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Synthesis and Biological Activity of New 2-Nitroimidazole Derivatives

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In an earlier paper we described the synthesis and the antitrichomonas activity of 2-nitro-α,α,1-trimethyl-1*H*-imidazole-5-methanol (**2**). Starting from this compound, several derivatives have been synthesized. Among these, the phenyl carbonate **8** has been shown to possess activity equal to that of **2** and to be less toxic. This compound therefore is interesting in comparison with some antitrichomonas agents currently in use clinically. Before undertaking an in-depth investigation, compound **8** was subjected to some studies to see whether it has any effects on the central nervous system (CNS). Preliminary results show that, at therapeutic doses, it might induce unwanted CNS effects to a lesser degree than metronidazole.

At the present time, human genital trichomoniasis can be listed among the more important sexually transmitted diseases. However, it is a completely curable and controllable condition. The WHO is collecting data and organizing prevention and treatment centers as part of a worldwide plan for its eradication.[1] For this purpose the nitroimidazoles are the most efficient drugs for systemic treatment. However, there are still some as yet unobtained goals (lowering of dosage, shortening treatment time, getting rid of adverse reactions and cross resistance, etc.) which make it worthwhile to continue research in this field.[2]

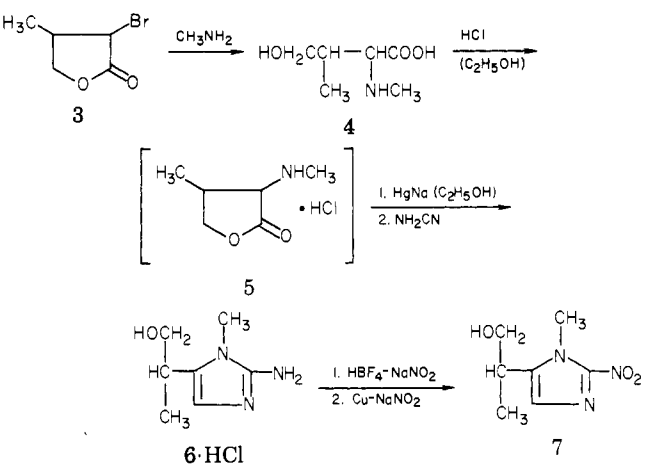
Earlier studies of the metabolism of a 2-nitroimidazole derivative **1** (I, R = H; R′ = CH_3), shown to be particularly active as an oral antitrichomonas agent,[3] led to the isolation[4] of its principal metabolite **2** (I, R = OH; R′ = CH_3) from urines of treated animals. This last compound has been synthesized[5] and shown to possess in vivo activity against *Trichomonas* similar to that of the parent compound, while at the same time it is less toxic.[5]

On the basis of these findings we have undertaken a limited project consisting of (a) synthesis of the isomer **7** (Table I), in which the hydroxyl is moved to the primary carbon; (b) the synthesis of some functional derivatives of **2**; and (c) comparison of **2** with its 5-nitro isomer **14**.

As a result of this program we have found a derivative, **8**, which has activity equal in vivo to that of **2** but is definitely less toxic (Table II) and has a therapeutic index which is even better than those of some antiprotozoan nitroimidazoles in clinical use.

Chemistry. Compound **7** was obtained by the general procedure previously published for the synthesis of 2-nitroimidazoles, outlined in Scheme I. The preparation of the intermediate 2-aminoimidazole **6**, and the transformation of the latter into the corresponding 2-nitroimidazole **7**, proceeded with rather low yields. No attempts were made to improve the yields, since the product showed an activity lower than that of **2**.

Scheme I



The syntheses of some derivatives on the *tert*-hydroxyl group of compound **2** presented some difficulties due to the tendency to dehydrate with formation of the 5-(1-methylethenyl) derivative (I, R, R′ = CH_2).[5] Among different reagents employed, phenyl chloroformate gave the phenyl carbonate **8**, which was also a useful intermediate for the preparation of compounds **9** and **10**. Compound **8** is quite stable in crystalline form and in ethanol or chloroform solution. It led to the hydroxylic starting compound **2** or the methoxy derivative (I, R = OCH_3; R′ = CH_3)[5] by treating it either with water–ethanol or with methanol. Aqueous suspensions of compound **8**, prepared under suitable conditions for use in experimental tests, were stable.

