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THE SULPHONATION OF INDOLE AND SOME OF ITS SIMPLE ALKYL DERIVATIVES

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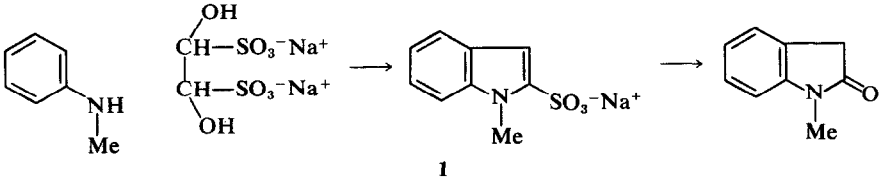
Abstract—The sulphonation of indole, 1-methyl-, 2-methyl-, and 1,2-dimethylindole by pyridinium-1-sulphonate in refluxing pyridine occurs smoothly at C3; analogous sulphonation of 3-methyl- and 1,3-dimethylindole occurs at C2; 2,3-dimethylindole does not react under these conditions.

The sulphonation of indoles by the pyridine-sulphur trioxide compound (pyridinium-1-sulphonate, referred to subsequently as $PySO_3$) has been the subject of a number of papers by Terentyev *et al.* over the period 1946 to 1952.[1] The picture which emerged from this work is not easy to understand: under mild conditions in the presence of alkali, N-sulphonates were obtained; heating indole and $PySO_3$ in the absence of solvent over the temperature range of 80–140° yielded indole-2-sulphonate anion; finally, in the additional presence of 0·6% of free SO_3, the formation of indole-3-sulphonate anion was reported.

Sulphonation of indole itself at C2 under any conditions is difficult to rationalise, and since the experimental data and structure proofs given by the Russian authors are far from satisfactory, it was decided to re-examine the question.

We have found that sulphonation of indole, 1-methyl-, 2-methyl-, and 1,2-dimethylindole by $PySO_3$ occurs smoothly in refluxing pyridine and leads as expected to C3 substitution, and that sulphonation of 3-methyl- and 1,3-dimethylindole leads to C2 substitution. N-substitution was not observed.

When we began our work, the only simple and properly characterised indole sulphonate was that prepared in 1894 by Hinsberg and Rosenzweig,[2] not by sulphonation, but by the interaction of N-methylaniline and glyoxal bisulphite.



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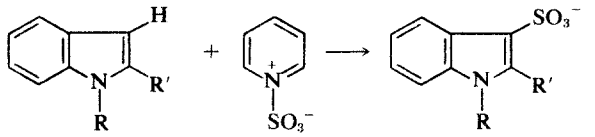
Structure **1** assigned to this compound was based on its easy hydrolysis under acid conditions to N-methyloxindole. This reaction does not however constitute a strict proof of structure, for one can envisage a plausible mechanism for the formation of N-methyloxindole by the hydrolysis of 1-methylindole-3-sulphonic acid, a reaction which would parallel the hydrolysis of 3-chloroindole to oxindole.[3] As things stood, then, Hinsberg's compound could have been either of the two sulphonates, and could not be used in arguments on structure proof of products of sulphonation of indoles.

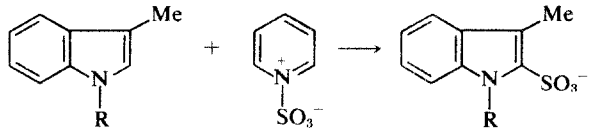
We now report the formation of pyridinium monosulphonates **2** to **7**. These salts were difficult to handle and characterise, and were converted into the corresponding methyl esters by way of the free acids (ion-exchange resin) which were then esterified by either of two methods, the action of diazomethane or of silver oxide followed by methyl iodide. The direct conversion of pyridinium salt into silver salt by an Ag^+ ion exchange system was also used. The esterification of 2-methylindole-3-sulphonic acid and of 3-methylindole-2-sulphonic acid, for reasons which are not at the moment obvious, gave very poor yields of esters **10** and **13**: we intend to study these reactions further, and will not describe them in this paper. The esterification of the remaining acids however proceeded satisfactorily to give moderate to good yields of esters **8**, **9**, **11**, and **14**, and **12** from Hinsberg's salt **1**.

