Synthetic and Structural Studies of Some Chloro-substituted Methyl 2,1-Benzisoxazole-3-carboxylates and Related Compounds

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Methyl 5-chloro- and 5,7-dichloro-2,1-benzisoxazole-3-carboxylates have been synthesized by treatment of *o*-nitromandelic and 5-chloro-2-nitroamandelic methyl esters, respectively, with thionyl chloride under appropriate reaction conditions. The structural assignments of both heterocyclic products were based on elemental and spectral analyses, and their conversion to the corresponding 5-chloro- and 5,7-dichloro substituted 2,1-benzisoxazole-3-carboxylic acids and isatins. Methyl α-chloro-*o*-nitrophenylacetate and *o*-nitrophenylcarbomethoxymethinyl sulfite were also obtained from reactions of methyl *o*-nitromandelate and thionyl chloride. A possible reaction mechanism involving two consecutive nucleophilic substitutions of methyl *o*-nitromandelate with thionyl chloride was proposed to account for the formation of methyl 5-chloro-2,1-benzisoxazole-3-carboxylate.

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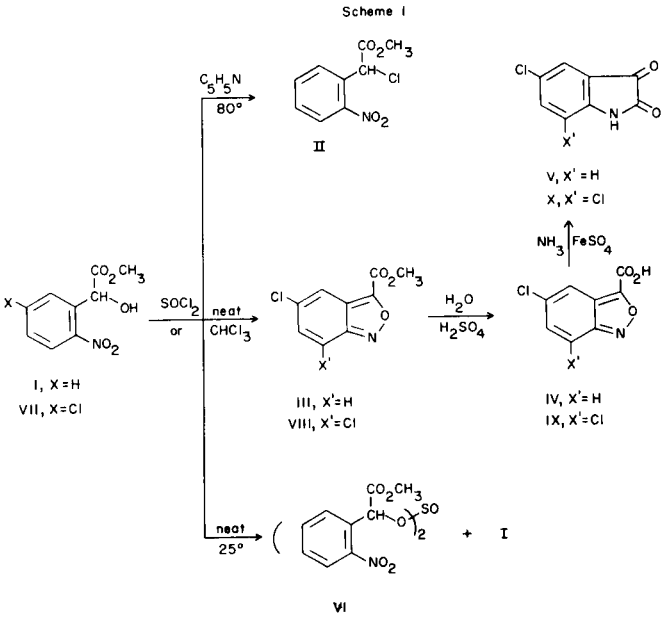
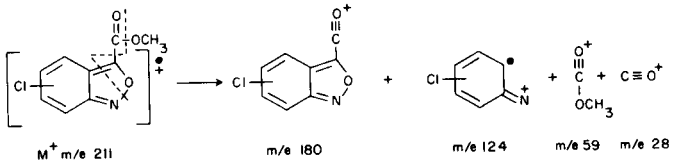
In previous work (1), we reported that methyl *o*-nitromandelate undergoes a straightforward nucleophilic displacement with phosphorus tribromide to afford methyl α-bromo-*o*-nitrophenylacetate in good yield. More recently, however, we found that the outcome of the reaction of the nitromandelic ester with neat thionyl chloride was completely different from that with phosphorus tribromide. This finding led us to study the reactions of *o*-nitromandelic and 5-chloro-2-nitromandelic methyl esters with thionyl chloride under different experimental conditions. Therefore, the purpose of this paper is to describe the results of our synthetic and structural studies of the heterocyclic and aromatic products which were obtained from the reactions of *o*-nitromandelic esters with thionyl chloride as depicted in Scheme I.

Scheme I



In an initial experiment, a solution of methyl *o*-nitromandelate (I) and thionyl chloride in a molar ratio of 1:4 was effected at 25°, and then was heated under reflux. From this reaction, a solid product was isolated and analyzed spectrally (ir, nmr, and mass) and elementally for the expected methyl α-chloro-*o*-nitrophenylacetate (II). As would be expected for the α-chloroester II, the infrared spectrum showed characteristic absorptions for an ester, but not for the starting α-hydroxyester (*i.e.*, the absence of the hydroxyl group absorption at 3360 cm^{-1}). However, the elemental analysis (C,H,Cl,N) was incorrect for II, but it was correct for $C_9H_6ClNO_3$ which was later confirmed by a molecular ion at m/e 211 in the mass spectra.

