Synthesis and Rearrangement Control of Substituted Benzobicycloheptane Aziridines

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A general synthesis of various substituted benzonorbornene derivatives is described. Benzenesulfonyl aziridines of these compounds were prepared and their acetolysis was studied. The influence of various substitution patterns on the direction of the aziridine rearrangement is discussed and it is shown that the rearrangements may be used as a convenient approach to the synthesis of ring B bridged diterpene alkaloids. Considerable general synthetic utility of these techniques is anticipated.

Une synthèse générale de plusieurs dérivés du benzonorbornène substitué est décrite. Les aziridines benzènesulphonyles de ces composés ont été préparés et leurs acétolyses furent étudiées. L'influence de plusieurs patrons de substitution sur la direction du réarrangement de l'aziridine est discutée. On a montré que ces réarrangements peuvent être utilisés pour une approche convenable à la synthèse de l'anneau B des diterpènes alcaloides pontés. Une utilité considérable en synthèse générale de ces techniques est envisagée. [Traduit par le journal]

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In connection with studies aimed at the synthesis of ring B bridged diterpene alkaloids, we wished to develop highly efficient regio and stereospecific routes to tricyclic compounds of the type **i** and **ii**.

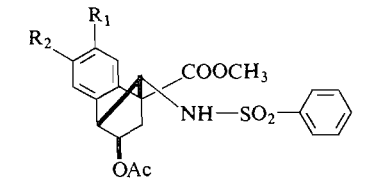
A simple and efficient synthesis of **i** in which the acetolysis of the aziridine **v** was the key step was worked out (1) and the product converted to the songorine intermediate **iii** (2).

The second target of our synthetic work was compound **ii**, which if available could be developed by the same techniques to the chasmanine intermediate **iv**. It turned out, however, that the aziridine **vi** cannot be used to this end since (not surprisingly) it does not yield compound **ii** on acetolysis. This problem has now been fully solved and the synthesis of **iv** is under way. Since the methods which we have developed for the synthesis and rearrangement-control of benzobicycloheptane aziridines are quite novel and of general synthetic interest, we report them in detail in the present paper.

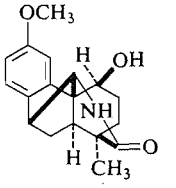
The derivatives which were found to be most suitable for acetolytic rearrangement were benzenesulfonyl aziridines prepared by the action of benzenesulfonyl azide on the corresponding substituted benzobicycloheptenes (3). Consequently, it was first necessary to devise regiospecific methods for the preparation of these last compounds with varying substitution.

The synthesis of the ester **3** was quite simple (3), since no problem with the orientation of a benzene ring substituent existed in this case. Cyclopentadiene carboxylic ester **1**, freshly prepared by distillation of the dimer, was added to the benzyne precursor **2** which had been previously used by Wittig (4). The oily adduct **3** was isolated in a 30% yield by chromatography.[1]

The synthesis of compound **8** had to be performed in an entirely different manner in order to achieve a regiospecific orientation of the methoxyl. The known keto ester **4** (5) was reduced with sodium borohydride to the alcohol **5** and this compound was dehydrated with a



i $R_1 = OCH_3; R_2 = H$
ii $R_1 = H; R_2 = OCH_3$



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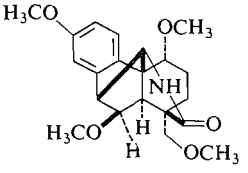

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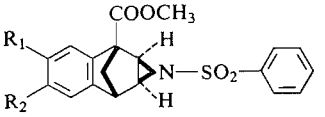


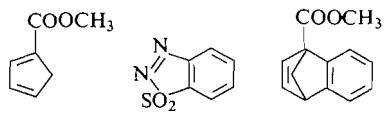
v $R_1 = OCH_3; R_2 = H$
vi $R_1 = H; R_2 = OCH_3$

[1]Full characterization and all spectral data for all compounds may be found in the Experimental.

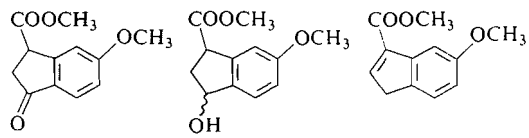
simultaneous double bond shift to the unsaturated ester **6**. Since it was known that indene adds maleic anhydride to yield the anhydride of benzonorbornane dicarboxylic acid (6), it was originally hoped that addition of acetylene or of an acetylene equivalent to **6** would yield directly the desired compound **8**. It turned out however, that while the crystalline adduct with maleic anhydride **7** was formed quantitatively, no other suitable dienophile reacted in an acceptable yield.

After many months of experimentation it was finally discovered that **7** may be bisdecarboxylated to **8** in refluxing diglyme by the action of bistriphenylphosphinenickel dicarbonyl (7) in a yield of 81%. Compound **8** was identical with one of the two products obtained by us previously by the non-regiospecific addition of cyclopentadiene carboxylic ester and methoxy benzyne (8). The entire sequence **4** → **8** was accomplished in a yield of 44% and is consequently quite satisfactory.

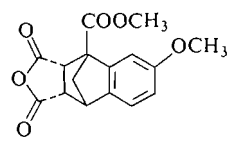
The synthesis of compound **16** starting with the ketoester **12** was performed precisely as described above for compound **8**. The ketoester **12** however was not known and it was synthesized as follows. *m*-Methoxyacetophenone



1 **2** **3**



4 **5** **6**



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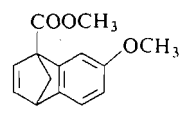

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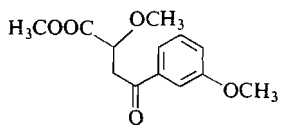

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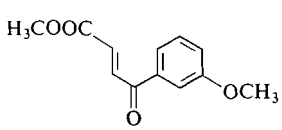

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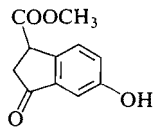

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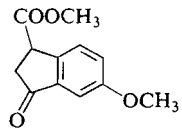

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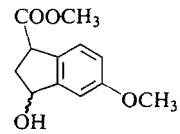

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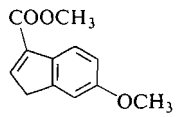

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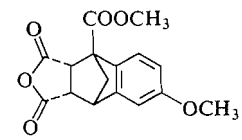

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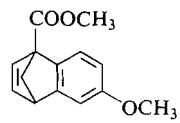

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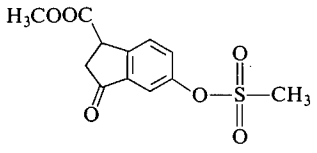
was condensed in methanolic sodium hydroxide with glyoxylic acid, freshly generated by periodate cleavage of tartaric acid. The oily mixture of compounds **9** and **10** which was produced almost quantitatively was directly used in the next step. The mixture was cyclized with aluminum chloride at 185 °C for 90 min. The crystalline phenol **11** was obtained in a yield of 46% based on the starting *m*-methoxyacetophenone. Finally, the phenol **11** was methylated with dimethyl sulfate in the presence of anhydrous potassium carbonate in benzene to yield quantitatively the crystalline methoxyester **12**.