The UV, NMR and mass spectra of five of the above esters are tabulated below.

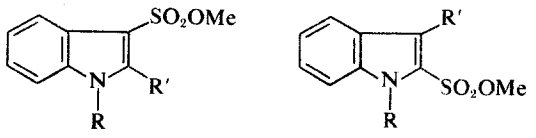
It is clear that the sulphonic esters can on the basis of their UV spectra be divided into two



2; R = R′ = H
3; R = Me, R′ = H
4; R = H′, R′ = Me
5; R = R′ = Me



6; R = H
7; R = Me



8: R = R′ = H
9: R = Me, R′ = H
11: R = R′ = Me
10: R = H, R′ = Me

12: R = Me, R′ = H
14: R = Me, R′ = Me
13: R = H, R′ = Me

groups (Fig 1): one group contains esters **8**, **9**, **11** with no differential absorption above 285 nm, and the other contains **12**, **14** with two inflections between 290 and 315 nm. This division is what one would expect if C3 substitution is the preferred mode, and strongly suggests that Hinsberg's salt is the 2-substituted isomer.

The NMR spectra are in accord with this interpretation: noteworthy is the coupling between the C2 hydrogen and the NH in methyl indole-3-sulphonate (**8**). The hydrogens at C2 in **8** and **9** are, as might be expected,[4] at lower field than the hydrogen at C3 in **12**.

The mass spectra do not help in differentiating between 2- and 3-sulphonates.

Given that the differences between the two groups of UV spectra discussed above are not very marked, and that so far these form the main basis for the structure assignments, additional proof was sought.

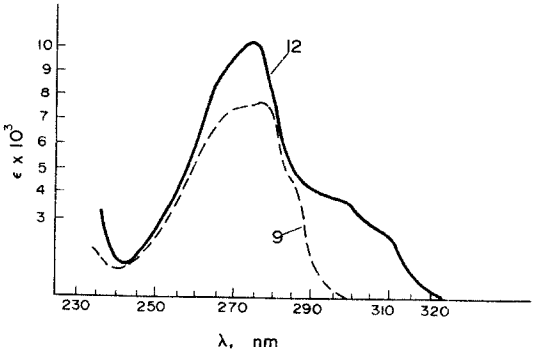


Fig 1.

2-Deutero-1-methylindole containing >99% deuterium was obtained by the action of D_2O on 2-litho-1-methylindole,[8] itself prepared by the method of Shirley and Roussel.[5]

Sulphonation of 2-deutero-1-methylindole by $PySO_3$ in refluxing pyridine, followed by ion-exchange on an Ag^+ loaded resin and a mild work-up involving freeze-drying of aqueous solutions led to a methyl 1-methylindole sulphonate which contained 96% of one atom of deuterium by mass spectral analysis: the analysis was straightforward, for this ester in undeuterated form shows absolutely no trace of a peak at *m/e* 224 (M-1), and the deuterated ester showed a peak at *m/e* 225 (M-1) which was 4% of M and which could only be due to undeuterated ester.

This 96% retention of C2-D was observed in two separate runs, and it establishes beyond reasonable doubt that 1-methylindole is sulphonated at C3.

At what stage the 3–4% of H-D exchange is occurring is not known, except that it is not taking place by protonation of the 2-D-1-methylindole by 1H-pyridinium cation (no exchange when 2-D-1-methylindole is refluxed with 1H-pyridinium chloride in pyridine) nor by protonation at the sulphonate anion stage during work-up (no exchange on prolonged reflux of 2-D-1-methylindole-3-sulphonate salt in water).