The structural assignment of the product was based primarily on its nmr and mass spectra. The nmr spectrum showed a singlet for the three methoxy protons at 5.9 τ and a complex multiplet for the aromatic protons in the 2.0-3.0 τ range, and the peak areas of the two types of protons were identical (a ratio of 3:3) in accord with the molecular formula. Moreover the signals of the aromatic protons were a characteristic ABC pattern which is consistent with a 1,2,4-trisubstituted benzene derivative. In addition to the molecular ion at m/e 211, the mass spectrum of the product showed predominant mass peaks at m/e values of 180, 124, 59, and 28. The structures assigned to these mass ions resulting from fragmentation of the molecular ion are presented in the accompanying equa-



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tion. The mass spectrum proved most useful in confirming the structure of the product as either the 5-chloro- or the 6-chloro-2,1-benzisoxazole-3-carboxylic methyl ester.

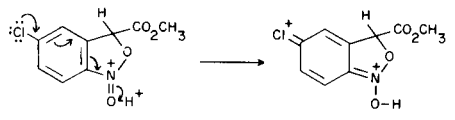
The position of the chlorosubstituent on the heterocyclic structure III was determined unequivocally as the 5-position by its hydrolysis with dilute sulfuric acid to yield the corresponding 5-chloro-2,1-benzisoxazole-3-carboxylic acid (IV), which was reduced with ferrous sulfate in aqueous ammonia to afford 5-chloroisatin (V), as shown in Scheme I. The melting point and infrared spectrum of the latter compound V were identical on comparison with those of an authentic sample. These results indicate that substitution of the chloro group on the benzenoid part of the heterocyclc occurs preferentially at the 5-position.

In a separate experiment, the reaction of the *o*-nitromandelic ester (I) with neat thionyl chloride in a molar ratio of 1:4 was repeated at 25°, but without heating under reflux. Under these reaction conditions, *o*-nitrophenylcarbomethoxymethinyl sulfite (VI) was isolated in low yield along with the recovery of unreacted starting material I. The sulfite ester VI was characterized by elemental and spectra (ir and nmr) and analysis. It appears that I has to be heated in neat thionyl chloride to effect its cyclization and chlorosubstitution to form the heterocyclic product III.

Since methyl α-chloro-*o*-nitrophenylacetate (II) was required for comparative purposes, its synthesis was accomplished by treatment of I with equimolar quantities of thionyl chloride and pyridine at -80°. The elemental and spectral analysis of the α-chloroester (II) were consistent with its assigned strucutre. Contrary to the results obtained earlier for the synthesis of methyl α-bromo-*o*-nitrophenylacetate under acidic conditions (1), the straightforward nucleophilic substitution of I with thionyl chloride to give methyl α-chloro-*o*-nitrophenylacetate takes place under basic conditions.

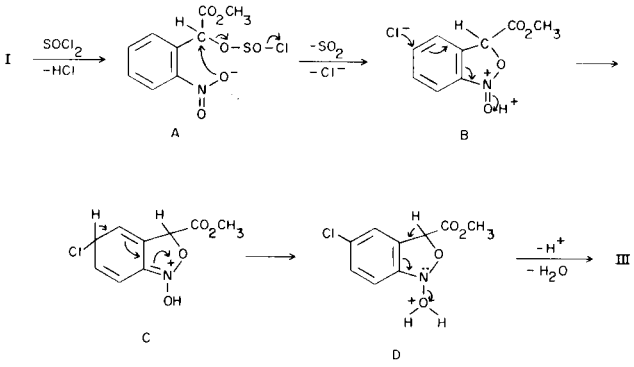
In view of these results, the reaction of methyl 5-chloro-2-nitromandelate (VII) with thionyl chloride was studied next to determine the nature and site of the reaction when the 5-position already contains the chloro group. In contrast to the conversion of I to III as previously described, no reaction was observed when VII was heated in neat thionyl chloride under the same experimental conditions. However, when VII was treated with thionyl chloride in a 1:70 molar ratio in refluxing chloroform solution for 12 hours, methyl 5,7-dichloro-2,1-benzisoxazole-3-carboxylate (VIII) was obtained in low yield with the recovery of unreacted starting material as shown in Scheme I. As in the case of III, this product (VIII) was also identified by elemental and spectral analysis, and by its conversion to 5,7-dichloro-2,1-benzisoxazole-3-carboxylic acid (IX) and 5,7-dichloroisatin (X). These results show that VIII was formed under more vigorous reaction conditions and in lower yield than III, and that chlorosubstitution occurs at the 7-position of VIII when the preferential site is blocked by a chloro group.