The phenol **11** was also mesylated with mesylchloride in pyridine to the mesyloxyketoester **17** and this compound was transformed by the already described route (via **18**, **19**, and **20**) to compound **21**. The yield in the transformation **19** → **20** was only approximately 50% as compared to the quantitative reaction of the methoxy derivatives **6** and **14**. It would appear that the thermal 1,5 hydride shift which presumably precedes the Diels–Alder addition of maleic anhydride is favored by an electron releasing substituent in the benzene ring.

Finally the compound **24** which contains a methoxy group at the bridgehead was required. It was prepared by a simple adaptation of our general indene approach. The ketoester **12** was stirred with trimethyl orthoformate and a small amount of hydrogen chloride in benzene–methanol to give a quantitative yield of the enolether **22**. The addition of maleic anhydride to **22** yielded the adduct **23** and bisdecarboxylation of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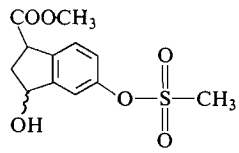
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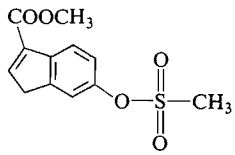
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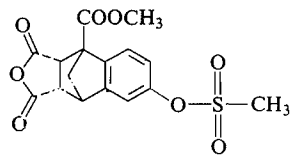
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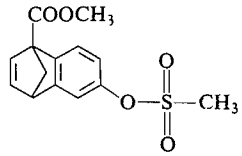
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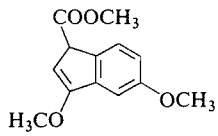
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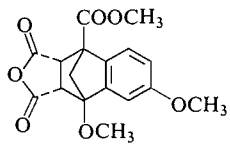
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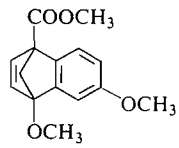

24

this compound gave finally the desired product **24**.

Having described the synthesis of all the desired substituted benzonorbornenes we shall now proceed and discuss the preparation and rearrangements of the corresponding aziridines.

The aziridine **25** (Chart 1) was prepared by treating compound **3** with benzenesulfonyl azide in anhydrous benzene. It was a somewhat unstable oil but gave spectral data (see Experimental) which confirmed its structure and the expected *exo* stereochemistry. In this respect the singlet of the two protons unshielded by the nitrogen (τ 6.65 p.p.m.) in the n.m.r. spectrum was significant. The absence of coupling with the bridgehead proton indicated clearly the *endo* configuration of the protons unshielded by the aziridine.

The acetolysis of the aziridine **25** was performed by heating the compound to 100 °C in glacial acetic acid. Under these conditions the aziridine ring opens with rearrangement and the resulting carbonium ion reacts with acetic acid. This process as portrayed by arrows in formula **25** (Chart 1) leads to the product **26**.

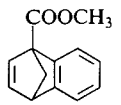
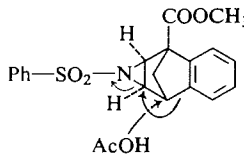
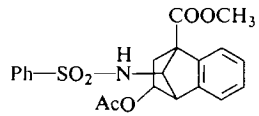
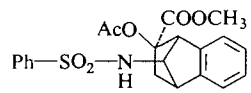
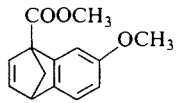
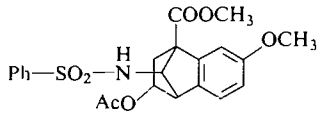
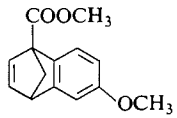
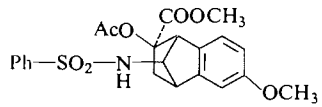
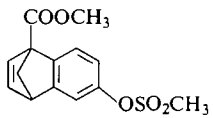
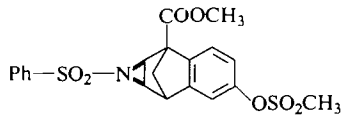
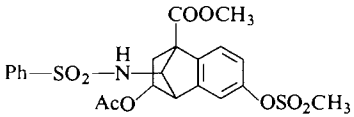
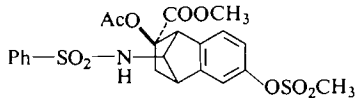
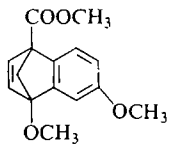
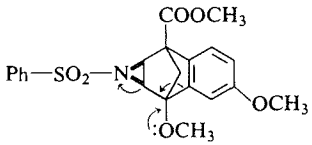
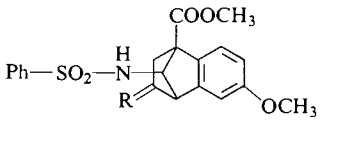
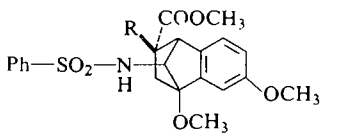
An exactly analogous process initiated by the opening of the second carbon–nitrogen bond yields the product **27**. It was anticipated that the product **26** will greatly predominate, since the formation of compound **27** requires the development of a carbonium ion adjacent to a carbonyl group, a situation known to be energetically very unfavorable.

Thus, we hoped that the ester group shall play a dual role in our projected terpene alkaloid syntheses. It was expected to serve in the annelation of ring A and as a site of a future substituent and at the same time to steer the aziridine rearrangement.