In a third run, esterification of the deuterated sulphonate was carried out differently by treating the aqueous solution of the pyridinium salt with silver oxide, boiling down the mixture to dryness under reduced pressure, and treating with methyl iodide: the resulting ester was found to have undergone 13% H-D exchange.

Table 1. UV spectra of indole sulphonic esters

	λ_{max} (nm, EtOH)	ε
8	283, 276	5800, 7800
9	288 (infl.), 277	4150, 7250
11	285, 277, 273	7700, 8700, 7950
12	306 (infl.), 294 (infl.), 274, 270 (infl.)	2770, 4100, 10200, 9500
14	314 (infl.), 304, 280, 275 (infl.)	3600, 5200, 10400, 9500

NMR spectra ($CDCl_3$ solutions)

	C—CH_3	N—CH_3	O—CH_3	aromatic region	N—H	C(4)H	C(3)H	C(2)H
8			6·30 (s)	2·54–2·90 (m)	0·45 (s) (v. broad)	2·17 (q) $J = 6·0$ $j = 3·1$		2·25 (d)[(i)] $J = 4·40$
9		6·15 (s)	6·30 (s)	2·65–2·80 (m)		2·05 (q) $J = 6·5$ $j = 3·0$		2·27 (s)
11	7·38 (s)	6·36 (s)	6·36 (s)	2·64–2·79 (m)		2·08 q $J = 6·5$ $j = 3·0$		
12		6·00 (s)	6·16 (s)	2·39–2·70 (m)		2·15 q $J = 9·1$ $j = 2·0$	2·56 (s)	
14	7·38 (s)	6·09 (s)	6·27 (s)	2·56–2·90 (m)		2·30 q $J = 8·0$ $j = 1·5$		

(i) becomes singlet on D_2O addition.

Mass spectra (figures give % relative to base peak)

	M	M-15 —CH_3	M-31 —OCH_3	M-47 —O_2CH_3	M-79 —SO_2CH_3	M-94 —SO_3CH_2	M-95 —SO_3CH_3	M-96 —SO_3CH_4	*m/e* 103 C_8H_7	*m/e* 102 C_8H_6
8	100	1	35	5	75	44	32	3	—	—
9	85	—	38	5	100	47	31	3	13	8
11	100	3	13	3	46	24	19	15	2	4
12	100	—	3	1	19	33	14	17	3	6
14	80	4	3	2	13	14	52	100	13	13

2,3-Dimethylindole does not react with $PySO_3$ in pyridine either at RT or at reflux. A quantitative recovery of the indole was made even when the work-up avoided the use of water, which might well easily hydrolyse a 1-sulphonate. There was no evidence of N-sulphonation in any of the other cases discussed above (cf reference 7).

Attempts to prepare indole-2-sulphonic acid by oxidation of sodium indoline-2-sulphonate (the indole-sodium bisulphite adduct)[6] were unsuccessful: reagents tried under a range of conditions were dichlorodicyanobenzoquinone, potassium ferricyanide, mercuric acetate, and manganese dioxide.

EXPERIMENTAL

Pyridinium indole-3-sulphonate (2)

A soln of indole (1·01 g) and of $PySO_3$ (1·21 g) in pyridine (5 ml) was refluxed for 1 hr with protection from atm moisture. The mixture was partitioned between water and ether, and the aqueous phase washed twice with ether. The resulting aqueous soln was boiled down at the water-pump and the residue dried over P_4O_{10}: this yielded a gum which slowly crystallised (1·47 g, 71%). Recrystallisation from EtOH-pyridine gave an off-white microcrystalline powder m.p. 161–2° (Found: C, 56·25; H, 4·26; N, 10·05; S, 11·60. $C_{13}H_{12}N_2SO_3$ requires: C, 56·51; H, 4·36; N, 10·14; S, 11·60%); λ_{max} 287, 277, 265, 258 nm (ϵ_{max} 4940, 5730, 8000, 8000) in EtOH.

