yielded crystalline material with only one azide. 1,3-Dimethylindole and 3-methylindole react with tosyl azide in the presence of pyridine forming compounds which contain two tolylsulphonyl groups.

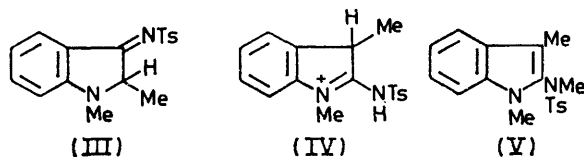
As part of our investigation of the reactions between indoles and arylsulphonyl azides,¹⁻³ the behaviour of 1,3-dialkylindoles has been examined. 1,3-Dimethylindole reacted smoothly with tosyl azide giving a high yield of the sulphonamide (Ia). The product was



a; R¹ = R² = Me
 b; R¹ = Me, R² = NO₂
 c; R¹ = Me, R² = Cl
 d; R¹ = Me, R² = H
 e; R¹ = Me, R² = NH·COMe

f; R¹ = Me, R² = OMe
 g; R¹ = Ph, R² = NO₂
 h; R¹ = PhCH₂, R² = Me
 i; R¹ = PhCH₂, R² = NO₂

different from the material obtained by the reaction of tosyl azide with 1,2-dimethylindole,⁴ showing that the methyl group had not migrated [C(3) → C(2)], and the n.m.r. spectrum of the compound in [²H]chloroform indicated that it was entirely in form (II). If the



product had had the alternative structure (III) the N-Me signal would have appeared at τ 7.1 and the material should have been orange-coloured.¹ In trifluoroacetic acid the compound was present as the cation (IV) and the n.m.r. spectrum of the substance in [²H₆]dimethyl sulphoxide showed it to be entirely in the indole form (Ia). The spectrum of a solution in a mixture of [²H]chloroform and [²H₆]dimethyl sulphoxide showed the presence of both forms. The effect of temperature on this equilibrium was studied by measuring the n.m.r. spectrum of such a solution at three temperatures. The proportion of (I) increased with increasing temperature and a plot of $\log K$ { $K = [(II)/(I)]$ } gave a straight line and a value of $\Delta H = -16.4$ kcal.

When a solution of the indole (Ia) in dilute alkali was shaken with dimethyl sulphate, compound (V), the product of *N*-methylation, was obtained. If *C*-methylation had occurred the known¹ compound (VI) would

¹ A. S. Bailey, R. Scattergood, and W. A. Warr, *J. Chem. Soc. (C)*, 1971, 2479.

² A. S. Bailey, R. Scattergood, and W. A. Warr, *J. Chem. Soc. (C)*, 1971, 3769.

have been obtained. Compounds (V) and (VI) were valuable reference compounds for spectroscopic measurements.

In order to obtain some indication of the effect of substitution on the reactivity of the azide molecule the reactions of 1,3-dimethylindole with five more sulphonyl azides were investigated. The *p*-nitro-derivative was the most reactive, yielding 85% of the indole (Ib) after 3.5 h; a similar yield of the indole (If) required 4 days heating. The n.m.r. spectra of these compounds are set out in the Table: the chemical shifts of the NH

N.m.r. data (τ values) for compounds (I) and (II)

	Solvent*	C(3)H (II) †	C(3)Me (I)(s)	C(3)Me (II) (d, J 8 Hz)	NMe (I)(s)	NMe (II)(s)	COMe or OMe	% (II)
a	C	5.41		8.28		6.71		100
	D		8.39		6.47			0
	T	5.02		8.20		6.20		100
	C/D	5.5		8.36		6.72		100
b	D		8.4		6.48			0
	T	5.30		8.26		6.41		100
	C/D	5.35	8.25	8.17	6.27	6.54		45
c	C	5.46	8.42	8.29	6.41	6.72		94
	D		8.38		6.46			0
	C/D	5.52	8.35	8.32	6.41	6.68		27
d	C	5.40		8.28		6.69		100
	D		8.43		6.49			0
e	C/D	5.28	8.18	8.08	6.24	6.48		80
	D		8.40		6.51		7.91	0
f	C/D	5.27	8.10	8.08	6.20	6.45	7.61	80
	C	5.47	8.41	8.31	6.37	6.74	6.16	37
g	D		8.39		6.48		6.16	0
	C/D	5.30	8.20	8.13	6.24	6.48	5.95	63
h	D				6.17			0
	T	4.12				6.20		100
i	C	5.1				6.84		100
	D				6.54			0
i	C	5.09				6.82		100
	D				6.42			0

