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THE METHANESULFONYLATION OF 2-BENZIMIDAZOLEMETHANOL AND α-(2-BENZIMIDAZOLYL)BENZYL ALCOHOL

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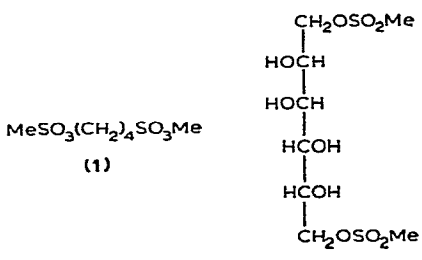
ABSTRACT

Treatment of 2-benzimidazolemethanol (**4**) with methanesulfonyl chloride and pyridine in chloroform afforded 2-(chloromethyl)-1-(methylsulfonyl)benzimidazole (**6**), which was also prepared by methanesulfonylation of 2-(chloromethyl)benzimidazole. Methanesulfonylation of α-(2-benzimidazolyl)benzyl alcohol (**8**) in chloroform yielded 2-(α-chlorobenzyl)-1-(methylsulfonyl)benzimidazole. 1-(Methylsulfonyl)-2-benzimidazolemethanol was obtained on methanesulfonylation of **4** in pyridine at 0°, and α-[1-(methylsulfonyl)-2-benzimidazolyl]benzyl alcohol (**12**) was prepared from **8** by using the same reaction conditions. The reaction of 1-acetyl-2-(chloromethyl)-benzimidazole with silver methanesulfonate in benzene gave 1-acetyl-*O*-(methylsulfonyl)-2-benzimidazolemethanol. Compound **6** has some antitumor acitvity in the KB cell-culture system, and some antibacterial activity in the *Staphylococcus aureus* test-system; it is also active in preventing anaphylactic shock in a mouse test-system.

INTRODUCTION

The biological alkylating properties of compounds containing methanesulfonic ester groups are now well known. Such compounds as Myleran (**1**) and "D-mannitol Myleran" (**2**) have pronounced anticancer activity[1]. Haddow and his coworkers[2] have claimed that **2** does not markedly attack bone-marrow. In view of a report[3] by Hirchberg, Gellhorn, and Gump that "benzimidazole mustard" (**3**) has antitumor activity in a variety of animal tumor systems, a study of the methanesulfonylation of some 2-(*aldo*-hydroxyalkyl)benzimidazoles has now been undertaken.



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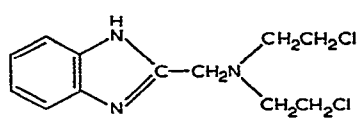

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The acylation of 2-(*aldo*-polyhydroxyalkyl)benzimidazoles does not appear to have been investigated to any great extent. By 1951, only three of these compounds had been acetylated[4]. In a review article, Richtmyer[4] stated that "it is not clear from these isolated cases whether *N*-acetylation as well as *O*-acetylation is to be expected or not". Staněk and Wollrab[5] reported the complete acetylation and benzoylation of 2,2′-(dihydroxyethylene)bisbenzimidazole in 1960. Even in the case of the parent, benzimidazole, the literature is not fully consistent. Oddo and Ingraffia[6] reported that imidazole is not *N*-acetylated by acetic anhydride or acetyl chloride. These workers[7] prepared *N*-acetylbenzimidazole by treating magnesiumbenzimidazole with acetyl chloride. However, Hofmann[8] stated that benzimidazole can be acetylated in boiling acetic anhydride, and benzoylated by benzoyl chloride in benzene in the cold. Simonov and co-workers[9] reported that treatment of benzimidazole in pyridine with *p*-toluenesulfonyl chloride affords the sulfonamide in good yield.

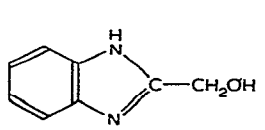
RESULTS AND DISCUSSION

In the present study, it was found that benzimidazole is readily methanesulfonylated in pyridine solution at room temperature. The microanalytical figures found for the product accorded well with the values calculated for *N*-(methylsulfonyl)-benzimidazole, and the infrared spectrum showed strong sulfonamide bands at 1370 and 1175 cm^{-1}; this result is consistent with those of Simonov *et al.*[9].