The result of the acetolysis experiment in fact bore out our prediction. The desired acetolysis product **26** predominated over compound **27** in a ratio 94:6. Compound **26** was crystalline and the small amount of **27** remained oily. Spectral data recorded in the Experimental leave no doubt about the assignment of structures to the two compounds. While **26** shows in the n.m.r. spectrum a proton unshielded by acetate (τ 5.33 p.p.m.), compound **27** displays two benzylic bridgehead protons (τ 6.65 p.p.m.) and a methoxy group highly shielded by the benzene ring (τ 7.82 p.p.m.) as a result of the *endo* configuration of the carbomethoxyl.

The songorine intermediate **8** was investigated next. In this case the aziridine formed in benzene by the action of benzenesulfonyl azide proved to be too unstable for isolation and it was acetolyzed at room temperature yielding exclusively the product **28**. The methoxyl located in para position to the migrating carbon–carbon bond greatly accelerates the reaction rate of the rearrangement leading to **28**. At the same time the carbomethoxy group slows down as before the rate of the alternative competing reaction. Thus, complete selectivity and a much faster reaction rate result. Compound **28** was beautifully crystalline and spectral data recorded in the Experimental leave no doubt about its structure. Moreover, the structure of an intermediate derived from **28** on the way to **iii** was corroborated by X-ray crystallography (2).

The unlikely possibility that compound **ii** could be prepared by acetolysis of the benzenesulfonyl aziridine derived from **16** was demolished by a single experiment. The acetolysis proceeded at room temperature and the single amorphous product had clearly the structure **29**. All n.m.r. data obtained for compound **29** were

Olefins	Aziridines	Rearranged products		Overall yields from olefins
				66.4%
3	**25**	**26** (94%)	**27** (6%)	
				75%
8		**28** (100%)		
				74%
16			**29** (100%)	
				52.5%
21	**30**	**31** (90%)	**32** (10%)	
				86%
24	**33**	**34** R = O **35** R =  (70%)	**36** R = OH **37** R = OAc (30%)	

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comparable to those of compound **27** and excluded the desired structure **ii**.

It was thus clear that the great increase in migratory aptitude of the bond para to the methoxyl overpowered the reaction rate decelerating influence of the carbomethoxyl.

Since a compound of the type **ii** was needed as a chasmanine starting material two devices were tried to steer the corresponding aziridine rearrangement.

First the methoxyl of compound **16** was replaced by a mesyloxy group and the substituted benzonorbornene derivative **21** was synthesized by the method which we have described above. Treatment of this product with benzenesulfonyl azide gave the stable crystalline aziridine **30**.

It was anticipated that the behavior of compound **30** on acetolysis will be similar to the unsubstituted aziridine **25**. We assumed that since the electron-releasing properties of a mesyloxy group are approximately equal to those of a hydrogen the aziridine rearrangement will be dominated by the already discussed influence of the carbomethoxyl.

This expectation was born out by experiment. The acetolysis of **30** was slow and had to be performed at 110 °C, but the ratio of the products **31** and **32** was favorable (9:1). However, the overall yield of the acetolysis was a low 52.5% and a few additional steps would be required to convert compound **31** into **ii**. Consequently we have turned to the examination of a still different possibility of rearrangement control.

As described above we have synthesized compound **24** which featured a methoxy group at the bridgehead. Treatment of **24** with benzenesulfonyl azide in a mixture of benzene and acetic acid presumably gave the unstable aziridine **33**. This compound underwent immediate acetolysis, in which the bridgehead methoxyl cooperated with the carbomethoxyl (as indicated by arrows in **33**) to counteract the influence of the aromatic methoxyl. The overall yield of the reaction was 86%. Of this 70% was the ketone **34** which was isolated after being converted into the crystalline ketal **35**. The alcohol **36** and the corresponding acetate **37** formed 30% of the mixture.

Compound **36** was characterized by conversion into the crystalline acetate **37** by acetic anhydride and pyridine.

The ketal **35** is a very advantageous chasmanine starting material and the synthesis is now underway using this supply route. Our methods of synthesis and rearrangement control of various substituted benzonorbornane aziridines are capable of wide synthetic application and consequently are described in the Experimental in considerable detail.

We shall report in the future on synthetic applications of these techniques in several fields unrelated to diterpene alkaloids.

Experimental

Preparation of the Olefin 3

A dimer of methyl cyclopentadiene carboxylate (9) (25 g) was distilled at 90–120 °C (12 mm Hg) and the monomeric ester **1** was collected in a cold flask (−80 °C). The monomer was dissolved in cold anhydrous tetrahydrofuran (200 ml) and added to freshly prepared crystalline 1,2,3-benzothiadiazol-1,1-dioxide (**2**) (4) at −20 °C. When the reaction mixture reached room temperature, evolution of nitrogen and sulfur dioxide occurred and the mixture was left overnight. Evaporation of solvent gave a crude product which was purified by chromatography on silica gel. Elution with benzene yielded 8.3 g (30%) of oily **3**, homogeneous in t.l.c., b.p. 50 °C (0.1 mm Hg).

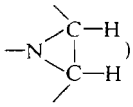
Anal. Calcd. for $C_{13}H_{12}O_2$ (mol. wt. 200): C, 77.98; H, 6.04; OMe, 15.50. Found (*m/e* 200): C, 78.07; H, 6.21; OMe, 15.13.

I.r. ($CHCl_3$): 1735 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 2.77–3.20 (m, 6H, aromatic and vinylic protons), 6.07 (m, 1H, bridgehead proton), 6.17 (s, 3H, $-\overset{\overset{O}{\|}}{C}-O-CH_3$), 7.47 (broad s, 2H, apex protons).

Preparation of Benzenesulfonyl Aziridine 25

A solution of the olefin **3** (1.03 g) and benzenesulfonyl azide (1.60 g) in anhydrous benzene (2 ml) was stirred at room temperature for 17 h and the mixture was chromatographed on silica gel. Elution with benzene – ethyl acetate (97:3) gave 1.52 g (83%) of the aziridine **25** as an oil, homogeneous in t.l.c.

Mol Wt. calcd. for $C_{19}H_{17}O_4NS$: 355. Found (*m/e*): 355.

I.r. ($CHCl_3$): 1730 (ester), 1160 cm^{-1} (aziridine); n.m.r. ($CDCl_3$): τ 6.16 (s, 3H, $-\overset{\overset{O}{\|}}{C}-O-CH_3$), 6.46 (broad s, 1H, bridgehead proton), 6.65 (broad s, 2H, ), 8.97 (two d, 2H, apex protons).