* C = CDCl₃; D = (CD₃)₂SO; T = CF₃·CO₂H; C/D = 20% w/w (CD₃)₂SO in CDCl₃. † (IIa-f) quartet, J 8 Hz.

signals [0.6 to -0.4 in (CD₃)₂SO and ca. 3.3 in CDCl₃] have been omitted and also those of the aromatic multiplets. In all cases the lowest field signal was from the protons *ortho* to the SO₂ group, the signals for the imino-compound (II) being to low field of the signals of the amino-form (I), e.g. compound (V) shows the signal at τ 2.28 and compound (VI) at 2.05. The coupling

³ A. S. Bailey, A. G. Holton, and J. F. Seager, *J.C.S. Perkin I*, 1972, 1003.

⁴ A. S. Bailey and J. J. Merer, *J. Chem. Soc. (C)*, 1966, 1345.

constant for the $\text{CH}\cdot\text{CH}_3$ group in compounds (IIa—f) was *ca.* 8 Hz.

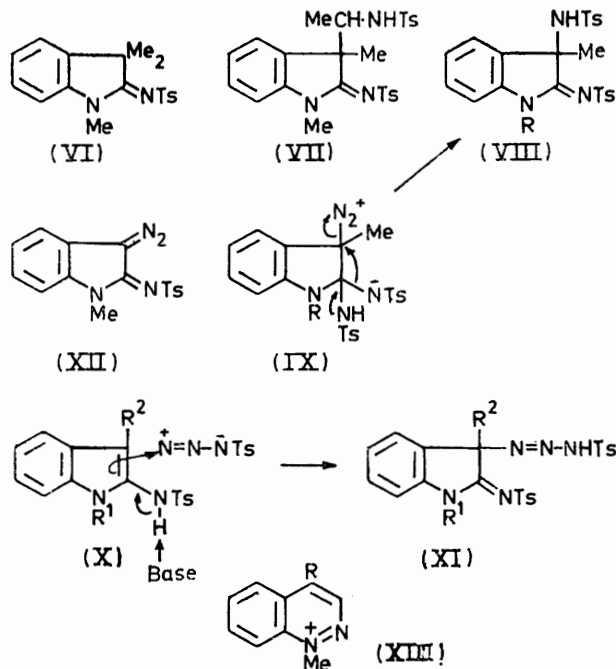
The Table shows that the isomer (I) is clearly favoured in dimethyl sulphoxide. The proportions of the isomers in chloroform solution do not change in a regular manner as the substituent (R^2) is varied, and we believe that the percentages of the isomers observed in pure chloroform are not equilibrium values. The values recorded in the Table for the chloroform–dimethyl sulphoxide mixtures were determined after the solutions had been kept for 24 h. The proportion of isomer (I) seems influenced by the inductive effect of the substituent R^2 , electron-withdrawing groups favouring the indole form. The two protons in the CH_2 group of (IIh) are non-equivalent; the signal from the 3-proton appears as a doublet of doublets at τ 5.1 (J 4 and 8 Hz) and one signal of the CH_2 group appears at 6.25 (J 4 and 14 Hz) and the other at *ca.* 6.9 (partially obscured by the NMe signal) (J 8 and 14 Hz). The signals of these protons in (IIi) were similar and the spectrum remained unchanged on heating the solution to 100°. The formation of (Ia) by boiling compound (VII) with alkali has already been described.² 1-Methyl-3-phenylindole was far less reactive than 1,3-dimethylindole and only yielded crystalline material (Ig) with the most reactive azide.