The methanesulfonylation of 2-benzimidazolemethanol (**4**) was of particular interest, as the anticipated product (**5**) would be a biological alkylating agent similar to **3**. As the Mylerans generally produce far less bone-marrow depression[1] than the "mustards"[1], compound **5** might be expected to be less toxic than **3**. An attempt to methanesulfonylate **4** in pyridine at room temperature proved unsuccessful; only a small proportion of amorphous product was obtained on treating the reaction mixture with water. Zeatin, the factor promoting plant cell-division, contains an allylic system, and readily affords a quaternary salt on treatment with methanesulfonyl chloride in pyridine[10]. Possibly, compound **4**, also, forms a quaternary compound under these conditions.

Accordingly, **4** was treated with methanesulfonyl chloride in chloroform containing a limited proportion of pyridine[11]. The product obtained was shown to be 2-(chloromethyl)-1-(methylsulfonyl)benzimidazole (**6**). Microanalytical figures and the infrared spectrum were in agreement with this formulation. Furthermore, the compound obtained on methanesulfonylation of 2-(chloromethyl)benzimidazole[12] (**7**) in chloroform containing a limited proportion of pyridine was shown to be identical with **6** on the basis of mixed melting-point, infrared comparisons, and rates of migration on t.l.c. plates. Methanesulfonylation of the well-known antiviral agent[13] α-(2-benzimidazolyl)benzyl alcohol (**8**) in chloroform containing a limited proportion of pyridine was also conducted; the product was 2-(α-chlorobenzyl)-1-(methylsulfonyl)benzimidazole (**9**).

Levene and Tipson[14] found that treatment of uridine with *p*-toluenesulfonyl



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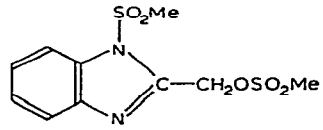

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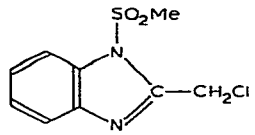

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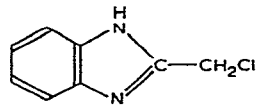

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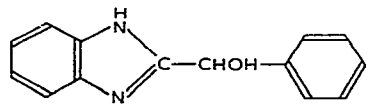

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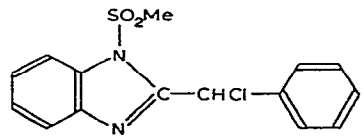

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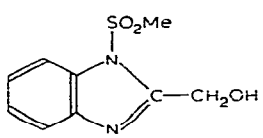
chloride in pyridine at 0° affords a product in which the secondary hydroxyl groups of the D-ribosyl group are *p*-toluenesulfonylated, but the primary carbon atom thereof is chlorinated This result was confirmed by Fox and collaborators[15], who found, in contrast, that methanesulfonylation of uridine in pyridine at 0° yields a completely methanesulfonylated product. In the present study, compound **4** was treated with two equivalents of methanesulfonyl chloride in pyridine for 5 h at 0°. A mono(methylsulfonyl) derivative (**10**) was isolated in 50% yield (crude). Acetylation of **10** with a mixture of acetic anhydride and pyridine gave a crystalline compound (**11**). The structure of **10** was confirmed as that of 1-(methylsulfonyl)-2-benzimidazolemethanol by treating it with a mixture of thionyl chloride and pyridine in chloroform; a product identical with **6** was obtained. When the methanesulfonylation of **4** was performed in pyridine for 18 h at 0°, compound **10** was obtained in low yield.