Acetolysis of the Aziridine 25

A solution of **25** (327 mg) in glacial acetic acid (10 ml) was heated to 100 °C for 2½ h. The mixture was poured into cold aqueous sodium bicarbonate and extracted with chloroform. The chloroform solution was washed with water, dried, and taken to dryness. Analysis of the residue by t.l.c. showed the presence of two products **26** and **27** (ratio, 94:6). The mixture was separated by preparative t.l.c. on silica gel using benzene – ethyl acetate (85:15) to afford 287 mg of **26** (75%) and 16 mg

(4.8%) of the tertiary acetate **27**. Recrystallization of **26** from chloroform–ether gave white crystals, m.p. 165–166 °C; **27** refused to crystallize in several solvents.

Anal. Calcd. for $C_{21}H_{21}O_6NS$ (secondary acetate **26** mol. wt. 415): C, 60.71; H, 5.10. Found (*m/e* 415): C, 60.51; H, 5.10.

I.r. (KBr pellet): 3300 (NH), 1735 (ester, acetate), 1335, 1170 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 4.16 (d, J = 9 Hz, 1H, —NH), 5.33 (m, 1H, proton adjacent to acetate), 6.23 (d, J = 9 Hz, 1H, apex proton), 6.40 (s, 3H, —C(=O)—OCH_3), 6.90 (broad s, 1H, benzylic proton), 7.90 (s, 3H, acetate methyl).

Mol. Wt. Calcd. for $C_{21}H_{21}O_6NS$ (tertiary acetate **27**): 415. Found (*m/e*): 415.

I.r. ($CHCl_3$): 3400 (NH), 1762, 1740 (acetate and ester), 1360, 1162 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 4.39 (d, J = 8 Hz, 1H, —NH), 6.40 (d, J = 8 Hz, 1H, apex proton), 6.65 (m, 2H, two benzylic protons), 6.72 (s, 3H, —C(=O)—OCH_3 shielded by aromatic ring), 7.82 (s, 3H, acetate methyl).

*Reduction of **4** to **5***

Sodium borohydride (2.3 g) was added in portions over a period of ½ h at room temperature to a stirred solution of the ketone **4** (5) (31.3 g) in tetrahydrofuran (250 ml) and methanol (250 ml). The mixture was stirred at room temperature for 1 h, diluted with water (1 l), and extracted with chloroform three times. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave 30.6 g (97%) of the alcohol **5**. For analysis, **5** was crystallized from benzene–hexane, m.p. 79–80 °C.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.79; H, 6.11.

I.r. (CCl_4): 3480 (OH), 1724 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 6.14 (s, 3H, aromatic methoxyl), 6.20 (s, 3H, —C(=O)—OCH_3), 6.00 (q, 1H, benzylic proton adjacent to —C(=O)—OCH_3), 4.87 (q, 1H, proton adjacent to OH).

*Preparation of the Indene **6***

A solution of the alcohol **5** (30.6 g) in methanol (150 ml) was added dropwise over a period of 1½ h to a refluxing solution of concentrated sulfuric acid (20 ml) in methanol (300 ml) and the mixture was kept at reflux for an additional 2 h. The reaction mixture was cooled, diluted with water (1 l) and extracted with chloroform three times. The extract was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled *in vacuo* to give the pure **6** (19.5 g, 67% based on **4**) as an oil homogeneous in t.l.c., b.p. 139 °C (0.3 mm Hg).

Mol. Wt. Calcd. for $C_{12}H_{12}O_3$: 204. Found (*m/e*): 204.

I.r. (CCl_4): 1727 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 2.47 (t, J = 2 Hz, 1H, vinylic proton), 6.05 (s, 3H, aromatic methoxyl), 6.08 (s, 3H, —C(=O)—OCH_3), 6.52 (d, 2H, benzylic protons).

*Preparation of the Adduct **7***

A mixture of compound **6** (19.5 g), maleic anhydride (9.36 g), and a small amount of hydroquinone (10 mg) was heated under nitrogen at 170 °C (oil bath temperature) for 3 h. The adduct **7** was homogeneous in t.l.c. and the yield was quantitative. Material of this purity was used in the subsequent step. An analytical sample was prepared by crystallization from benzene as white crystals, m.p. 147–148 °C.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.45; H, 4.39.

I.r. ($CHCl_3$): 1870, 1790 (anhydride), 1740 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 6.03 (s, 3H, aromatic methoxyl), 6.15 (broad s, 1H, bridgehead proton), 6.18 (s, 3H, —C(=O)—O—CH_3), 7.67 (m, 2H, apex protons).

*Preparation of the Olefin **8***

The Diels–Alder adduct **7** (16.4 g) was dissolved in anhydrous diglyme (300 ml) to which bistriphenylphosphinenickel dicarbonyl (42 g) was added. The mixture was heated under reflux in a dry nitrogen atmosphere for 6 h. The solvent was distilled off under reduced pressure. The residue was dissolved in chloroform and the black precipitate was removed by filtration. After evaporation of the solvent, the product was isolated by chromatography on silica gel. Elution with benzene gave the crystalline olefin **8** (10.2 g, 81%), homogeneous in t.l.c. The analytical sample had m.p. 63–64 °C after recrystallization from hexane.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.05; H, 5.92.

I.r. (CCl_4): 1745 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 3.17 (broad d, 2H, vinylic protons), 6.10 (broad s, 1H, bridgehead benzylic proton), 6.09 (s, 3H, aromatic methoxyl) 6.21 (s, 3H, —C(=O)—OCH_3), 7.45 (broad s, 2H, apex protons).

*Preparation of Rearranged Sulfamido Acetate **28***

A solution of the olefin **8** (38 g) and benzenesulfonyl azide (80 g) in anhydrous benzene (150 ml) was stirred at room temperature for 3 days. Glacial acetic acid (240 ml) was then added to this stirred solution and the reaction mixture was kept at room temperature for 2 days. After this time, benzene and most of the acetic acid was distilled off *in vacuo*. The residue was then dissolved in benzene–hexane and the product **28** crystallized on standing. Recrystallization of the product from benzene–hexane gave 56.5 g (75%) of **28**, m.p. 137 °C.

Anal. Calcd. for $C_{21}H_{23}O_7NS$ (mol. wt. 445): C, 59.13; H, 5.24; N, 3.14. Found (*m/e* 445): C, 59.23; H, 5.26; N, 3.19.