The first sample of 1,3-dimethylindole used in this work was prepared by treating *N*-methylaniline with chloroacetone.⁵ When this material was warmed with a tosyl azide a compound (VIII; $\text{R} = \text{Me}$) containing two tosyl groups was obtained. G.l.c. analysis of the 1,3-dimethylindole used showed it to contain 15% of 1,2-dimethylindole and traces of unidentified materials. We subsequently observed that the production of compound (VIII; $\text{R} = \text{Me}$) was catalysed by base, the addition of a small quantity of pyridine to a mixture of *pure* 1,3-dimethylindole (prepared from 3-methylindole) and tosyl azide giving (VIII; $\text{R} = \text{Me}$) in 72% yield. This compound was also obtained from compound (Ia) by warming it with azide in the presence of pyridine; the isolation of (VIII; $\text{R} = \text{Me}$) from the reaction between 1,2,3-trimethylindole and tosyl azide has already been described.¹

Although 1-methylindole⁶ and 2-methylindole⁴ react readily with tosyl azide, 3-methylindole reacts very slowly. After heating a mixture of 3-methylindole and the azide for 1 week at 50° the only crystalline material isolated (in 11% yield) was the product (VIII; $\text{R} = \text{H}$) of the reaction between two molecules of the azide and 1 molecule of the indole. In the presence of pyridine the yield (25%) was improved but the reaction is still much slower than the reactions of other indoles. Compound (VIII; $\text{R} = \text{H}$) was obtained in small quantity from the reaction between 2,3-dimethylindole and tosyl azide.¹

The compounds containing two tosyl groups may be formed by the addition of a second molecule of the azide

to compound (I) forming the intermediate (IX), which eliminates nitrogen and rearranges to (VIII). Alternatively the function of the base may be to produce the anion (X) which attacks a molecule of azide forming (XI).⁷ When $\text{R}^2 = \text{Me}$, (XI) collapses with formation



of (VIII) and nitrogen. But when $\text{R}^2 = \text{H}$ the diazo-compound (XII) is formed⁸ with loss of toluene-*p*-sulphonamide; the formation of this diazo-compound supports this suggested mechanism. The mass spectra of the compounds (Ia—f) were very similar; the molecular ion signals were weak [*e.g.* (Ib), m/e 345 (16%)] and the base peak [m/e 159 (XIII; $\text{R} = \text{Me}$)] was the only strong signal. The base peak in the spectrum of (Ig) was (XIII; $\text{R} = \text{Ph}$), the molecular ion (m/e 407) signal being weak (7%). In the mass spectrum of (V), the molecular ion signal (m/e 328) was weak (14%), the base peak appearing at m/e 173 ($M - \text{Ts}$), and the peak at m/e 158 ($173 - \text{Me}$) was small (4%). In contrast the isomer (VI) gave an intense molecular ion [m/e 328 (63%)] with the base peak at m/e 173, and the spectrum included m/e 158 ($173 - \text{Me}$, 15%) and 146 ($173 - \text{HCN}$, 27%). In the mass spectrum of (VIII; $\text{R} = \text{H}$) the molecular ion was of moderate intensity [m/e 469 (35%)] and other signals included m/e 341 ($M - 2\text{SO}_2$, 37%), 314 ($M - \text{Ts}$, 100), 250 ($314 - \text{SO}_2$, 22), 159 ($M - 2\text{Ts}$, 100), and 144 ($159 - \text{Me}$, 32).

EXPERIMENTAL

General directions and instruments used have been reported.^{1,2} I.r. spectra are for Nujol mulls unless otherwise stated. 3-Methylindole was a commercial sample;

⁶ A. S. Bailey, W. A. Warr, G. B. Allison, and C. K. Prout, *J. Chem. Soc. (C)*, 1970, 956; W. A. Warr, D.Phil. Thesis, Oxford, 1970.

⁷ M. Regitz, *Angew. Chem. Internat. Edn.*, 1967, **6**, 733.

⁸ A. J. Buckley, unpublished work.

⁵ C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 1964, 938; J. Meisenheimer, L. Angermann, O. Finn, and E. Vieweg, *Ber.*, 1924, **57**, 1753.