In an analogous series of experiments, compound **8** was shown to give α-[1-(methylsulfonyl)-2-benzimidazolyl]benzyl alcohol (**12**) in 55% crude yield after



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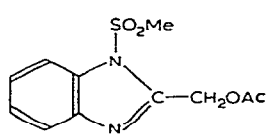

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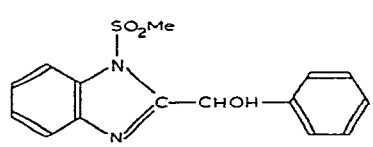

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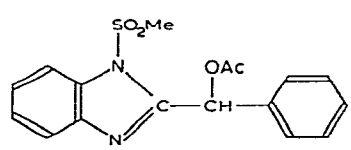

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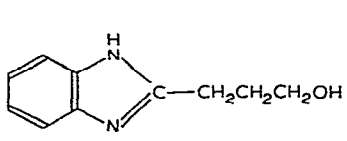
treatment with two equivalents of methanesulfonyl chloride in pyridine for 6 h at 0°. After a reaction time of 18 h, compound **12** was obtained in approximately the same yield. However, only a small yield of **12** was obtained when the methanesulfonylation was continued for 170 h. Treatment of **12** with a mixture of acetic anhydride and pyridine gave the acetate (**13**), and **9** was isolated after treating **12** with thionyl chloride and pyridine in chloroform. It is tempting to speculate that the imino group in **4** reacts faster than the hydroxyl group with methanesulfonyl chloride, and that the methanesulphonic ester (or the chloride) formed reacts with pyridine to give a quaternary compound. The diminished yield of **10** when the reaction is conducted for 18 h would thus be accounted for, as the quaternary compound would be expected to be soluble in the water used in processing the reaction mixture. As primary hydroxyl groups are generally sulfonylated faster than secondary hydroxyl groups[11], the results obtained regarding methanesulfonylation of **8** can also be rationalized on the basis of this suggestion.

Although the hydroxyl groups in **4** and **8** could not be methanesulfonylated by using methanesulfonyl chloride, 2-benzimidazolepropanol (**14**) in pyridine at 0° was readily converted into the fully methanesulfonylated compound (**15**) by means of this reagent. In order to prepare the methanesulfonate of the allylic system, the alternative methanesulfonylation procedure was used. 1-Acetyl-2-(methylsulfonyl)-oxymethylbenzimidazole (**16**) was prepared by treating 1-acetyl-2-(chloromethyl)-benzimidazole (**17**) with the silver salt of methanesulfonic acid in benzene. Treatment of **16** with sodium iodide in acetone afforded 1-acetyl-2-(iodomethyl)benzimidazole (**18**), which was also obtained by treating **17** with the Finkelstein reagent[16].



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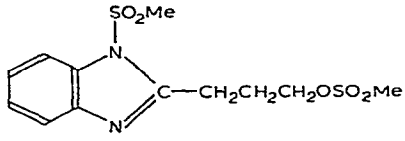

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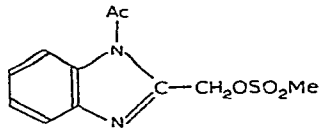

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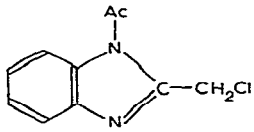

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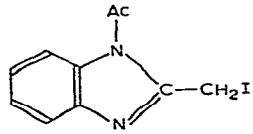

18

Several of the compounds prepared during the course of this investigation were screened for antitumor activity by the National Cancer Institute in Bethesda, Maryland. Compound **6** was found to pass the first stage of the sequential screen in the KB cell-culture test-system[17]. The same compound has been shown to have some antibacterial activity against *Staphylococcus aureus, in vitro*[18], and it also protects mice against anaphylactic shock[19]. The last two tests were performed by the Pharmaceuticals Division of Imperial Chemical Industries Limited.

EXPERIMENTAL

General. — Benzimidazole, 2-benzimidazolemethanol (**4**), and α-(2-benzimidazolyl)benzyl alcohol (**8**) were prepared according to the method of Phillips[20]. Unless otherwise stated, melting points (m.p.) are uncorrected, and infrared (i.r.) spectra were recorded, for Nujol or hexachlorobutadiene mulls, with a Perkin–Elmer 237 G infrared spectrophotometer. Thin-layer chromatography (t.l.c.) was conducted on plates of silica gel, with solvent *A*, 5:2 chloroform–ethyl acetate; *B*, 2:1 benzene–*p*-dioxane; *C*, 5:2 *p*-dioxane–water; or *D*, 3:2 methanol–water. After spraying the plates with 20% ammonium hydrogen sulfate and heating for 0.5 h at 100°, benzimidazoles were detected as fluorescent, violet spots under ultraviolet light. Microanalyses were performed by Dr. K. Führ at the University of Cape Town, South Africa, Dr. W. C. Alford and his associates at the National Institutes of Health, Bethesda, Maryland, U. S. A., and Dr. R. D. MacDonald, University of Melbourne, Australia.