Treatment of **2** with phenyl isocyanate furnished the phenyl carbamate **11**. The benzoate **12** was obtained in low yields, while attempts under various conditions to prepare the acetate led to production of the previously mentioned 5-(1-methylethenyl) derivative.

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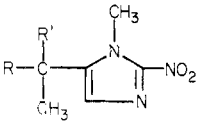
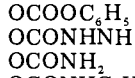
Table I[a]



I

compd	R	R'	recrystn solvent	yield, %	TLC, R_f	mp, °C	formula
7	H	CH_2OH	Et_2O	0.5	0.14	88-90	$C_7H_{11}N_3O_3$[b]
8	$OCOOC_6H_5$	CH_3	EtOH	52.1	0.65	119 (DSC)	$C_{14}H_{15}N_3O_5$[b]
9	$OCONHNH_2$	CH_3	*i*-PrOH	83.7	0.10	166 (DSC)	$C_6H_{13}N_5O_4$[b]
10	$OCONH_2$	CH_3	EtOH	76.5	0.17	143-146	$C_6H_{12}N_4O_4$
11	$OCONHC_6H_5$	CH_3	PhH	63.0	0.47	155-158	$C_{14}H_{16}N_4O_4$
12	$OCOC_6H_5$	CH_3	*i*-Pr_2O	6.0	0.64	125-128	$C_{14}H_{15}N_3O_4$
13		CH_3	EtOH	45.8	0.00	160-163	$C_{13}H_{18}N_4O_5S$

[a] See the introduction to the Experimental Section. [b] Molecular weight confirmed by the M^+ peak in the mass spectrum.

Table II

compd	in vitro act. against selected organisms,[a] MIC, μg/mL					in vivo act.[b] against *T.v.*, ED_{50}, mg/kg	rel ED_{50}[c] (metronidazole)	LD_{50}, mg/kg[d]	T.I.
	S.a. Tour[e]	*S.p.* C 203	*C.p.* ISS 30543	*M.g.* S6 Weybridge	*T.v.*[f]				
2	100	>300	25	40	25	1.65	0.28	698.0	423
7	25	200	0.8	50	25	>10	>0.7	n.d.[h]	
8	100	100	10	>100	2	1.65	0.28	3250.0	1969
9	>100	100	3.1	25	100	4.67	0.33	660.0	141
10	>100	100	10	>100	10	5.74	0.40	900	156
11	>100	>100	3.1	25	100	28.83	2.88	n.d.	
12	100	100	3.1	50	>100	16.2	1.62	n.d.	
13	>100	>100	>100	>100	>100	>40	>4	n.d.	
14	>100	>100	5	>100	5	8.12	0.81	805.0	99
metronidazole[g]	>300	>300	0.6	>300	5	5.77	1	3800.0	658
tinidazole[g]	300	>300	0.3	>300	3.1	2.5	0.43	3200.0	1280
nimorazole[g]	>300	>300	0.6	>300	12.5	37.9	4.66	1530.0	40

[a] MIC values for *S. aureus* (*S.a.*) and *S. pyogenes* (*S.p.*) were determined by a microtiter method[22] and for *C. perfringens* (*C.p.*), *M. gallisepticum* (*M.g.*), and *T. vaginalis* (*T.v.*) by a broth dilution method.[23] [b] Subcutaneous infection in mice, oral administration. Details are given in ref 3. Compounds 2, 8, 10, and 12 were suspended in an aqueous solution of 0.75% sodium carboxymethylcellulose, ~5000 (SIPA); compound 7 was dissolved in DMF-H_2O; compounds 9 and 11 in DMF-phosphate buffer, pH 7.38; compounds 13, 14, metronidazole, tinidazole, and nimorazole in H_2O. The values found for metronidazole under the experimental conditions used varied from 5.77 to 14.1 mg/kg. [c] The figures express the ratio between the ED_{50} (test compound) and ED_{50} (metronidazole) run in parallel. [d] Acute toxicity[24] in mice, oral administration. The compounds were suspended in an aqueous solution of 0.5% Methocel 90-HG Dow. [e] The values were unaffected by the addition of 30% bovine serum. [f] Cidal concentration. [g] See ref 11-13. [h] n.d. = not determined.

Finally, when **2** was allowed to react with methanesulfonyl chloride, an undesired side reaction[6] took place, and the pyridinium quaternary salt **13** was obtained.

