The Identification of 10 and 11 Substituted 7*H*-Benzimidazo[2,1-*a*]benz[*de*]isoquinolin-7-ones through ^{1}N NOE Studies on their Methyl *p*-Toluenesulfonate Salts

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The spectral similarities of 10 and 11 substituted 7*H*-benzimidazo[2,1-*a*]benz[*de*]isoquinolin-7-ones hinder the identification of the individual isomers. Preparation of the 13-methyl *p*-toluenesulfonate salts of these compounds has allowed the assignment by the use of NOE techniques. Saturation of the *N*-methyl caused an NOE at H-12. The coupling pattern of H-12 then provides identification of the compound.

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The reaction of 1,8-naphthalic anhydride (**1**) with 4-substituted *o*-phenylenediamines (**2**) as illustrated in Scheme 1, yields a mixture of 10 and 11 substituted 7*H*-benzimidazo[2,1-*a*]benz[*de*]isoquinolin-7-ones (**3** and **4**) [1-5]. These mixtures are readily separated into the pure regio isomers by preparative hplc. However, absolute identification of the isomers has only been accomplished by comparison with samples synthesized in an unambiguous manner [1-5].

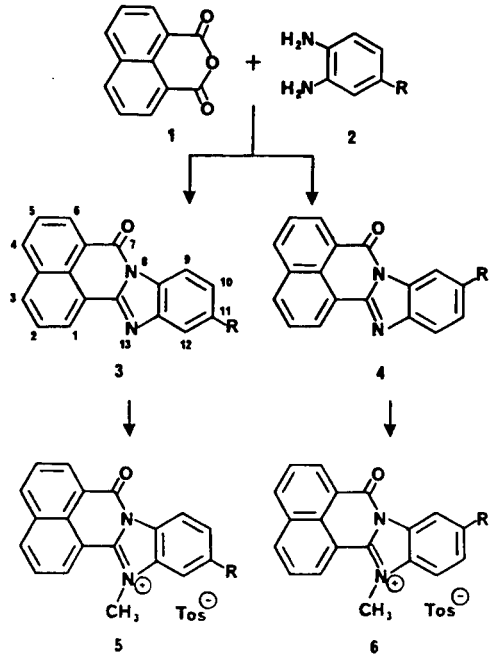
The identification of the regio isomers is hampered because of the subtle differences in the molecules. The ^{1}H nmr spectra are reasonably resolved at 360 MHz. The spectra, however, contain three spin systems consisting of two 1,2,3 trisubstituted benzenes and one 1,2,4 trisubstituted benzene. Changing the substituent from position 10 to 11 does not change the coupling pattern; therefore, decoupling cannot be used for assignment.

Europium shift reagents were not used because of the uncertainty in determining the site of complexation. This in turn could lead to errors in the analysis of the data since the shift changes are related to the angle and distance between the various resonances and the europium ion.

The nmr spectra of suitable polycyclic rings were not available for comparison. The use of substituent parameters was insufficient to allow assignments with a high degree of certainty.

The formation of the methyl *p*-toluenesulfonate salts **5** and **6** provided a means, through NOE's, to the identification of these compounds. Saturation of the *N*-methyl resonance caused an observable NOE at H-12. In compounds **5a, 5b**, and **5c**, the resonance identified as H-12 is a doublet with a coupling constant of approximately 3 Hz. The coupling constant is typical of aromatic meta couplings. This requires that a proton be at carbon 10 and the substituent be at carbon 11. In compounds **6a, 6b**, and **6c**, H-12 is a doublet with a coupling of approximately 8 Hz; since this value is typical of an aromatic ortho coupling, it establishes the position of substitution for these compounds at carbon 10.

SCHEME 1



A NOE is also observed at H-1 when the *N*-methyl resonance is saturated. Decoupling then allows the assignment of H-2 and H-3. The assignments of H's 4, 5, and 6 were made from a comparison to the shifts of the H-1, 2, and 3 resonances, since the chemical environments are similar. The nmr data are tabulated in Table 1.

The use of NOE's of the methyl *p*-toluenesulfonate salts could be extended to the identification of the 9/12 isomer pairs and could undoubtedly be used in determining the position of isomers in other ring systems such as 6,7-dihydrobenzimidazol[1,2-*c*]quinazolin-6-one [6].