Preparation of 1-(methylsulfonyl)benzimidazole. — A solution of benzimidazole (5.3 g) in dry pyridine (50 ml) was treated with methanesulfonyl chloride (5.7 g), kept for 20 h at room temperature, and treated with ice–water. The crystalline product was collected by filtration, washed well with water, and dried. This material (6.8 g) was recrystallized from a mixture of benzene–ligroin, yielding white crystals (5.1 g), m.p. 153–154°. I.r. bands at 1175 (in Nujol) and 1370 cm^{-1} (in hexachlorobutadiene) were strong, and the spectrum was blank in the range 3600–3200 cm^{-1}. In chloroform solution, the strong i.r. bands were at 1375 and 1165 cm^{-1} (lit.[21] sulfonamide bands, 1175–1160 and 1370–1330 cm^{-1}).

Anal. Calc. for $C_8H_8N_2O_2S$: C, 50.0; H, 4.1; N, 14.3; S, 16.3. Found: C, 49 3; H, 4.3; N, 14.2; S, 16.4.

Preparation of 2-(chloromethyl)-1-(methylsulfonyl)benzimidazole (**6**) *from* **4**. — A suspension of compound **4** (4.0 g) in a mixture of dry chloroform (25 ml) and pyridine (7 ml) was chilled in an ice–bath, and a solution of methanesulfonyl chloride (7.4 g) in chloroform (25 ml) was added during 15 min with vigorous stirring. The mixture was allowed to warm to room temperature and then heated at 50°, with stirring, until a clear solution was obtained; this was kept overnight at room temperature, and then treated with ice–water. Methanol (50 ml) was added to dissolve solid material that had separated, the chloroform layer was separated, and the aqueous layer was extracted twice with chloroform. The chloroform layer and extracts were combined, washed successively with cold M hydrochloric acid, sodium hydrogen carbonate solution, and water, dried (sodium sulfate), and evaporated to dryness *in vacuo*. The semi-solid residue was recrystallized from benzene containing ethanol and decolorizing carbon, to give white needles (0.8 g) that had m.p. 138° (dec.) and showed strong i.r. bands at 1180 and 1371 cm^{-1}; R_F values: 0.70 (solvent *A*), 0.88 (*B*), 0.93 (*C*), and 0.85 (*D*). When the plates were sprayed with sodium iodide in acetone and developed at 90°, compound **6** was detected on each as a yellow spot.

Anal. Calc. for $C_9H_9ClN_2O_2S$: C, 44.2; H, 3.7; Cl, 14.5; N, 11.5; S, 13.1. Found: C, 45.0; H, 3.7; Cl, 14.4; N, 11.2; S, 13.4.

Conversion of compound **7** *into* **6**. — Chloroacetic acid was condensed with phenylenediamine in 4M hydrochloric acid[12], and the product (**7**) was recrystallized from *p*-dioxane. A suspension of purified **7** (3.8 g) in chloroform (25 ml) and pyridine (3 ml) was treated with methanesulfonyl chloride (2.7 g) in chloroform (25 ml) as already described. After treatment with ice–water, methanol (50 ml) was added, and crystalline product (3 g) was obtained from the chloroform solution. Recrystallization from benzene containing a little ethanol afforded white needles (1.8 g), m.p. 137° (dec.). The m.p. was not changed on admixture with **6** obtained from **4**, and the i.r. spectra of the two samples were identical; R_F values: 0.70 (solvent *A*), 0.88 (*B*), 0.93 (*C*), and 0.85 (*D*).

