Substituent Interaction with Ring Sulfur in some Heterocyclic Compounds

David M. McKinnon* and A. A. Abouzeid

Chemistry Dept., University of Manitoba,
Winnipeg, Manitoba Canada R3T 2N2

Received October 30, 1990

The infrared carbonyl absorptions of 7-acetyl-1,2-benzisothiazoles are similar to 7-acetylbenzo[*b*]thiophenes, but are lower by approximately 15 cm^{-1} than the corresponding benzo[*b*]furans. The reasons for this are discussed.

J. Heterocyclic Chem., **28**, 749 (1991).

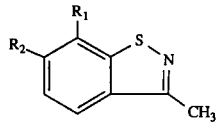
In earlier work [1], 7-acetyl-3-methyl-6-methylthio-1,2-benzisothiazole (**1a**), made by the acetylation under Friedel-Crafts conditions of 3-methyl-6-methylthio-1,2-benzisothiazole (**1b**), exhibited an infrared carbonyl absorption at 1640 cm^{-1}. As this value is somewhat lower than is usual for aromatic ketones and one possibility is that this low frequency is due to some d-orbital participation, it was useful to compare this compound with a number of other compounds to determine if this factor was involved. This work describes the synthesis of some other acetyl-1,2-benzisothiazoles and related compounds for comparison purposes.

To synthesise the compound **1c**, which lacks a methylthio- group, 2-chloroisophthalic acid (**2a**) was converted *via* its acid chloride **2b**, reaction with diethyl ethoxymagnesiummalonate, and hydrolysis to the diketone **2c**. This was converted to 2-methylthio-1,3-diacetylbenzene (**2d**) by treatment with lithium methanethiolate, whose monooxime cyclised to the ketone **1c** on treatment with acetic anhydride in pyridine, as used in a number of other cases [1-3] for 1,2-benzisothiazole formation. This ketone had an absorption at 1655 cm^{-1}.

5-Acetyl-3-methyl-1,2-benzisothiazole (**3a**) was made starting from 3-methyl-5-nitro-1,2-benzisothiazole (**4a**). This was reduced to the amine **4b**, which was converted *via* a diazonium salt to the nitrile **4c** and hydrolysis to the acid **4d**. This was converted to the ketone **3a** *via* reaction of its acid chloride with diethyl ethoxymagnesiummalonate, and hydrolysis. The ketone had an infrared absorption at 1685 cm^{-1}.

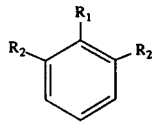
5-Acetyl-3-methyl-6-methylthio-1,2-benzisothiazole (**3b**) was made by cyclisation of the monooxime of 4,5-bismethylthio-1,3-diacetylbenzene (**5a**). It absorbed at 1676 cm^{-1}. By a similar method the 6-acetyl-5-methylthio compound **3c** was made by cyclisation of the monooxime of 2,5-bismethylthio-1,4-diacetylbenzene (**5b**). This had an infrared absorption at 1674 cm^{-1}. The similar values of the infrared carbonyl stretching frequencies in **3b** and **3c**, 1676 and 1674 cm^{-1} respectively, indicate that there is little effect of the heterocyclic ring sulfur on the carbonyl group in positions 5- and 6-, but by comparison with **3a**, which absorbs at 1685 cm^{-1}, a small effect, by approximately 10 cm^{-1}, of the neighboring methylthio- group. The extra displacement in 7-substituted compounds, *ie* in **1a** and **1c**, by approximately 30 cm^{-1}, compared to **3b** and **3a** respectively, appears to be attributable to some interaction of a 7-carbonyl group with the heterocyclic ring.

Diagram 1



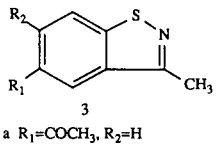
1

a R_1=CH_3CO, R_2=SCH_3
b R_1=H, R_2=SCH_3
c R_1=CH_3CO, R^2=H



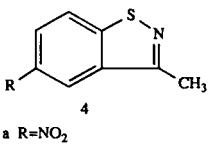
2

a R_1=Cl, R_2=CO_2H
b R_1=Cl, R_2=COCl
c R_1=Cl, R_2=$COCH_3$
d R_1=SCH_3, R_2=$COCH_3$



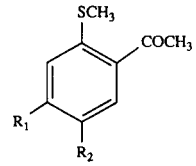
3

a R_1=$COCH_3$, R_2=H
b R_1=$COCH_3$, R_2=SCH_3
c R_1=SCH_3, R_2=$COCH_3$



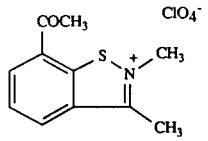
4

a R=NO_2
b R=NH_2
c R=CN
d R=CO_2H



5

a R_1=SCH_3, R_2=$COCH_3$
b R_1=$COCH_3$, R_2=SCH_3



6

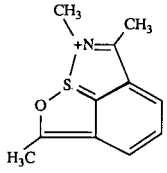
Also, the salt **6**, produced from **1c** by quaternisation with dimethyl sulfate and then reaction with perchloric acid, exhibited an absorption at 1645 cm^{-1}. Inductively the effect of the charge on the heterocyclic ring might be expected to increase the frequency of the carbonyl absorption. These results are also inconsistent with a simple conjugative interaction of the sulfur atom with the carbonyl group, which would have been expected to decrease the frequency of the absorption, as 7-acetyl-5-methoxybenzo-