For the formation of III from I, we have proposed that the cyclization and chlorosubstitution of the ester result from two consecutive nucleophilic substitution reactions, one internal and the other, acid-catalyzed heteroaromatic, as shown in Scheme II. The initial intermediate which forms is presumably the chlorosulfite ester (**A**). This ester (**A**) is internally attacked by the nitro group on the benzylic carbon with simultaneous loss of sulfur dioxide and chloride to give the benzisoxazole-type intermediate (**B**). Then, an acid-catalyzed heteroaromatic nucleophilic substitution of **B** occurs by an attack of the chloride ion at the electron-deficient 5-position brought about by the resonance effect of the protonation to afford the quinoid-type intermediate **C**. The latter intermediate **C** undergoes a prototropic change which restores the aromatic ring, reduces the nitrogen atom, and forms the protonated *N*-hydroxybenzisoxazole intermediate **D**. In the final step, a 1,4-conjugate elimination of water and the benzylic proton takes place to produce the 2,1-benzisoxazole ring system of III.



B' C'

Scheme II



A B C D

A similar mechanism would also account for formation of VIII even though the thionyl chloride reaction of VII was observed to occur with greater difficulty than that of I. This observation may be attributed to the 5-chloro group of intermediate **B'** which enters into resonance interaction with the ring on protonation to accomodate the electron deficiency on itself. The dispersal of electron deficiency to the chloro group causes the 7-position of the in-

termediate C′ to become less susceptible to nucleophilic attack by chloride ion.

In summary, some chlorosubstituted derivatives of 2,1-benzisoxazole-3-carboxylic methyl esters and acids have been synthesized from *o*-nitromandelic esters and thionyl chloride, and some of their spectral and chemical properties have been described.

EXPERIMENTAL

General.

Melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Model IR-10 spectrophotometer (potassium bromide) and were calibrated with polystyrene film. Nmr spectra were recorded on a Perkin-Elmer Model R12-B spectrometer at 60 MHz. Chemical shifts are given in τ units downfield from an internal TMS standard. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona. The mass spectrum of III was measured and provided by Dr. Bill Smith at the Department of Chemistry, Texas Christian University, Fort Worth, Texas.

Methyl 5-Chloro-2,1-benzisoxazole-3-carboxylate (III).

A suspension of 7.35 g. (0.035 mole) of methyl *o*-nitromandelate (2) in 16.5 g. (0.14 mole) of thionyl chloride (97%) was stirred continuously at 25° for 15 hours to effect solution. The reaction mixture was heated on a steam cone under gentle reflux for 0.5 hour. The reaction mixture was reduced in volume by heating for an additional 0.5 hour with the removal of the condenser from the reaction flask. Upon cooling, the reaction mixture solidified. Next, the solid mass was dissolved in a minimum amount of chloroform. The chloroform solution was washed successively with several 10 ml. portions of 10% aqueous sodium bicarbonate solution followed by water. An equal volume of isopropanol was added to the chloroform layer and the resulting solution was stored overnight at -15°. A small amount of insoluble material was removed by filtration, and the filtrate was reduced *in vacuo* to about one-half of its original volume and chilled overnight at -15°. There was recovered 4.6 g. (63%) of the product, m.p. 115-116°. The analytical sample was further purified by vacuum sublimation, m.p. 116-117°; ir: 1735, 1550, 1445, 1340, 1280, 1225, 1225, 1080, 960, 930 810, and 770 cm^{-1}; nmr (deuteriochloroform): τ 5.0 (s, 3, OCH_3) and 2.0-3.0 (m, 3, Ar-*H*); ms: m/e (rel. intensity) 211 (100), 180 (63), 124 (72), 59 (49), 28 (38).