The preparation of compound **14** (the 5-nitro isomer of **2**) starting from α-hydroxyisobutyraldehyde has been described.[7] We found it more convenient to prepare **14** by acetic acid–concentrated sulfuric acid hydrolysis of the corresponding methoxy derivative, obtained from α-methoxyisobutyraldehyde as reported by the same authors.[7]

^1H NMR and IR data were in accordance with the assigned structures.

Biological Results. Table II lists the minimal inhibitory concentrations (MIC) for the compounds, tested against selected organisms. In some cases the products showed only minimal activity against the gram-positive bacteria in the test and against *Mycoplasma*, but almost all of them had definite activity against *Clostridium perfringens* and *Trichomonas vaginalis*, except compound **12**, which had a trichomonastatic MIC of 100 μg/mL, and compound **13** which, although soluble in water, had no activity against any of the microorganisms in the test.

It has been hypothesized[8,9] that the ability of the microorganism to reduce the nitroimidazoles, which is related to the reduction potential (expressed as $E_{1/2}$), is correlated with the activity of the 2-nitroimidazoles. Therefore, we measured[10] the $E_{1/2}$ values for compounds **2** (-0.65 V), **8** (-0.56 V), **14** (-0.67 V), and metronidazole[11] (-0.50 V). The values found explain the very minor activity against *Staphylococcus aureus* and *Streptococcus pyogenes*, since it is probable that values of $E_{1/2}$ of the order of -0.30 V would be needed for these compounds to be metabolized by these microorganisms.[9] However, they do not explain the greater activity in vitro of **2** as compared to the other compounds. It is obvious that other parameters, such as lyo- or lipophilia and steric hindrance, must also enter into the picture.

Table II contains the ED_{50} values for oral treatment of *T. vaginalis* infection in the mouse. The relative ED_{50}, which is the ratio between the ED_{50} of the test compound and that of metronidazole, used as standard of reference in the same experiment, is useful for rapid comparison. Although we did not obtain an absolute value, we can still see that compound **7** is about half as active as compound **2**, which has the *tert*-hydroxyl.

Formation of the phenyl carbonate derivative **8** or the hydrazine carboxylate derivative **9** did not cause any change in activity, while other substitutions generally resulted in less active compounds. However, it is remarkable how drastically the toxicity of compound **8** is

Table III. Sleeping Time of Mice Given Hexobarbital Sodium, 75 mg/kg ip, T = 25–26 °C

compd	dose, mg/kg po	mean ± SE	change, %	p^a
8	250	39.2 ± 3.32	+15.5	N.S.
	500	40.0 ± 2.54	+18.1	N.S.
metronidazole	300	43.9 ± 3.79	+29.2	<0.05
	600	53.0 ± 3.51	+55.9	<0.01
chlorpromazine hydrochloride[b]	1	53.6 ± 3.93	+57.7	<0.01
physiological saline[c]	0.2 mL	34.0 ± 1.9		

[a] Dunnett's t test.[25] [b] The product was administered 60 min before the barbiturate. [c] 90 animals.

Table IV. Antagonism of Death Induced by Strychnine or Pentetrazole (Mice)

compd	dose, mg/kg po	strychnine, protected/ treated	pentetrazole, protected/ treated
8	250	2/10	3/10
	500	1/10	1/10
metronidazole	300	5/10	3/10
	600	5/10	6/10
phenobarbital sodium[a]	30	8/10	
chlordiazepoxide	2.5		4/10
physiological saline	0.2 mL	0/10	0/10

[a] The product was given 60 min before the strychnine or pentetrazole.

reduced, to a point where it is even better than the other systemic antiprotozoal agents listed (metronidazole,[11] tinidazole,[12] and nimorazole[13]).

Comparison of compound 2 with its 5-nitro isomer 14 shows that the latter is one-fourth as active, while the value of the LD_{50} is about the same.

Compound 8 was subjected to a preliminary pharmacological evaluation. It has a rather unimportant effect on carrageenin-induced edema in the rat and no pressor effect in the conscious normotensive rat up to a dose of 50 mg/kg.