Anal. Calc. for $C_9H_9ClN_2O_2S$: C, 44.2; H, 3.7; Cl, 14.5; N, 11.5; S, 13.1. Found: C, 44.3; H, 3.8; Cl, 14.4; N, 11.2; S, 13.3.

Synthesis of **9**. — A suspension of compound **8** (10 g) in chloroform (50 ml) containing pyridine (10 ml) was treated with a solution of methanesulfonyl chloride (10.4 g) in chloroform (50 ml), and the product was isolated in the usual way. Recrystallization from methanol afforded white crystals (1.2 g) which melted to a pink liquid at 138° (dec.), and which showed strong i.r. bands at 1370 and 1165 cm^{-1}; R_F values: 0.88 (solvent *A*), 0.86 (*B*), 0.90 (*C*), and 1.0 (*D*).

Anal. Calc. for $C_{15}H_{13}ClN_2O_2S$: C, 56.2; H, 4.1; Cl, 11.1; N, 8.7; S, 10.0. Found: C, 56.4; H, 4.3; Cl, 10.5; N, 8.7; S, 9.8.

Reaction of **4** *with methanesulfonyl chloride in pyridine at 0°*. — To a solution of **4** (2.0 g) in pyridine (20 ml), chilled in ice–salt, was added methanesulfonyl chloride (3.1 g); the mixture was kept for 5 h at 0°, and then treated with ice–water, and kept for 24 h at 5°. The crystalline product was filtered off, washed well with water, and dried (yield, 1.5 g). Recrystallization of the product (**10**) from methanol containing decolorizing carbon afforded white crystals (0.8 g) melting to a red liquid at 149°, and showing strong i.r. bands at 1372 and 1170 cm^{-1} and a broad band at 3400–3180 cm^{-1} (OH).

Anal. Calc. for $C_9H_{10}N_2O_3S$: C, 47.8; H, 4.5; N, 12.4; S, 14.2. Found: C, 47.9; H, 4.6; N, 12.1; S, 14.3.

In a second experiment, compound **4** (2.0 g) was methanesulfonylated as just described but with a reaction time of 18 h. The product (0.2 g) was recrystallized from methanol, giving white crystals (0.07 g), m.p. 149°. The m.p. was not changed on admixture with **10**.

Acetylation of **10**.—Compound **10** (0.6 g) was treated with a mixture of pyridine (4 ml) and acetic anhydride (10 ml). After being kept overnight at room temperature, the solution was diluted with ice-cold water, and the resulting crystalline material was filtered off, washed with water, and dried. A solution of the crude product (0.33 g) in benzene was filtered, and the filtrate was evaporated to dryness in a stream of nitrogen. The residue, consisting of acetate **11**, was recrystallized from methanol, yielding crystals (0.15 g), m.p. 114°; i.r. bands at 1372, 1170, and 1745 cm^{-1} (C=O).

Anal. Calc. for $C_{11}H_{12}N_2O_4S$: C, 49.2; H, 4.5; N, 10.4; S, 12.0. Found: C, 49.2; H, 4.7; N, 10.4; S, 11.7.

Conversion of **10** *into* **6**. — A suspension of **10** (0.7 g) in chloroform (7 ml) containing pyridine (0.5 ml) was cooled in an ice-bath, and a solution of thionyl chloride (0.5 g) in chloroform (5 ml) was added, with stirring, during 15 min. The mixture was allowed to warm to room temperature, and stirring was continued for 1 h. Ice-cold water was added, and the product was isolated from the chloroform solution in the usual way. After recrystallization of the product (0.5 g) from benzene containing ethanol, the resulting white needles had m.p. 136° (dec.) The m.p. was not changed on admixture with **6** from **4**, and the i.r. spectra of the two samples were identical; R_F values: 0.70 (solvent *A*), 0.88 (*B*), 0.93 (*C*), and 0.85 (*D*).

Anal. Calc. for $C_9H_9ClN_2O_2S$: C, 44.2; H, 3.7; Cl, 14.5; N, 11.5; S, 13.1. Found: C, 44.4; H, 3.6; Cl, 14.3; N, 11.4; S, 13.1.