Methyl indole-3-sulphonate (8)

(a) An aqueous soln of the pyridine salt 2 (1·19 g) was passed down a Zeokarb 226 (acid form) cation exchange column (30 ml wet). The aqueous soln of the sulphonic acid was boiled down at the oil pump, and the gummy residue treated with ethereal diazomethane until the yellow colour persisted. The ether soln was washed with Na_2SO_3aq, three times with water and dried over $MgSO_4$. The dried soln was passed down a short neutral alumina column. This yielded the crystalline ester (0·29 g, 32%) recrystallisation of which from benzene gave methyl indole-3-sulphonate as light brown platelets m.p. 115·5–116·5° (Found: C, 51·40; H, 4·20; N, 6·62; S, 15·20. $C_9H_9NSO_3$ requires: C, 51·19; H, 4·27; N, 6·63; S, 15·17%). Spectral properties quoted in Tables 1, 2, and 3.

(b) An aqueous soln of crude indole-free pyridine salt 2 (1·45 g) was passed down a column of Amberlite IR 120 (Ag) resin (30 ml). The aqueous soln of the Ag salt was then boiled down at the water-pump (protection from light) the residue dried overnight over P_4O_{10}, and left under MeI for 15 hr. The MeI was removed, the residue dissolved in ether, washed with Na_2CO_3aq, then four times with water. The dried ether soln gave the crystalline ester (564 mg, 51%), recrystallisation of which from benzene gave methyl indole-3-sulphonate as buff platelets, m.p. 120–1°.

Pyridinium 1-methylindole-3-sulphonate (3)

A soln of 1-methylindole (1·06 g) and $PySO_3$ (1·14 g) in pyridine was refluxed for 1 hr and worked up as for 2. This yielded a gum (1·81, 87%) which slowly solidified but which could not be recrystallised. It was not analysed: λ_{max} 292, 281, 263, 257 nm in EtOH.

Methyl 1-*methylindole*-3-*sulphonate* (**9**)

(a) An aqueous soln of **3**, (1·81 g) was passed down an Amberlite IR-120 (H) column (12 ml resin). The aqueous soln of the sulphonic acid thus obtained was treated with an excess of freshly prepared Ag_2O. The neutral soln of the Ag salt was then boiled down at the water pump (protection from light), and the residue dried by azeotroping with benzene. This was left overnight under MeI (30 ml). The AgI and excess Ag_2O were filtered off, the excess MeI was removed, and an ether soln of the product washed with Na_2CO_3aq, then with water, and dried over $MgSO_4$. This yielded the ester as a brown, crystalline solid (0·65 g, 47%) two recrystallisations of which from abs EtOH gave buff-coloured prisms, m.p. 127–8° (Found: C, 52·84; H, 5·21; N, 6·12; S, 14·22. $C_{10}H_{11}NSO_3$ requires: C, 53·30; H, 4·89; N, 6·20; S, 14·22%). Spectral properties given in Tables 1, 2 and 3.

(b) The pyridinium salt **3** (1·34 g) was converted into the Ag salt by means of Amberlite IR-120 (Ag) and then into the methyl ester by the action of MeI as described in the preparation of **8** by method (b). The yield of crystalline ester was 0·75 g (72%).

Pyridinium 2-*methylindole*-3-*sulphonate* (**4**)

A soln of 2-methylindole (1·02 g) and $PySO_3$ (1·11 g) in pyridine (5 ml) was refluxed for 1 hr and worked up as for **2**. This yielded a pink crystalline solid (1·35 g, 67%) which was recrystallised from pyridine-EtOH to give pyridinium 2-methylindole-3-sulphonate as an off white microcrystalline powder, m.p. 136–8° (Found: C, 57·37; H, 4·82; N, 9·51; S, 11·10. $C_{14}H_{14}N_2SO_3$ requires: C, 57·93; H, 4·82; N, 9·66; S, 11·04%); λ_{max} 287, 280, 264, 258 nm (ϵ_{max} 5450, 6500, 7550, 7150) in EtOH.