3-phenylindole⁹ and 3-benzylindole¹⁰ were prepared by established methods. They were methylated with methyl iodide-sodium-liquid ammonia and the products were purified by heating to 150° under nitrogen for 24 h with sodium and distilled *in vacuo*. 1-Methyl-3-phenylindole was prepared from phenacyl bromide and *N*-methylaniline.¹¹

1,3-Dimethyl-2-p-tolylsulphonylaminoindole (Ia).—A mixture of tosyl azide (8.0 g) and 1,3-dimethylindole (6.0 g) was heated at 50° for 22 h and methanol (10 ml) added. The solid was collected, washed with methanol, and dried; yield 7.7 g, m.p. 142–144°. Recrystallisation from benzene gave white crystals, m.p. 146–147°. When the proportion of azide was increased to 2 mol. equiv. the product was obtained in 72% yield (Found: C, 64.7; H, 5.7; N, 9.2; S, 10.1. C₁₇H₁₈N₂O₂S requires C, 65.0; H, 5.7; N, 8.9; S, 10.2%). ν_{\max} (CHCl₃) 1495, 1572br,s, and 1625 cm⁻¹ (no NH band); λ_{\max} 225, 282, and 287.5 nm (ϵ 32,800, 12,900, and 12,500). The equilibrium (Ia) \rightleftharpoons (IIa) was studied for a solution containing 100 mg of the compound in [²H]chloroform (0.5 ml) and [²H₆]dimethyl sulphoxide (0.1 ml) by measuring the intensities of signals at τ 6.4 [NMe of (I)] and 6.7 [NMe of (II)], the intensities of the signals for the CMe groups providing a check [Found: 60°, $K = 4.0$; 70°, $K = 1.99$; 80°, $K = 1.04$] [$K = \frac{[(II)]}{[(I)]}$]. The compound was unaffected by sodium borohydride and by pyridinium bromide perbromide; it was recovered after being boiled for 22 h with alcoholic 25% potassium hydroxide.

The indole (0.6 g) was dissolved in warm 2*M*-sodium hydroxide solution (10 ml), the solution was cooled rapidly, and water (5 ml) was added to give clear solution. Dimethyl sulphate (0.3 ml) was added in three portions and the mixture shaken vigorously. The solid which separated was collected, washed with alkali and with water, and dried. **1,3-Dimethyl-2-(*N*-methyl-*p*-tolylsulphonylamino)indole (V)** formed rods (0.33 g), m.p. 131–132° (from ethanol) (Found: C, 65.9; H, 6.1; N, 8.5. C₁₈H₂₀N₂O₂S requires C, 65.9; H, 6.1; N, 8.5%). ν_{\max} (CHCl₃) 1488, 1498, 1570w, 1601, and 1619w cm⁻¹; λ_{\max} 226, 282.5, and 290 nm (ϵ 36,900, 7760, and 8040); τ (CDCl₃) 8.42 [3H, s, C(3)Me], 7.54 (3H, s, tosyl Me), 6.69 (3H, s, NMeTs),¹² 6.29 (3H, s, indole NMe), 2.4–3.0 (6H, m, aromatic), and 2.28 (2H, d, *J* 8 Hz, low-field half of tosyl signal).

The other compounds (Ib–i) were prepared by heating the indole with 1.1 mol. equiv. of azide for times stated; methanol was added and the solid collected.

1,3-Dimethyl-2-p-nitrophenylsulphonylaminoindole (Ib).—Indole (0.10 g), 47°, 3.5 h, yield 84%; pale yellow crystals, m.p. 184–185° (from propan-1-ol) (Found: C, 55.6; H, 4.5; N, 12.3; S, 9.6. C₁₆H₁₅N₃O₄S requires C, 55.7; H, 4.4; N, 12.2; S, 9.3%). ν_{\max} 1499, 1530, 1575br,s, 1610, and 1628 cm⁻¹; λ_{\max} 224 and 269 (ϵ 21,600 and 11,600).

2-p-Chlorophenylsulphonylamino-1,3-dimethylindole (Ic). Indole (1.6 g), 47°, 20 h, 85% yield; crystals, m.p. 128–130° (from chloroform-methanol) (Found: C, 57.7; H, 4.8; Cl, 10.6; N, 8.7; S, 10.1. C₁₆H₁₃ClN₂O₂S requires C, 57.4; H, 4.5; Cl, 10.6; N, 8.4; S, 9.6%). ν_{\max} (CHCl₃) 1499, 1571br,s, and 1629w cm⁻¹; λ_{\max} 223, 282, 287, and 292infnm (ϵ 18,000, 13,800, 13,800, and 11,900).