I.r. ($CHCl_3$): 3300 (NH), 1740 (ester and acetate), 1345, 1170 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 4.20 (d, J = 9 Hz, 1H, —NH), 5.24 (broad t, 1H, proton adjacent to acetate), 6.17 (d, J = 9 Hz, 1H, apex proton), 6.24 (s,

3H, aromatic methoxyl), 6.34 (s, 3H, —C(=O)—OCH_3), 6.70 (s, 1H, bridgehead benzylic proton), 7.84 (s, 3H, acetate methyl).

*Preparation of the Condensed Products (**9**, **10**)*

A solution of *d*-tartaric acid (20 g) in distilled water (30 ml) was added to a cooled suspension of trisodium periodate (para) (30 g) in concentrated sulfuric acid (3 ml) and distilled water (160 ml), and the mixture was stirred at room temperature for ½ h. *m*-Methoxyacetophenone (20 g), sodium hydroxide (20 g) in distilled water (360 ml), and methanol (300 ml) were added in sequence. The reaction mixture was stirred at room temperature overnight. The solution was poured into ice-water, acidified with dilute hydrochloric acid and extracted with ether (3 × 500 ml). The ethereal extract was washed with water and dried over anhydrous sodium sulfate. The volume of the dried ethereal solution was reduced to 200 ml, and treated with diazomethane. The solvent was removed *in vacuo*, the mixture (30 g) was immediately used in the subsequent step.

Analysis by t.l.c. showed that the mixture consisted of two components, **9** and **10** (ratio, 8:1). A portion (121 mg) was separated by preparative t.l.c. Compound **9** (85 mg) was oily; compound **10** (15 mg) was a waxy solid.

Mol. Wt. Calcd. for $C_{13}H_6O_5$ (saturated ketone **9**): 252. Found (*m/e*): 252.

I.r. ($CHCl_3$): 1750 (ester), 1690 cm^{-1} (ketone); n.m.r. ($CDCl_3$): τ 6.17 (s, 3H, aromatic methoxyl), 6.24 (s, 3H, —C(=O)—OCH_3), 6.54 (s, 3H, methoxyl), 6.64 (d, 2H, methylene protons).

Mol. Wt. Calcd. for $C_{12}H_{12}O_4$ (unsaturated ketone **10**): 220. Found (*m/e*): 220.

I.r. ($CHCl_3$): 1725 (ester), 1675 cm^{-1} (conjugated ketone); n.m.r. ($CDCl_3$): τ 2.14 (d, J = 15 Hz, 1H, vinylic proton), 3.15 (d, J = 15 Hz, 1H, vinylic proton), 6.15 (s, 3H, aromatic methoxyl), 6.19 (s, 3H, —C(=O)—OCH_3); u.v. (EtOH): λ_{max} 235 nm (ε 12 000).

*Preparation of the Phenol **11***

A solution of **9** and **10** (30 g) in a small volume of anhydrous dichloromethane (30 ml) was added dropwise over a period of 5 min to a preheated (at 130 °C) mixture of anhydrous aluminum chloride (300 g) and sodium chloride (45 g). The mixture was shaken mechanically and at the same time the temperature was raised to 185 °C (oil bath temperature) and maintained at this temperature for 1½ h. While the mixture was cooled to 100 °C, water and concentrated hydrochloric acid (200 ml) were added slowly in sequence. The product was extracted with ether and the ethereal solution was dried over anhydrous sodium sulfate and evaporated to dryness. The resulting brown residue (20 g) was dissolved in methanolic hydrogen chloride (300 ml) and heated under reflux for 2 h. After removal of the solvent, the residue was chromatographed on silica gel to give 12 g (46%, based on *m*-methoxylacetophenone) of the crystalline phenol **11**. Recrystallization from acetone–ether gave an analytical sample as white crystals, m.p. 141–142 °C.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.88. Found: C, 64.20; H, 4.88.

I.r. ($CHCl_3$): 3600, 3500 (OH), 1740, 1710 cm^{-1} (ester and ketone); n.m.r. ($CDCl_3$): τ 5.82 (q, 1H, benzylic proton), 6.20 (s, 3H, —C(=O)—OCH_3), 6.99 (t, 2H, methylene).

*Preparation of the Methyl Ether **12***

A mixture of the phenol **11** (1.03 g), benzene (20 ml), anhydrous potassium carbonate (1.42 g), and dimethyl sulfate (1 ml) was refluxed under nitrogen for 8 h and then stirred at room temperature overnight. The precipitate was filtered and washed with dichloromethane. The filtrate was washed with dilute aqueous hydrochloric acid and water, dried over anhydrous sodium sulfate, and evaporated to give the methyl ether **12** (1.10 g, 100%) homogeneous in t.l.c. Recrystallization of **12** from benzene–hexane gave colorless plates, m.p. 73–74 °C.

Anal. Calcd. for $C_{12}H_{12}O_4$ (mol. wt. 220): C, 65.44; H, 5.49. Found (*m/e* 220): C, 65.46; H, 5.55.

I.r. (CCl_4): 1750, 1725 cm^{-1} (ester, ketone); n.m.r. (CCl_4): τ 5.87 (two d, 1H, benzylic proton), 6.17 (s, 3H, aromatic methoxyl), 6.27 (s, 3H, —C(=O)—OCH_3).

*Reduction of **12** to **13***

The ketone **12** (678 mg) was dissolved in methanol (10 ml) and tetrahydrofuran (5 ml), and sodium borohydride (90 mg) was added at 0 °C. The mixture was stirred for 40 min and the same work-up as described above yielded 680 mg (100%) of the alcohol **13** as white crystals. Recrystallization of **13** from chloroform–ether gave crystals, m.p. 93–94 °C.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.81; H, 6.10.

I.r. ($CHCl_3$): 3612, 3484 (OH), 1740 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 4.10 (q, 1H, benzylic proton), 4.97 (m, 1H, proton unshielded by OH), 6.22 (s, 3H, aromatic methoxyl), 6.27 (s, 3H, —C(=O)—OCH_3).

*Dehydration of **13** to **14***

A solution of **13** (324 mg) in 12% methanolic sulfuric acid (15 ml) was heated under reflux for 2 days. The reaction mixture was worked-up in the same way as described above. Recrystallization of the product from ether gave 120 mg (40%) of **14** as colorless needles, m.p. 96 °C.