Particular attention was paid to effects on the CNS. It is known that nitroimidazoles show an unusual range of toxic effects in experimental animals.[14]

In particular, they have caused neurological disorders such as depression, ataxia, and tremors. The incidence of these effects in man is less frequent, but they cannot be excluded a priori.[15-17] For this reason we have studied in the mouse the depressive and toxic effects on the CNS of compound 8 compared with those of metronidazole. The tests of behavior and of interaction carried out with compound 8 and metronidazole, also in comparison with other drugs, showed that compound 8 has little toxicity and almost no depressive effect on the CNS. Metronidazole is the same as compound 8 qualitatively, in the tests carried out, but there are definite differences quantitatively. One can conclude that compound 8, at therapeutic doses, might induce unwanted CNS effects to a lesser degree than metronidazole.

Experimental Section

Biological Procedures and Results. Materials. Male mice of the CF1 strain, weighing from 19 to 22 g, were used. The products were dissolved in water (hexobarbital sodium, chlorpromazine hydrochloride, phenobarbital sodium, chlordiazepoxide, strychnine sulfate, pentetrazole) or suspended in 0.5% Methocel 90-HG Dow (compound 8, metronidazole). Volumes of 10 mL/kg were administered. The control animals received the same volume of physiological saline solution.

(1) **Behavior in Mice.** The changes in behavior of the mice which could be observed directly were studied by the method of Irwin.[18] Compound 8 induced a decrease in curiosity, spontaneous activity and body tone, heart and respiratory rates, and opening of the eyelid, beginning at 60 mg/kg po. It also induced ataxia and cyanosis. These effects were not very marked even at the highest dose given (600 mg/kg). Metronidazole induced the same effects, beginning at the dose of 10 mg/kg. These effects became somewhat more marked at the higher doses, until flaccid paralysis appeared at the highest dose tested (600 mg/kg).

(2) **Interaction with a Hypnotic Barbiturate in Mice.** Groups of 30 animals were treated orally with compound 8, metronidazole, chlorpromazine, or physiological saline. Thirty minutes later they were given hexobarbital sodium at a dose of 75 mg/kg ip. The percentage difference in the sleeping time of treated and control mice was determined. The results are summarized in Table III. Compound 8, at doses of 250 and 500 mg/kg orally, did not affect the sleeping time. Metronidazole, at doses of 300 and 600 mg/kg orally, increased the sleeping time by 29 and 56%, respectively.

(3) **Antagonism against Death Induced by Strychnine or Pentetrazole in Mice.** These experiments were carried out essentially as described by Mustala[19] and Bastian.[20]

Groups of ten animals were treated orally with compound 8, metronidazole, or physiological saline. Thirty minutes later they were injected sc with a LD_{100} dose of strychnine sulfate (1.5 mg/kg) or of pentetrazole (140 mg/kg). The number of surviving animals was recorded. The results can be seen in Table IV. Compound 8 at doses of 250 and 500 mg/kg did not affect the numbers of dead induced by the two convulsant agents. Doses of 300 and 600 mg/kg orally of metronidazole did have some effect against both convulsants.

Chemical Synthesis. Melting points (uncorrected) were determined in open capillary tubes or by differential scanning calorimetry (DSC). IR spectra were determined with a Perkin-Elmer Model 137 spectrophotometer as Nujol mulls. UV spectra were recorded with a Unicam S.P. 800 spectrophotometer. ^1H NMR spectra were recorded at 60 MHz by a Varian A-60 spectrometer (Me_4Si, δ 0.00 ppm). TLC were run on Merck silica gel 60 F_{254} plates to a distance of 10.0 cm (developed with a 5:95 mixture of MeOH and $CHCl_3$). The spots were detected by visual examination under UV light. Solvents were dried over Na_2SO_4. All evaporations were carried out under reduced pressure. Analytical results for C, H, N, and, where applicable, for S were within ±0.4% of the theoretical values.

4-Hydroxy-2-methylamino-3-methylbutanoic Acid (4). To 56 mL of 35% aqueous $MeNH_2$ cooled in ice 8.08 g (45 mmol) of 3-bromo-4-methyl-4,5-dihydro-2(3*H*)-furanone (3)[21] was added. The reaction mixture was allowed to stand at room temperature for 4 days; then the solvent was removed. The residue was dissolved in 37.5 mL of H_2O and treated with 75 mL of 6 N H_2SO_4 with cooling. The reaction mixture was heated on a steam bath for 40 min, allowed to stand at room temperature overnight, and finally poured onto a boiling solution of 75 g of $Ba(OH)_2$ in 300 mL of H_2O. Heating was continued for 40 min; then an aqueous solution of $(NH_4)_2CO_3$ was added until no further precipitate was formed. After filtering, the solution was evaporated and the residue was washed throughly with Me_2CO and dissolved in a minimal amount of H_2O. EtOH was added while heating until a clear solution was obtained; then Et_2O was added to cloudiness. On standing, 4.07 g (61%) of 4, mp 243–245 °C, was obtained. Anal. ($C_6H_{13}NO_3$) C, H, N.