1,3-Dimethyl-2-phenylsulphonylaminoindole (Id).—Indole (2 g), 45°, 48 h, 44%; m.p. 112–114° (softened 105°) [from

methanol-water (9:1)] (Found: C, 64.0; H, 5.6; N, 9.3; S, 10.8. C₁₆H₁₆N₂O₂S requires C, 64.0; H, 5.3; N, 9.3; S, 10.7%). ν_{\max} (CHCl₃) 1499, 1577br,s, and 1629 cm⁻¹; λ_{\max} 219, 281.5, and 285 nm (ϵ 25,100, 17,900, and 17,100). The m.p. of the compound could not be increased but the material appeared homogeneous (t.l.c.).

2-p-Acetamidophenylsulphonylamino-1,3-dimethylindole (Ie). A solution of the indole (0.6 g) in chloroform (10 ml) containing the azide (1 g) was boiled for 4 days; the chloroform was evaporated and the residue triturated with methanol (yield 1.0 g). The product had m.p. 214–217° (from propan-1-ol) (Found: C, 60.2; H, 5.8. C₁₈H₁₉N₃O₃S requires C, 60.5; H, 5.4%). ν_{\max} 1500, 1530br, 1560br, 1598, 1708s, and 3360 cm⁻¹.

2-p-Methoxyphenylsulphonylamino-1,3-dimethylindole (If). Indole (1.5 g), 45° 4 days, 68%; recrystallisations (ethanol) gave large crystals, melting and resolidifying 136–141°, m.p. 162–163° (Found: C, 62.0; H, 5.5; N, 8.3. C₁₇H₁₈N₂O₃S requires C, 61.8; H, 5.5; N, 8.5%). ν_{\max} (CHCl₃) 1502, 1577br,s, 1602, 1629, and 3365 cm⁻¹; λ_{\max} 227, 281, 286sh, and 295infnm (ϵ 34,300, 14,000, 13,100, and 10,700).

1-Methyl-2-p-nitrophenylsulphonylamino-3-phenylindole (Ig). Indole (3.1 g), 50°, 9 days, 36%; fibrous mass of orange-yellow needles, m.p. 196–197° (from benzene) (Found: C, 62.1; H, 3.9; N, 10.5. C₂₁H₁₇N₃O₄S requires C, 61.9; H, 4.2; N, 10.3%). ν_{\max} (CHCl₃) 1429br, 1448sh, 1479, 1533, 1608, and 3370 cm⁻¹; λ_{\max} 227 and 267 nm (ϵ 32,800 and 16,300). Tosyl azide did not react with 1-methyl-3-phenylindole (no sign of reaction after 1 week at 50°).

3-Benzyl-1-methyl-2-p-tolylsulphonylaminoindole (Ih). Indole (0.3 g), 47°, 6 days, 66%; m.p. 176–178° (from chloroform-methanol) (Found: C, 70.3; H, 5.6; N, 7.4%; *M*, 390. C₂₃H₂₂N₂O₂S requires C, 70.8; H, 5.6; N, 7.8%; *M*, 390); ν_{\max} (CHCl₃) 1529, 1561sh, 1574s, 1580sh, 1600sh, and 1628 cm⁻¹; λ_{\max} 223, 283, 287, and 296 nm (ϵ 32,900, 15,300, 15,100, and 12,100).

3-Benzyl-1-methyl-2-p-nitrophenylsulphonylaminoindole (Ii). Indole (0.6 g), 47°, 2 days, 81%; pale yellow crystals, m.p. 185–186° (from chloroform-methanol and then from propan-1-ol) (Found: C, 63.2; H, 4.5. C₂₂H₁₉N₃O₄S requires C, 63.2; H, 4.5%). ν_{\max} (CHCl₃) 1497, 1532, 1570s, 1595sh, and 1608w cm⁻¹; λ_{\max} 266, 312, and 316 nm (ϵ 13,500, 8020, and 7780); τ (CDCl₃) 5.2 (*J* 4 and 8 Hz, CH·CH₂), 6.2 (*J* 4 and 13 Hz, CH·CHH), and 6.9 (*J* 8 and 13 Hz, CH·CHH).