Anal. Calcd. for $C_{12}H_{12}O_3$ (mol. wt. 204): C, 70.57; H, 5.92. Found (*m/e* 204): C, 70.52; H, 5.84.

I.r. ($CHCl_3$): 1708 cm^{-1} (unsaturated ester); n.m.r. ($CDCl_3$): τ 2.72 (t, 1H, vinylic proton), 6.12 (s, 3H, aromatic methoxyl), 6.20 (s, 3H, —C(=O)—OCH_3), 6.57 (d, 2H, benzylic protons).

*Preparation of the Diels–Alder Adduct **15***

The indene **14** (230 mg) and maleic anhydride (140 mg) were heated to 168 °C for 13 h in a sealed tube. The adduct **15** was recrystallized from acetone–ether to a m.p. of 154–155 °C. The yield was 270 mg (80%).

Anal. Calcd. for $C_{14}H_{14}O_6$ (mol. wt. 302): C, 63.57; H, 4.67. Found (*m/e* 302): C, 63.35; H, 4.66.

I.r. ($CHCl_3$): 1844, 1792 (anhydride), 1744 cm^{-1} (ester); n.m.r. (acetone-d_6): τ 6.14 (s, 3H, aromatic methoxyl), 6.21 (broad s, 1H, bridgehead proton), 6.25 (s, 3H, —C(=O)—OCH_3), 7.70 (t, 2H, apex protons).

Preparation of the Olefin ***16***

The crude adduct **15** (370 mg) was dissolved in anhydrous diglyme (6 ml) and bistriphenylphosphinenickel dicarbonyl (1.2 g) was added. The mixture was refluxed under nitrogen for 40 min and it was worked-up as described above. The product was isolated by preparative t.l.c. on silica gel to give 126 mg (48% based on **14**) of oily **16**, homogeneous in t.l.c.

Mol. Wt. Calcd. for $C_{14}H_{14}O_3$: 230.0943. Found (*m/e*): 230.0947.

I.r. ($CHCl_3$): 1733 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 3.20 (m, 2H, vinylic protons), 6.11 (broad s, 1H, bridgehead proton), 6.14 (s, 3H, aromatic methoxyl), 6.25 (s, 3H, —C(=O)—OCH_3), 6.57 (d, 2H, apex protons).

Preparation of the Rearranged Product ***29***

A mixture of **16** (91 mg) and an excess of benzenesulfonyl azide (1 ml) in anhydrous benzene (0.5 ml) was stirred at room temperature for 3 days. Glacial acetic acid (1.5 ml) was added, the solution was stirred for an additional day, and the reaction mixture was worked-up as described above. Examination of the residue by t.l.c. in several solvent systems showed one product only. Preparative t.l.c. on silica gel gave 129 mg (74%) of **29** (homogeneous in t.l.c.) as a foam which refused to crystallize in several solvents.

Mol. Wt. Calcd. for $C_{21}H_{23}O_7NS$: 445.1195. Found (*m/e*): 445.1183.

I.r. ($CHCl_3$): 3400 (NH), 1756, 1740 cm^{-1} (acetate and ester); n.m.r. ($CDCl_3$): τ 4.50 (d, J = 8 Hz, 1H, —NH), 6.26 (s, 3H, aromatic methoxyl), 6.36 (broad s, 1H, benzylic proton), 6.40 (d, J = 8 Hz, 1H, apex proton), 6.67 (s, 3H, —C(=O)—OCH_3 shielded by benzene ring), 6.70 (s, 1H, benzylic proton), 7.84 (s, 3H, acetate methyl).

Preparation of the Mesylate ***17***

The phenol **11** (5.3 g) was dissolved in anhydrous pyridine (35 ml) and methane sulfonyl chloride (3 ml) was added at 0 °C. The reaction mixture was stirred for 5 h at that temperature and worked-up in the usual manner. The product **17** was recrystallized from chloroform to a m.p. 141–142 °C. The yield was 6.6 g (90%).

Anal. Calcd. for $C_{12}H_{12}O_6S$: C, 50.69; H, 4.25. Found: C, 50.66; H, 4.30.

I.r. ($CHCl_3$): 1744, 1725 (ester and ketone), 1375, 1144 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 5.67 (q, 1H, benzylic proton), 6.20 (s, 3H, —C(=O)—OCH_3), 6.80 (s, 3H, —OSO_2—CH_3).

Reduction of ***17*** *to the Alcohol* ***18***

The ketone **17** (2.0 g) was dissolved in methanol (30 ml) and tetrahydrofuran (15 ml), and sodium borohydride (250 mg) was added at 0 °C. The mixture was stirred for 20 min and the same work-up as described above yielded 2.0 g (quantitative yield) of the alcohol **18** as a colorless oil, homogeneous in t.l.c.

Mol. Wt. Calcd. for $C_{12}H_{14}O_6S$: 286. Found (*m/e*): 286.

I.r. (film): 3490 (OH), 1735 (ester), 1365, 1125 cm^{-1} (—OSO_2—); n.m.r. ($CDCl_3$): τ 4.90 (q, 1H, proton adjacent to hydroxyl), 6.09 (q, 1H, benzylic proton), 6.25 (s, 3H, —C(=O)—OCH_3), 6.89 (s, 3H, —OSO_2—CH_3), 7.50 (m, 2H, methylene).

Dehydration of ***18*** *to the Indene* ***19***

A mixture of the alcohol **18** (690 mg) and potassium bisulfate (700 mg) in anhydrous benzene (25 ml) was heated under reflux for 20 min with a water separator. The solid was removed by filtration, the filtrate was diluted with benzene (200 ml), washed, dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was recrystallized from ether to give 445 mg (70%) of pure **19**, m.p. 106–107 °C.

Anal. Calcd. for $C_{12}H_{12}O_5S$: C, 53.72; H, 4.51. Found: C, 53.57; H, 4.55.

I.r. ($CHCl_3$): 1719 cm^{-1} (unsaturated ester); n.m.r. ($CDCl_3$): τ 2.54 (t, 1H, vinylic proton), 6.09 (s, 3H, —C(=O)—OCH_3), 6.45 (d, 2H, benzylic protons), 6.85 (s, 3H, —OSO_2—CH_3).