Anal. Calcd. for $C_9H_6ClNO_3$: C, 51.08; H, 2.86; N, 6.62; Cl, 16.75. Found: C, 50.90; H, 2.80; N, 6.38; Cl, 16.89.

5-Chloro-2,1-benzisoxazole-3-carboxylic Acid (IV).

A 300 mg. sample (1.42 mole) of III was refluxed in 100 ml. of 1*N* sulfuric acid for 24 hours. The solution was reduced to about one-half of its original volume *in vacuo* to separate a white precipitate. The solid (240 mg., 86%) was removed by filtration and dried *in vacuo* over phosphorus pentoxide. The reaction product, m.p. 210°, gave an acceptable elemental analysis without further purification; ir: 2900 (b), 2560 (b), 1730, 1550, 1470, 1450, 1280, 1230, 1200, 1085, 790, and 755 cm^{-1}.

Anal. Calcd. for $C_8H_4NO_3Cl$: C, 48.62; H, 2.04; N, 7.11. Found: C, 48.57; H, 2.01; N, 6.86.

5-Chloroisatin (V).

This compound was synthesized by following a previously reported procedure which was used to convert a substituted 2,1-benzisoxazole-3-carboxylic acid to the corresponding isatin (3). To a solution of 1 ml. of concentrated ammonium hydroxide and 2.5 ml. of water was added 50 mg. (0.25 mmole) of IV and 330 mg. (1.2 mmole) of ferrous sulfate heptahydrate. The mixture was shaken occasionally at 25° for 0.5 hour prior to the addition of 6 ml. of water. The reaction mixture was filtered and the insoluble material was washed with water. The *p*H of the filtrate was adjusted to 2 by the dropwise addition of 2*N* hydrochloric acid. After standing at 25° for several hours, an orange solid precipitated from solution. The product (27 mg., 59%) was collected on a filter, dried, and identified as 5-chloroisatin by comparison of its m.p. (248-250°) and ir spectrum with those of an authentic sample (Research Organic/Inorganic Chemical Corporation).

Methyl α-Chloro-(*o*-nitrophenyl)acetate (II).

To a solution of 2.0 g. (9.5 mmole) of I in 0.7 g. (9.5 mmole) of freshly distilled pyridine was added 1.3 g. (10 mmole) of thionyl chloride (97%) dropwise at -80°. After the addition was complete, the reaction mixture was allowed slowly to reach 23°, at which temperature the reaction mixture was allowed to stand for 30 hours. The resulting yellow solution was extracted with a water-ether mixture. The ether layer was separated and dried over anhydrous sodium sulfate. The drying agent was removed by filtration, and the filtrate was evaporated *in vacuo* to yield 1.75 g. (80%) of crude product, m.p. 61-64°. An analytical sample, m.p. 64-65°, was obtained by recrystallization from ether; ir: 1765, 1530, 1350, 1250, 1205, 1180, 1165, and 725 cm^{-1}; nmr (deuteriochloroform): τ 6.2 (s, 3, OCH_3), 5.9 (s, 1, C*H*); 1.8-2.8 (m, 4, Ar-*H*).

Anal. Calcd. for $C_9H_8ClNO_4$: C, 47.07; H, 3.51; N, 6.10; Cl, 15.44. Found: C, 46.83; H, 3.29; N, 5.92; Cl, 15.29.

o-Nitrophenylcarbomethoxymethinyl Sulfite (VI).