Reaction of **8** *with methanesulfonyl chloride in pyridine at 0°*. — A suspension of compound **8** (2 g) in pyridine (10 ml) was chilled in ice–salt, and treated with methanesulfonyl chloride (2 1 g). After being kept for 6 h at 0°, the mixture was treated with ice–water, and refrigerated overnight, giving crystalline **12**. Recrystallization of this material (1.5 g) from methanol afforded white crystals (0.8 g), having m.p. 152° (dec.), and strong i.r. bands at 1370 and 1170 cm^{-1}, and a broad band at 3400–3200 cm^{-1} (OH).

Anal. Calc. for $C_{15}H_{14}N_2O_3S$: C, 59.6; H, 4.7; N, 9.3; S, 10.6. Found: C, 59.4; H, 4.9; N, 9.3; S, 10.5.

In a second experiment, the reaction mixture was kept for 18 h in an ice-box. The product, which was obtained in 55% yield, did not depress the m.p. of **12**, and the two samples gave identical i.r. spectra. When the methanesulfonylation was continued for 170 h, a very small yield of **12** was isolated.

Acetylation of **12**. — A suspension of compound **12** (0.3 g) in acetic anhydride (5 ml) and pyridine (2 ml) at 40° was kept for 18 h at room temperature, treated with ice–water, and the product collected by filtration, washed with water, and dried. The crude acetate (0.33 g) was dissolved in benzene, the suspension filtered, and the filtrate evaporated to dryness in a stream of nitrogen. The residue, consisting of **13**, was recrystallized from ethanol, yielding crystalline material (0.18 g) having m.p. 152–153°, and strong i.r. bands at 1370, 1180, and 1740 cm^{-1} (C=O).

Anal. Calc. for $C_{17}H_{16}N_2O_4S$: C, 59.3; H, 4.7; N, 8.1; S, 9.3. Found: C, 59.5; H, 4.8; N, 8.1; S, 9.2.

Conversion of **12** *into* **9**. — Pyridine (0.7 ml) was added to an ice-cold suspension of **12** (1.2 g) in chloroform (10 ml), and a solution of thionyl chloride (0.6 g) in chloroform (5 ml) was added to the stirred mixture during 15 min. The mixture was allowed to warm to room temperature, stirring was continued for 1 h, the solution was mixed with ice-cold water, and the product was isolated from the chloroform layer in the usual way. Recrystallization of this material (1.0 g) from methanol afforded needles, m.p. 137–139° (dec.). The m.p. was not changed on admixture with **9** from **8**, and the i.r. spectra of the two substances were identical. The

product showed the following R_F values: 0.88 (solvent *A*), 0.86 (*B*), 0.90 (*C*), and 1.0 (*D*).

Anal. Calc. for $C_{15}H_{13}ClN_2O_2S$: C, 56.2; H, 4.1; Cl, 11.1; N, 8.7; S, 10.3. Found: C, 57.0; H, 4.3; Cl, 10.2; N, 8.7; S, 10.3.

Reaction of 2-benzimidazolepropanol (**14**) *with methanesulfonyl chloride in pyridine at °0.* — Compound **14** was prepared by the method of Day and co-workers[22], and recrystallized from 50% aqueous ethanol. A solution of **14** (2.0 g) in pyridine (20 ml) was cooled in ice–salt, and treated with methanesulfonyl chloride (2.7 g). After being kept in an ice-box for 20 h, the mixture was treated with water containing crushed ice. The gelatinous precipitate resulting was filtered off, washed with water, and dried. Recrystallization of this product (2.0 g) from benzene afforded very fine, white needles of the dimethanesulfonate **15** (1.5 g), m.p. 93°. The melting point was raised to 95° by a further recrystallization from methanol. Compound **15** showed strong i.r. bands at 1370 and 1180 cm^{-1}, and the following R_F values: 0.53 (solvent *B*) and 0 73 (*C*). When the t.l.c. plates were sprayed with sodium iodide in acetone, and developed at 90°, compound **15** on each was detected as a yellow spot.

Anal. Calc. for $C_{12}H_{16}N_2O_5S_2$: C, 43.4; H, 4.9; N, 8.4; S, 19.3. Found: C, 42.9; H, 5.0; N, 8.7; S, 19.7.