[*b*]thiophenes absorb at approximately 15 cm^{-1} lower than the corresponding 7-acetyl-5-methoxybenzo[*b*]furans [5], despite the greater mesomeric effect of the oxygen compared to the sulfur. The results are however consistent with an expanded valency of the sulfur atom, leading to structures such as **7** for **6** and **8** for **1c**. In **6** the sulfur atom now bears a more electronegative substituent, the conditions for d-orbital participation. For two 6-acetylbenzo[*b*]-thiophenes, in which the sulfur atom and the carbonyl group, cannot so interact, absorptions are at 1670 and 1669 cm^{-1} respectively. [6, 7 respectively]. However no data are available on 6-acetylbenzofurans. A 7-acetylbenzothiazole absorbs in a similar region to **1c** [8].

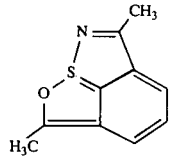
Obviously these effects are rather small, and are not comparable in magnitude to those observed for 3-acylmethylene-1,2-dithioles, in which some sulfur to oxygen bonding has been proposed [9]. *Eg*, in the diketones of type **9a**, the carbonyl group *cis* to the sulfur atom is displaced from that *trans* by almost 100 cm^{-1}. Nevertheless this interaction appears to be dependent on the nature of the heterocyclic ring, as X-ray studies on a 1,2,3-thiadiazol-3-ylidene ester indicated no sulfur-oxygen interaction [10]. Unfortunately few other data on compounds related to **1c** are available for comparison, but nmr studies on 7-acetylbenzo[*b*]thiophene indicate suitable conformations for carbonyl-sulfur interaction [10,11], and these are more favored than in the corresponding benzofurans [12]. However, a comparison of the ^{13}C chemical shifts of the carbonyl carbons in **1c** with 7-acetylbenzo[*b*]furan and 7-acetylbenzo[*b*]thiophene, indicates little difference in the carbonyl carbon shift values (δ values of 196.61, 196.24, and 197.33 ppm respectively [11,13]). Nevertheless ^{13}C substituent chemical shifts in trithiapentalenes do not reflect the 10π character of that system [14], and it may be that it is also an unsatisfactory technique for the systems above. 7-Acetyl-1,2-benzisoxazoles would be useful for comparative studies but only some 6-hydroxy-substituted derivatives are reported, and in these carbonyl absorptions are likely to be affected by hydrogen bonding [15,16]. An attempt to make 3-methyl-7-acetyl-1,2-benzisoxazole by reaction of the diketone **2c** with hydroxylamine gave only a complex mixture.

As no ^{13}C nmr data are reported for 3-acylmethylene-1,2-dithioles, we have examined the spectra of **9b** and **9c**. These demonstrated absorptions due to the carbonyl group carbons at 183.98 and 185.30 ppm. respectively. Although this range is rather different from that for the compounds **1a**, **1c** and 7-acetylbenzo[*b*]furan and benzo-[*b*]furan above, these are probably poor models for comparison.

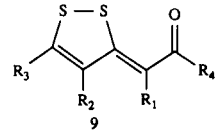
Diagram 2



7



8



9

a R_1=COR_4
b R_1=R_2=H, R_3=Ph
c R_1=H, R_2:R_3=-(CH=CH)$_2$-

EXPERIMENTAL

^1H nmr spectra were obtained on a Bruker model AM 300 spectrometer, and, unless otherwise stated, in deuteriochloroform solutions using tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer model 881 spectrometer in liquid paraffin mulls for solids and as thin films for liquids. Mass spectra, by electron impact and FAB methods, were obtained on a model VG 707E mass spectrometer. Solutions were dried over anhydrous magnesium sulfate. Where necessary, chromatography was performed on Merck silica gel type 60 PF 254 on 1 mm thick layers using hexane as an eluent with varying proportions of ethyl acetate. Analytical data were provided by Guelph Chemical Laboratories, Guelph, Ontario, Canada.

2-Chloro-1,3-diacetylbenzene (**2c**).