Table 1

^{1}H NMR Data [a] (δ) of Compounds **5** and **6**

Proton	**5a**	**6a**	**5b**	**6b**	**5c**	**6c**
1	9.32	9.31	9.37	9.39	9.31	9.32
2	8.18	8.18	8.20	8.22	8.19	8.19
3	8.84	8.84	8.89	8.90	8.86	8.86
4	8.86	8.86	8.89	8.90	8.87	8.88
5	8.19	8.21	8.21	8.22	8.20	8.20
6	9.02	9.02	9.05	9.05	9.03	9.03
9	8.78	8.79	9.01	9.06	8.73	8.94
10	7.94	--	8.25	--	8.07	--
11	--	8.02	--	8.32	--	8.15
12	8.67	8.45	8.96	8.67	8.80	8.40
13-CH_3	4.67	4.67	4.74	4.74	4.46	4.68
Tosyl	7.41/7.06 2.27	7.42/7.07 2.27	7.40/7.05 2.27	7.43/7.02 2.26	7.44/7.10 2.29	7.44/7.09 2.28

[a] 360 MHz or 270 MHz in $DMSOd_6$, chemical shifts relative to the center peak of DMSO at δ 2.50.

Table 2

Compound	MP°C	Molecular Formula	Analysis, % Calcd./Found C	H	N
3a [3-5]	233-235	$C_{18}H_9N_2ClO$	70.95	2.98	9.19
			71.24	3.21	9.11
4a [3-5]	228-230	$C_{18}H_9N_2ClO$	70.95	2.98	9.19
			70.68	2.87	9.34
3b [5]	212-214	$C_{19}H_9N_2F_3O$	67.46	2.68	8.28
			67.24	2.81	8.03
4b [5]	236-238	$C_{19}H_9N_2F_3O$	67.46	2.68	8.28
			67.39	2.66	7.97
3c [5]	228-230	$C_{18}H_9N_2BrO$	61.91	2.60	8.02
			61.64	2.63	7.92
4c [5]	227-229	$C_{18}H_9N_2BrO$	61.91	2.60	8.02
			62.15	2.43	7.86
5a	248-250	$C_{26}H_{19}N_2ClO_4S$	63.61	3.90	5.71
			63.66	4.01	5.71
6a	237-239	$C_{26}H_{19}N_2ClO_4S$	63.61	3.90	5.71
			63.33	4.08	5.41
5b [5]	263-265	$C_{27}H_{19}N_2F_3O_4S$	61.83	3.65	5.34
			61.54	3.64	5.11
6b	248-250	$C_{27}H_{19}N_2F_3O_4S$	61.83	3.65	5.34
			61.84	3.73	5.54
5c	253-255	$C_{26}H_{19}N_2BrO_4S$	58.33	3.58	5.23
			58.01	3.65	5.20
6c	245-247	$C_{26}H_{19}N_2BrO_4S$	58.33	3.58	5.23
			58.24	3.65	5.26

EXPERIMENTAL

The hplc separations were performed on a Waters Associates Prep LC System 500. The nmr data were collected on a Bruker WH-360 or WM-270 spectrometer, using the Aspect 2000 data system. The NOE data were obtained by using the difference method [7].

Preparation of 10- and 11-Substituted 7*H*-Benzimidazo[2,1-*a*]benz[*de*]-isoquinolin-7-ones **3** and **4**. General Procedure.

A mixture of 0.2 mole quantities of naphthalic anhydride (**1**) and the appropriate 4-substituted *o*-phenylenediamine **2** were heated with 400 ml of methanol or ethanol in an autoclave at 180° for 14 to 36 hours. After cooling, the solid was collected and recrystallized from DMF providing 60-80% yields of a mixture of **3** and **4** as demonstrated by two fluorescent spots on tlc (silicagel, 4:1 toluene:ethyl acetate, uv) [8]. Compounds **3** and **4** were separated by preparative hplc and the pure compounds were recrystallized from DMF. The data for these compounds are recorded in Table 2.

Reaction of **3** and **4** with Methyl *p*-Toluenesulfonate. General Procedure.

Pure **3** or **4** (0.05 mole) was heated under nitrogen on a steam bath overnight in 100-200 ml of methyl *p*-toluenesulfonate. After cooling to room temperature, the reaction mixture was slurried with a large quantity of ethyl ether, and the yellow crystals of **5** or **6** that separated were collected and recrystallized from methanol-ethyl ether. The data on these compounds are listed in Table 2.

REFERENCES AND NOTES

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[8] With this system, the 11 substituted compounds were less polar and had the higher Rf.