1,3-Dimethyl-3-p-tolylsulphonylamino-2-p-tolylsulphonylaminoindole (VIII) (R = Me).—(a) The impure sample of 1,3-dimethylindole (6.0 g; prepared from *N*-methylaniline and chloroacetone) and tosyl azide (8.0 g) were heated at 50° for 24 h and methanol (20 ml) was added. The solid (3.9 g) was collected and recrystallised from chloroform-methanol (yield 1.2 g).

(b) A mixture of pure 1,3-dimethylindole (1 g), tosyl azide (2.8 g), and pyridine (1 ml) was heated at 55° for 18 h. Methanol (3 ml) was added and the solid collected (72% yield) and recrystallised from chloroform-methanol.

(c) Compound (Ia) (1 g), tosyl azide (1 g), and pyridine (1 ml) were heated for 24 h at 55°. The usual work-up gave the product (1.2 g, 65%).

¹¹ A. F. Crowther, F. G. Mann, and D. Purdie, *J. Chem. Soc.*, 1943, 58; M. Julia and J. Lenzi, *Bull. Soc. chim. France*, 1962, 2263.

¹² J. C. N. Ma and E. W. Warnhoff, *Canad. J. Chem.*, 1965, 43, 1849.

⁹ Aktieselskabet Dumex, B.P. 959,203 (*Chem. Abs.*, 1964, 61, 10,659g).

¹⁰ E. F. Pratt and L. W. Botimer, *J. Amer. Chem. Soc.*, 1957, 79, 5248.

All the samples were identical (i.r. and n.m.r. spectra; t.l.c.), m.p. 228—229° (Found: C, 59.8, 60.0; H, 5.3, 5.4; N, 8.6; S, 13.9. $C_{24}H_{25}N_3O_4S_2$ requires C, 59.6; H, 5.2; N, 8.7; S, 13.3%); ν_{\max} (CHCl₃) 1495, 1582br,s, 1625, and 3240 cm⁻¹; λ_{\max} 225, 280sh, 286, and 303 nm (ϵ 23,200, 9660, 10,400, and 7750); τ [(CD₃)₂SO] 8.29 [3H, s, C(3)Me], 7.60 and 7.69 (2 × tosyl Me), 6.77 (3H, s, NMe), 2.5—3.5 (10H, m, aromatic), 2.14 (2H, d, *J* 8 Hz, low-field half of tosyl signal), and 1.66 (1H, NH, exchanged in D₂O).

3-Methyl-3-p-tolylsulphonylamino-2-p-tolylsulphonylimino-indole (VIII; R = H).—(a) 3-Methylindole (6.0 g) and tosyl azide (8.0 g) were heated at 50° for 1 week and benzene was added. The solid was collected (1.0 g) and recrystallised from propan-1-ol; m.p. 238—239° (0.6 g).

(b) The indole (1 g), the azide (3.3 g), and pyridine (1 ml) were heated at 55° for 48 h and methanol (3 ml) was added. The solid (0.9 g, 25%) was recrystallised from propan-1-ol-acetic acid; m.p. 238—240°.

The two samples were identical (n.m.r. and i.r. spectra; t.l.c.) (Found: C, 58.6; H, 4.9; N, 9.4; S, 14.2. $C_{23}H_{23}N_3O_4S_2$ requires C, 58.9; H, 4.9; N, 9.0; S, 13.6%); ν_{\max} 1485, 1602br,s, 1620br,s, 3225, and 3275 cm⁻¹; λ_{\max} 224, 273, 278, and 297 nm (ϵ 31,100, 14,000, 14,000, and 9310); τ [(CD₃)₂SO] 8.67 [3H, s, C(3)Me], 7.64 and 7.68 (2 × tosyl Me), 3.2—3.4 (2H, m, aromatic), 2.5—3.0 (8H, m, aromatic), 2.16 (2H, d, *J* 8 Hz, low-field half of tosyl signal), 1.37 (1H, s, NH), and -1.10 (1H, s, NH).

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