Preparation of the Diels–Alder Adduct ***20***

The indene carboxylic ester **19** (200 mg) and maleic anhydride (90 mg) were heated to 165 °C for 3 h in a sealed tube. The adduct **20** was homogeneous in t.l.c. and was used in the crude form for further work. For analysis it was purified by recrystallization from acetone to a constant, m.p. 223–224 °C.

Anal. Calcd. for $C_{16}H_{14}O_8S$ (mol. wt. 366): C, 52.45; H, 3.85. Found (*m/e* 366): C, 52.39; H, 3.88.

I.r. ($CHCl_3$): 1844, 1792 (anhydride), 1744 cm^{-1} (ester); n.m.r. (acetone-d_6): τ 6.02 (broad s, 1H, bridgehead proton), 6.07 (s, 3H, —C(=O)—OCH_3), 6.67 (s, 3H, —OSO_2—CH_3), 7.57 (t, 2H, apex protons).

Preparation of the Olefin ***21***

The crude adduct **20** (290 mg) was dissolved in anhydrous diglyme (6 ml) and bistriphenylphosphinenickel dicarbonyl (1.1 g) was added. The reaction mixture was refluxed under nitrogen for 2 h and worked-up as described above. Chromatography of the residue on silica gel gave 62 mg (30%, based on the indene **19**) of the pure olefin **21** as an oil homogeneous in t.l.c.

Mol. Wt. Calcd. for $C_{14}H_{14}O_5S$: 294.0562. Found (*m/e*): 294.0568.

I.r. ($CHCl_3$): 1737 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 3.17 (m, 2H, vinylic protons), 6.03 (broad s, 1H, bridgehead proton), 6.10 (s, 3H, —C(=O)—OCH_3), 6.90 (s, 3H, —OSO_2—CH_3), 7.42 (d, 2H, apex protons).

Preparation of the Aziridine ***30***

A solution of the olefin **21** (210 mg) and benzenesulfonyl azide (1.5 ml) in benzene (1 ml) was stirred at room

temperature for 2 days. The reaction mixture was purified by preparative t.l.c. on silica gel to yield 223 mg (70%) of the pure aziridine **30** as the only crystalline product. Recrystallization from benzene gave an analytical sample, m.p. 155–156 °C.

Anal. Calcd. for $C_{20}H_{19}O_7NS_2$ (mol. wt. 449): C, 53.44; H, 4.26; N, 3.11. Found (*m/e* 449): C, 53.47; H, 4.41; N, 3.20.

I.r. ($CHCl_3$): 1740 (ester), 1370, 1325 (OSO_2), 1160 cm^{-1} (aziridine); n.m.r. ($CDCl_3$): τ 6.35 (s, 3H, —C(=O)—OCH_3), 6.39 (broad s, 1H, bridgehead proton), 6.67 (broad s, 2H, —CH—CH— as N), 6.87 (s, 3H, —OSO_2—CH_3), 7.67 (d, J = 9 Hz, 1H, one apex protons), 8.20 (d, J = 9 Hz, 1H, one apex protons).

Acetolysis of the Aziridine 30

A solution of **30** (130 mg) and *p*-toluenesulfonic acid (4 mg) in glacial acetic acid (2.5 ml) was heated to 110 °C for 2 h. After removal of the solvent *in vacuo*, chloroform (150 ml) was added to the residue and the solution was washed with water three times, dried, and evaporated to dryness. Analysis of the residue by t.l.c. showed the presence of two acetates **31** and **32** (ratio 9:1). This mixture was separated by preparative t.l.c. on silica gel to give 97 mg (67%) of crystalline **31** and 11 mg (7.5%) of the tertiary acetate **32** as an oil, homogeneous in t.l.c. Recrystallization of **31** from benzene gave an analytical sample, m.p. 196–197 °C.

Anal. Calcd. for $C_{22}H_{23}O_9NS_2$ (acetate **31** mol. wt. 509): C, 51.85; H, 4.55; N, 2.75. Found (*m/e* 509): C, 51.56; H, 4.67; N, 2.66.

I.r. ($CHCl_3$): 3400 (NH), 1750 cm^{-1} (acetate and ester); n.m.r. ($CDCl_3$): τ 4.20 (d, J = 8.5 Hz, 1H, —NH), 5.24 (m, 1H, proton unshielded by acetate), 6.17 (d, J = 8.5 Hz, 1H, apex proton), 6.30 (s, 3H, —C(=O)—OCH_3), 6.59 (s, 1H, benzylic proton), 6.85 (s, 3H, —OSO_2—CH_3), 7.85 (s, 3H, acetate, methyl).

Mol. Wt. Calcd. for $C_{22}H_{23}O_9NS_2$ (tertiary acetate **32**): 509. Found (*m/e*): 509.

I.r. ($CHCl_3$): 3400 (NH), 1755, 1738 cm^{-1} (acetate and ester); n.m.r. ($CDCl_3$): τ 4.40 (d, J = 8 Hz, 1H, —NH), 6.40 (d, J = 8 Hz, 1H, apex proton), 6.62 (broad s, 1H, benzylic proton), 6.89 (s, 1H, benzylic proton), 6.69 (s, 3H, —C(=O)—OCH_3 shielded by benzene ring), 6.91 (s, 3H, —OSO_2—CH_3), 7.80 (s, 3H, acetate).

Preparation of the Enol Ether 22

Methanol (1 ml), trimethyl orthoformate (1.2 ml), and saturated methanolic hydrogen chloride (10 drops) were added in sequence to a solution of the ketoester **12** (1.13 g) in benzene. The mixture was stirred under nitrogen at room temperature for 24 h after which time it was evaporated to dryness *in vacuo*. The residue was heated under reflux for 20 min in 10 ml of xylene. After evaporation of the solvent *in vacuo*, **22** was obtained quantitatively as an oil homogeneous in t.l.c. and it was used immediately for further work.

Mol. Wt. Calcd. for $C_{13}H_{14}O_4$: 234.0892. Found (*m/e*): 234.0887.

I.r. (CCl_4): 1745, 1625 cm^{-1} (ester, enol ether); n.m.r. (CCl_4): τ 4.75 (d, J = 2 Hz, 1H, vinylic proton), 5.82 (d, J = 2 Hz, 1H, benzylic proton), 6.14 (s, 3H, aromatic methoxyl), 6.34 (s, 3H, —OCH_3); u.v. (EtOH): λ_{max} 237 (log ε 4.06), 257 (log ε 3.66), 293 nm (log ε 3.43).