5-(2-Hydroxy-1-methylethyl)-1-methyl-1*H*-imidazol-2-amine (6). A solution of 10 g of crude 3-methylamino-4-methyl-4,5-dihydro-2(3*H*)-furanone hydrochloride (5) (obtained by refluxing for 1 h a mixture of 10.2 g of 4 in 120 mL of absolute EtOH saturated with HCl) in 100 mL of H_2O and 45 mL of EtOH was treated in portions with a total of 653.4 g of 2.5% NaHg under vigorous stirring, with the temperature kept between −3 and 3 °C and the pH at 2.5–3.5 (by addition of 15% HCl). The reaction was then worked up essentially as previously described[3] for similar compounds, yielding 7.5 g of 6·HCl as a crude oil, which was used in the next step. A sample was dissolved in H_2O and treated with an aqueous saturated solution of picric acid. The picrate was filtered, washed with H_2O, and recrystallized from MeOH: mp

180–184 °C. Anal. ($C_{13}H_{16}N_6O_8$) C, H, N.

1,β-Dimethyl-2-nitro-1*H*-imidazole-5-ethanol (7). A solution of 2.65 g of $NaNO_2$ in 10 mL of H_2O was added dropwise at −20 °C, over 30 min, to a stirred solution of 7 g of crude **6**·HCl in 10 mL of H_2O and 31 mL of 40% fluoboric acid. Stirring was continued for 15 min; then the solution was maintained at −10 °C and poured in portions into a stirred mixture of 7.25 g of Cu powder and 25.1 g of $NaNO_2$ in 300 mL of H_2O, while N_2 was bubbled in. After 20 min the insoluble material was filtered out; the solution was brought to pH 2 with 10% HCl and extracted with EtOAc. The extracts were washed with $NaHCO_3$ solution and evaporated. The oily residue (0.9 g) was dissolved in a few milliliters of $CHCl_3$ and chromatographed on 50 g of silica gel (0.06–0.2 mm). Fractions of 25 mL were collected, the first elution being with $CHCl_3$ (fractions 1–8), then $CHCl_3$ containing 1% (v/v) MeOH (fractions 9–41), and $CHCl_3$ containing 4% MeOH (fractions 42–51).

Fractions 48–51 contained the desired compound. On evaporation to dryness 0.079 g of **7** was obtained which was recrystallized: IR 3350 (ν OH), 3120 (ν C=H), 1540 and 1480 (ν C=C and ν C=N), 1525 (ν_{asym} NO_2), 1355 (ν_{sym} NO_2), 1060 (ν CO), 838 cm^{-1} [ν CN(O_2)]; ^1H NMR ($CDCl_3$) 1.33 [d, 3 H, J_{CH_3CH} = 7 Hz, CH_3(CH)], 2.8–3.5 [m, 1 H, CH(CH_3)], 3.6–4.2 (m, 3 H, CH_2OH), 4.02 (s, 3 H, CH_3N), 6.97 (s, 1 H, CH=).

2-Nitro-α,α,1-trimethyl-1*H*-imidazole-5-methyl Phenyl Carbonate (8). Phenyl chloroformate (6.8 mL, 52.9 mmol) was added dropwise to a solution of 10 g (54 mmol) of **2** in 10 mL of anhydrous pyridine at a temperature between 5 and 10 °C. After stirring for 6 h at room temperature and standing overnight, the reaction mixture was poured into ice–water. A solid separated which was filtered, washed with H_2O, and crystallized to give 6.7 g of **8**: IR 3130, 3050 (ν CH arom), 1765 (ν C=O), 1600, 1550, and 1485 (ν C=N and ν C=C), 1525 (ν_{asym} NO_2), 1355 (ν_{sym} NO_2), 1260 (ν_{asym} COC), 1200 and 1180 (CH_3CCH_3), 1120 (ν_{sym}COC), 850 and 840 [ν CN(O_2)], 783, 733, and 698 cm^{-1} (γ CH); ^1H NMR (Me_2SO-d_6) δ 1.92 (s, 3 H, CH_3), 4.11 (s, 3 H, CH_3N), 7.1–7.6 (m, 5 H, C_6H_5), 7.27 (s, 1 H, CH=); UV ($CHCl_3$) λ_{max} 319 nm (log ε 3.95).