Acetylation of **7**. — Acetic anhydride (10 ml) and pyridine (5 ml) were added to a stirred suspension of **7** (4.6 g) in chloroform (50 ml). A clear solution was obtained on heating the mixture at 50°. After being kept overnight at room temperature, the solution was cooled in an ice-bath, and ice-cold water was added, with stirring. Solid sodium hydrogen carbonate was added in small portions to the stirred mixture until vigorous effervescence subsided. The chloroform layer was separated, and washed with water; it was then washed twice with dilute hydrochloric acid and several times with water, dried (sodium sulfate), and evaporated to dryness *in vacuo*. The residue (compound **17**) was recrystallized from a mixture of benzene and ligroin (decolorizing carbon) to yield faintly colored crystals (2.3 g), m.p. 104–106°. A second recrystallization afforded white crystals, m.p. 106–107°; R_F: 0.70 (solvent *A*) and 0.65 (*D*).

Anal. Calc. for $C_{10}H_9ClN_2O$: C, 57.6; H, 4.4; Cl, 17.0; N, 13.4. Found: C, 57.5; H, 4.5; Cl, 16.6; N, 13.2.

Reaction of **17** *with silver methanesulfonate.* — A mixture of compound **17** (7.5 g) silver methanesulfonate (7.7 g), and dry benzene (100 ml) was boiled under reflux for 18 h, cooled, and filtered. The filtrate was evaporated *in vacuo*, the residue was dissolved in chloroform and the solution was washed successively with sodium hydrogen carbonate and water, dried (sodium sulfate), and evaporated *in vacuo*, to give a yellow residue (4.5 g). Recrystallization from ethyl acetate afforded white needles (2.0 g) of **16**, m.p. 130–131°; strong i.r. bands at 1715 (C=O), 1350, and 1165 cm^{-1} (lit.[21] 1420–1330 and 1200–1145 cm^{-1} for covalent sulfonates); R_F values: 0.35 (solvent *A*), 0.60 (*B*), 0.71 (*C*), and 0.90 (*D*). The m.p., i.r. spectrum, and rates of movement on t.l.c. plates were different from the corresponding properties of the isomeric compound **11**.

Anal. Calc. for $C_{11}H_{12}N_2O_4S$: C, 49.2; H, 4.5; N, 10.4; S, 12.0. Found: C, 49.3; H, 4.3; N, 10.8; S, 11.9.

Reaction of **17** *with sodium iodide in acetone.* — A solution of **17** (2.1 g) and sodium iodide (1.5 g) in acetone (50 ml) was boiled under reflux for 2 h, and cooled, and the sodium chloride was filtered off and washed with acetone. The filtrate and washings were combined, and evaporated to dryness *in vacuo*, and the residue was dissolved in chloroform; the solution was washed with water containing a little sodium thiosulfate, and then with water, dried (sodium sulfate), and evaporated *in vacuo*, to give a crystalline residue; this afforded dark-yellow needles (1.2 g) from a mixture of benzene and petroleum ether. A further recrystallization from ethyl acetate afforded light-yellow needles of **18**, m.p. 112–113° (dec.). The product showed a strong i.r. band at 1710 cm^{-1} (C=O), and the following R_F values: 0.69 (solvent *A*), 0.80 (*B*), 0.80 (*C*), and 0.85 (*D*).

Anal. Calc. for $C_{10}H_9IN_2O$: C, 40.0; H, 3.0; I, 42.3; N, 9.3. Found: C, 40 3; H, 3.2; I, 41.8; N, 9.6.

Conversion of **16** *into* **18**. — Compound **16** (2.0 g) was treated with sodium iodide in acetone (30 ml). The product (1.2 g), which was isolated and purified as already described, had m.p. 112–113° (dec.), and did not depress the m.p. of **18** from **17**; and the two substances had identical i.r. spectra.

Anal. Calc. for $C_{10}H_9IN_2O$: C, 40.0; H, 3.0; N, 9.3. Found: C, 39.8; H, 3.0; N, 9.5.

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