The Diels–Alder Adduct 23

The enol ether **22** (1.19 g) was dissolved in xylene (5 ml) and maleic anhydride (500 mg) was added. The mixture was heated under nitrogen to 170 °C (oil bath temperature) for 12 h. The solvent was evaporated to give a solid (1.68 g), homogeneous in t.l.c. An analytical sample of **23** was obtained by recrystallization from chloroform as colorless plates, m.p. 206–207 °C.

Anal. Calcd. for $C_{17}H_{16}O_7$ (mol. wt. 332): C, 61.44; H, 4.85. Found (*m/e* 332): C, 61.34; H, 4.78.

I.r. ($CHCl_3$): 1870, 1790 (anhydride), 1740 cm^{-1} (ester); n.m.r. ($CDCl_3$): τ 6.07 (s, 3H, aromatic methoxyl), 6.20 (s, 3H, —C(=O)—OCH_3), 6.40 (s, 3H, bridgehead —OCH_3), 7.54 (d, J = 2 Hz, 2H, apex protons).

Preparation of the Olefin 24

The crude Diels–Alder adduct **23** (1.68 g) was dissolved in anhydrous diglyme (30 ml) and bistriphenylphosphinenickel dicarbonyl (3.84 g) was added. The mixture was heated under nitrogen to 200–210 °C for 7 h and worked-up in the usual manner. The residue was chromatographed on silica gel. Elution with benzene gave 765 mg (58%, based on **22**) of **24** as an oil homogeneous in t.l.c.

Mol. Wt. Calcd. for $C_{15}H_{16}O_4$: 260.1049. Found (*m/e*): 260.1041.

I.r. (CCl_4): 1740 cm^{-1} (ester); n.m.r. (CCl_4): τ 3.33 (m, 2H, vinylic protons), 6.18 (s, 3H, aromatic methoxyl), 6.27 (s, 3H, —C(=O)—OCH_3), 6.50 (s, 3H, bridgehead methoxyl), 7.38 (q, J = 6 Hz, 2H, apex protons).

Preparation of Rearranged Products From 24

The olefin **24** (205 mg) was dissolved in anhydrous benzene (2 ml) to which benzenesulfonyl azide (275 mg), *p*-toluenesulfonic acid (10 mg), and glacial acetic acid (0.4 ml) were added. The solution was stirred under nitrogen at room temperature for 7 days. Removal of the solvent *in vacuo* gave a light brown residue which was chromatographed on silica gel. Elution with ether–benzene (1:9) yielded 336 mg of foam. This material appeared to be homogeneous when examined by t.l.c. on silica gel in several solvent systems. However, its n.m.r. spectrum showed that it consisted of three products, **34**, **36**, and **37** which could not be separated.

The mixture was refluxed with *p*-toluenesulfonic acid (42 mg) and ethylene glycol (1 ml) in dry benzene (50 ml) for 18 h with a water separator. After cooling the solution was diluted with methylene chloride, washed with aqueous sodium bicarbonate and water, dried, and taken to dryness. The residue was chromatographed by preparative t.l.c. on silica gel to yield 213 mg of the crystalline

ketal **35** (60%, based on **24**) and 94 mg of the mixture **36** and **37**. After recrystallization from benzene–ether the pure **35** melted at 149–150 °C.

Anal. Calcd. for $C_{22}H_{23}O_7NS$ (ketal **35**, mol. wt. 445): C, 59.32; H, 5.21; N, 3.14. Found (*m/e* 445): C, 59.20; H, 5.20; N, 3.07.

I.r. ($CHCl_3$): 3340 (NH), 1740 (ester), 1350, 1160 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 3.70 (d, J = 10 Hz, 1H, —NH), 5.97 (d, J = 10 Hz, 1H, apex proton), 6.13 (m, 4H, dioxolane), 6.23 (s, 3H, aromatic methoxyl), 6.37 (s, 3H, $-\overset{\overset{O}{\|}}{C}-O-CH_3$), 7.21 (broad s, 1H, bridgehead benzylic proton).

The mixture of **36** and **37** was dissolved in pyridine (3 ml) and acetic anhydride (2 ml) was added. The reaction mixture was heated to 45 °C for 3 h, kept at room temperature for 10 h and worked-up in the usual manner. Preparative t.l.c. (silica gel) of the product followed by recrystallization from chloroform–benzene gave 94 mg (26%, based on **24**) of the tertiary acetate **37**, m.p. 217–218 °C.

Anal. Calcd. for $C_{23}H_{25}O_8NS$ (acetate **39**, mol. wt. 475): C, 58.10; H, 5.30; N, 2.95. Found (*m/e* 475): C, 58.08; H, 5.28; N, 2.83.

I.r. ($CHCl_3$): 3390 (NH), 1755, 1745 (acetate and ester), 1340, 1165 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 4.25 (d, J = 9 Hz, 1H, —NH), 6.20 (d, J = 9 Hz, 1H, apex proton), 6.21 (s, 3H, aromatic methoxyl), 6.57 (s, 3H, bridgehead $-OCH_3$), 6.67 (s, 3H, $-\overset{\overset{O}{\|}}{C}-OCH_3$, shielded by aromatic ring), 6.80 (broad s, 1H, bridgehead benzylic proton), 7.83 (s, 3H, acetate methyl).

Deketalization of 35 to 34

A solution of the ketal **35** (96 mg) in 70% aqueous acetic acid (4 ml) was heated to 80 °C for 20 h. After cooling dichloromethane (100 ml) was added and the solution was washed with aqueous sodium carbonate, then with water, dried, and evaporated to dryness. The product **34** was recrystallized from benzene–hexane to a m.p. of 180–181 °C. The yield was 85 mg (98%).

Mol. Wt. Calcd. for $C_{20}H_{19}O_6NS$: 401.0933. Found: (*m/e*): 401.0927.

I.r. ($CHCl_3$): 3350 (NH), 1755, 1730 (ketone and ester), 1330, 1160 cm^{-1} (sulfonyl); n.m.r. ($CDCl_3$): τ 4.13 (d, 1H, —N—H), 6.08 (broad s, 2H, apex and bridgehead protons), 6.13 (s, 3H, aromatic methoxyl), 6.22 (s, 3H, $-\overset{\overset{O}{\|}}{C}-OCH_3$), 7.46 (two d, 2H, methylene).

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