Pyridinium 1,2-*dimethylindole*-3-*sulphonate* (**5**)

A soln of 1,2-dimethylindole (0·99 g) and $PySO_3$ (1·02 g) in pyridine (5 ml) was refluxed for 1 hr. Work-up as in the preparation of **2** gave a crystalline solid (1·52 g, 78%) which could not be recrystallised. It was not analysed; λ_{max} 290, 281, 268, 257 nm in EtOH.

Methyl 1,2-*dimethylindole*-3-*sulphonate* (**11**)

The above salt (1·52 g) was converted into the methyl ester as described for the preparation of **9** by method (a). The crude ester (0·73 g, 62%) was crystallised from abs EtOH to give methyl 1,2-dimethylindole-3-sulphonate as buff needles m.p. 148°. (Found: C, 55·09; H, 5·61; N, 6·01; S, 13·11. $C_{11}H_{13}NSO_3$ requires: C, 55·24; H, 5·44; N, 5·86; S, 13·39%). Spectral properties given in Tables 1, 2, and 3.

Pyridinium 3-*methylindole*-2-*sulphonate* (**6**).

A soln of 3-methylindole (1·10 g) and $PySO_3$ (1·30 g) in pyridine (5 ml) was refluxed for 1 hr, and worked up as for **2**. This gave a gum (1·49 g, 62%) which gave an unsatisfactory analysis but which gave the expected UV absorption: λ_{max} 285, 277, 273, 258 nm (ϵ_{max} 6800, 6800, 6350, 6050 in EtOH).

Pyridinium 1,3-*dimethylindole*-2-*sulphonate* (**7**)

A soln of 1,3-dimethylindole (0·99 g) and $PySO_3$ (1·01 g) in pyridine (5 ml) was refluxed for 1 hr and worked up as in the preparation of **2**. The crude salt was a red gum (1·33 g, 64%) which slowly crystallised. Attempted recrystallisation failed because of the highly hygroscopic nature of the salt. It was not analysed; λ_{max} 305 (infl.), 281, 261 (infl.), 257 nm in EtOH.

Methyl 1,3-*dimethylindole*-2-*sulphonate* (**14**)

The above salt **7** (1·29 g) was converted into the methyl ester as in the preparation of **9** by method (a). The sulphonic acid (λ_{max} 309 (infl.), 281 nm in EtOH) was not isolated. The crude crystalline ester (0·71 g, 70%) was recrystallised 4 times from EtOH to give methyl 1,3-dimethylindole-2-sulphonate as off white needles, m.p. 102–4° (Found: C, 54·8; H, 5·54; N, 6·05; S, 13·61. $C_{11}H_{13}NSO_3$ requires: C, 55·24; H, 5·44; N, 5·86; S, 13·39%). Spectral properties are given in Tables 1, 2, and 3.

Methyl 1-*methylindole*-2-*sulphonate* (**12**)

Sodium 1-methylindole-2-sulphonate[2] (0·49 g) was converted into the methyl ester as described for the preparation of **9** by method (a). This gave crude crystalline ester (0·42 g, 92%) which was recrystallised twice from EtOH to give methyl 1-methylindole-2-sulphonate as white platelets, m.p. 66–8° (Found: C, 53·00; H, 5·16; N, 6·08; S, 14·09. $C_{10}H_{11}NSO_3$ requires: C, 53·30; H, 4·89; N, 6·20; S, 14·22%). Spectral properties are given in Tables 1, 2, and 3.

Attempted sulphonation of 2,3-*dimethylindole*

A soln of 2,3-dimethylindole (0·10 g) and $PySO_3$ (0·11 g) in pyridine (5 ml) was refluxed with exclusion of atm moisture for 30 min. After removal of the pyridine under reduced pressure, the residue was extracted with dry ether, which led to an almost quantitative recovery of 2,3-dimethylindole. The ether-insoluble portion was very soluble in water and showed simple pyridinium UV absorption (λ_{max} 257 nm in EtOH). The same result was obtained by allowing the reactants to stand for 24 hr at 20°.

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