A suspension of 2.1 g. (0.01 mole) of I and 4.9 g. (0.04 mole) of thionyl chloride (97%) was stirred continuously at 25° for 15 hours. Then, 10 ml. of chloroform was added to the reaction mixture. The resulting solution was washed with two 5 ml. portions of 10% aqueous sodium bicarbonate followed by 5 ml. of water. On concentrating the chloroform solution *in vacuo* to a very low bulk, a solid separated. There was obtained 0.510 g. (22%) of product, m.p. 116-117°, and about the same quantity of starting material from the work-up of the filtrate. The product gave an acceptable elemental analysis without further purification; ir: 1770, 1535, 1445, 1205-1265, 1035, 960, 825, and 770 cm^{-1}, nmr (deuteriochloroform): 6.30 τ (s, 6, OCH_3), 3.45 (s, 2, C*H*), and 1.90-290 τ (m, 8, Ar-*H*).

Anal. Calcd. $C_{18}H_{16}N_2O_{11}S$: C, 46.15; H, 3.44; N, 5.98; S, 6.84. Found: C, 45.99; H, 3.25; N, 5.98; S, 6.65.

Methyl 5,7-Dichloro-2,1-benzisoxazole-3-carboxylate (VIII).

A solution of 2.1 g. (0.0085 mole) of methyl 5-chloro-2-nitromandelate (4) (VII) and 68.5 g. (0.58 mole) of thionyl chloride in 40 ml. of chloroform was heated under reflux for 12 hours. The reaction mixture was reduced to dryness *in vacuo*. The oily residue was dissolved in methanol, and the resulting dark solution was treated with charcoal (Darco) and filtered. The filtrate was reduced *in vacuo* to approximately 10 ml. to form an incipient precipitate. After standing at 25° for 1 hour, the solid was collected on a filter and dried. There was recovered 0.79 g. of product, m.p. 124-125°. A total of 0.5 g. of starting material (VII) was recovered from the filtrate. Accounting for the amount of starting material recovered, the product was obtained in 49.3% yield. Recrystallization from isopropanol gave an analytical sample; ir: 1735, 1515, 1440, 1275, 1210, 1180, 1165, and 725 cm^{-1}; nmr (deuteriochloroform): τ 5.9 (s, 3, OCH_3), 2.65 (d, 1, Ar-*H*), 2.15 (d, 1, Ar-*H*).

Anal. Calcd. for $C_9H_5Cl_2NO_3$: C, 43.93; H, 2.05; Cl, 28.82. Found: C, 43.84; H, 1.67; Cl, 28.85.

5,7-Dichloro-2,1-benzisoxazole-3-carboxylic Acid (IX).

A 95 mg. (0.39 mmole) sample of VIII was refluxed in 100 ml. of 1*N* sulfuric acid for 12 hours. The reaction mixture was cooled to yield 63 mg. (63%) of product, m.p. 179-181°; ir: 3450 (b), 2910 (b), 1730, 1540, 1510, 1450, 1265, 1200, 940, 850, 775, 740, and 690 cm^{-1}.

Anal. Calcd. for $C_8H_3Cl_2NO_3$: C, 41.41; H, 1.31. Found: C, 41.43; H, 1.10.

5,7-Dichloroisatin (X).

A mixture of 49 mg. (0.21 mmole) of IX and 330 mg. (1.2 mmole) of ferrous sulfate heptahydrate in 1 ml. of concentrated ammonium hydroxide and 2.5 ml. of water was shaken occasionally at 25° for 45 minutes, after which time 6 ml. of water was added. The mixture was filtered and the in-

soluble material was washed with water. The *p*H of the filtrate was adjusted by 2 the dropwise addition of 2*N* hydrochloric acid. The acidified solution was extracted with chloroform, and the organic layer was separated and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the filtrate was reduced in volume to dryness *in vacuo*. Vacuum sublimation of the resulting residue gave 19 mg. (42%) of orange solid, m.p. 213-217°. The melting point and ir spectrum of this product were identical on comparison with those of an authentic sample (Aldrich Chemical Company).

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