The starting compound (2.6 g, crystallized from PhH) was recovered from the aqueous solutions by acidification with 10% HCl and extraction with EtOAc.

2-Nitro-α,α,1-trimethyl-1*H*-imidazole-5-methanol-carboxhydrazide (9). A solution of 3 g (9.8 mmol) of **8** in 60 mL of $CHCl_3$ and 0.28 mL of 95% hydrazine was stirred at room temperature for 1 h; then an additional 0.1 mL of hydrazine was added and the reaction mixture was allowed to stand overnight. The solvent was removed, the residue was dissolved with a little $CHCl_3$, and Et_2O was added. A solid product precipitated, which was filtered and recrystallized (2 g).

2-Nitro-α,α,1-trimethyl-1*H*-imidazole-5-methyl Carbamate (10). Liquid NH_3 (90 mL) was added over 15 min to a solution of 3.34 g (10.9 mmol) of **8** in 90 mL of $CHCl_3$ cooled to −30 °C; then the temperature was raised to 25 °C over 2 h. The solvent was removed and the crude product was triturated with Et_2O, filtered, and recrystallized to give 1.54 g of **10**. On concentration of the mother liquor, an additional 0.37 g was obtained.

2-Nitro-α,α,1-trimethyl-1*H*-imidazole-5-methyl *N*-Phenylcarbamate (11). Phenyl isocyanate (2.6 mL, 23.9 mmol) was added dropwise to a solution of 3 g (16.2 mmol) of **2** in 25 mL of anhydrous pyridine. The reaction mixture was heated with stirring at 80 °C for 5 h; then additional phenyl isocyanate (2 mL, 18.4 mmol) was added and heating was continued for 1 h. After cooling at room temperature, ligroine was added. An oily product separated out which, after decantation of the solution, was triturated with Et_2O. A solid was formed which was filtered (3.1 g) and recrystallized twice from PhH.

2-Nitro-α,α,1-trimethyl-1*H*-imidazole-5-methyl Benzoate (12). Freshly distilled benzoyl chloride (0.8 mL, 6.9 mmol) was added dropwise to a solution of 3 g (16.2 mmol) of **2** in 10 mL of anhydrous pyridine with stirring. An additional 10 mL of pyridine was added, followed by 1.6 mL (13.8 mmol) of benzoyl chloride. Stirring was continued for 5 h; then Et_2O was added. The oily product which separated was discarded and the ether solution was washed with H_2O and evaporated. The residue was crystallized from Et_2O–petroleum ether to give 0.8 g of a product which was dissolved in 5 mL of $CHCl_3$ and chromatographed on silica gel (0.06–0.2 mm) in $CHCl_3$, eluting with $CHCl_3$ containing 1% (v/v) MeOH. Fractions containing the desired compound were collected and evaporated. The residue was recrystallized to give 0.28 g of **12**.

1-[1-Methyl-1-(1-methyl-2-nitro-1*H*-imidazol-5-yl)-ethyl]pyridinium Methanesulfonate (13). Freshly distilled methanesulfonyl chloride (1.7 mL, 22 mmol) was added to a solution of 2.2 g (11 mmol) of **2** in 16 mL of anhydrous pyridine. After stirring for 2 h at room temperature, the reaction mixture was allowed to stand overnight. On treating with Et_2O a solid precipitated out which was filtered and recrystallized to give 1.86 g of **13**: ^1H NMR (Me_2SO-d_6) δ 2.23 [s, 6 H, $(CH_3)_2C$], 2.30 (s, 3 H, $CH_3SO_3^-$), 3.42 (s, 3 H, CH_3N), 7.60 (s, 1 H, CH=), 8.19 (t, 2 H, J = 7 Hz, phenyl H_3 and H_5), 8.73 (t, 1 H, phenyl H_4), 9.15 (d, 2 H, phenyl H_2 and H_6).

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