2-Chloroisophthalic acid (**2a**) (20.25 g, 0.1 mole) in benzene (50 ml) and thionyl chloride (10 ml) were heated under reflux for 24 hours. Evaporation gave the acid chloride **2b**, which was dissolved in benzene (40 ml) and added to a benzene solution (30 ml) of diethyl ethoxymagnesiummalonate (prepared from magnesium, (4.8 g, 0.2 mole), diethyl malonate (32.0 g, 0.2 mole) and ethanol (20 ml)). The mixture was warmed at 60° for 3 hours, then poured into ice cold 10% sulfuric acid solution. The organic layer was extracted with dichloromethane and this was evaporated to an oil, which was hydrolysed by boiling in a mixture of acetic acid (60 ml), water (40 ml), and sulfuric acid (1 ml), for 6 hours. The mixture was added to ice and extracted with dichloromethane. The dried extract on evaporation gave **2c** as a pale yellow oil (84%). While this was satisfactory for further reaction, an analytical sample was purified by chromatography; ^1H nmr: δ = 2.62 ppm (6H, s, methyl), 7.31-7.71 (3H, m, aromatics); ms: M Calcd. = 198, 196. Found, M^+ = 198, 196; 183, 181 (M^+ = CH_3); ir: 1706 cm^{-1} (C=O str).

Anal. Calcd. for $C_{10}H_9ClO_2$: C, 61.22; H, 4.59; Cl, 8.11. Found: C, 61.36; H, 4.81; Cl, 7.78.

1,3-Diacetyl-2-methylthiobenzene (**2d**).

To a solution of 2-chloro-1,3-diacetylbenzene (**2c**) (5.88 g, 0.03 mole) in dimethyl formamide (20 ml) was added lithium hydroxide monohydrate (10 g), and liquid methanethiol (5 ml). The mixture was stirred at 30° for 1 hour then poured into ice cold hydrochloric solution. The chloroform extract was washed with water, dilute sodium hydroxide solution, dried and evaporated to give a pale yellow oil (87%). While this was satisfactory for further reac-

tions, an analytical sample was purified by chromatography; ^{1}H nmr: δ = 2.35 ppm (3H, s, *S*-methyl), 2.66 (6H, s, acetyl), 7.43 (3H, m, aromatic); ms: M Calcd. = 208. Found, M^+ = 208, 193 (M^+-CH_3), 165 (M^+-$COCH_3$); ir: 1714 cm^{-1} (C=O str).

Anal. Calcd. for $C_{11}H_{12}O_2S$: C, 63.46; H, 5.76; S, 15.38. Found: C, 63.52; H, 5.84; S, 15.12.

7-Acetyl-3-methyl-1,2-benzisothiazole (**1c**).

A mixture of the diketone **2d** (2.08 g, 0.01 mole), and hydroxylamine hydrochloride (0.69 g, 0.01 mole) was heated under reflux for 8 hours, then the methanol was removed under reduced pressure and the residue diluted with water. The dried chloroform extract was evaporated to a yellow solid, which was heated under reflux with a mixture of acetic anhydride (3 ml) and pyridine (5 ml) for 24 hours. This was added to dilute hydrochloric acid and extracted with chloroform. The extract was dried, treated with charcoal, and evaporated to a pale yellow solid. It was recrystallised from ethanol as colorless prisms, mp 96-97°; ^{1}H nmr: δ = 2.75, 2.76 ppm (two 3H, s, methyls), 7.55 (1H, t, J = 7.6 Hz, H5), 8.12 (two H, t, J = 7.6 Hz, 0.8 Hz, apparently two overlapping 3H, t, H4 and H6); ^{13}C nmr: 17.14 (3-methyl), 25.47 (acetyl methyl), 124.64, 128.33, 129.54 (C5, C6, C7), 129.67, 135.87, 150.33 (3a, 7, 7a), 161.12, C3, 196.61 (C=O); ms: M Calcd. = 191. Found, M^+ = 191, 176 (M^+-CH_3), 148 (M^+-CH_3C=O); ir: 1655 cm^{-1} (C=O str).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.71; N, 7.32; S, 16.75. Found: C, 62.67; H, 4.65; N, 7.19; S, 16.59.

2,3-Dimethyl-7-acetyl-1,2-benzisothiazolium Perchlorate (**6**).

The ketone **1c** (48 mg, 0.25 mmole) and dimethyl sulfate (0.5 ml) were warmed at 100° for 5 minutes. 70% Perchloric acid, (0.05 ml) was added, then ether, (5 ml) and the mixture was triturated to crystallise the precipitate. This was collected and recrystallised from nitromethane with precipitation with ether, as pale buff prisms, mp 209-210° (93%); ^{1}H nmr (acetone d_6): δ = 2.97 ppm (3H, s, acetyl), 3.24 (3H, s, 3-methyl), 4.46 (3H, s, the *N*-methyl), 8.13 (1H, t, J = 7.9 Hz, H5), 9.10 (two overlapping 1H, d, J = 7.9 Hz, H4 and H6); ir: 1645 cm^{-1} (C=O str); ms: (FAB technique, using 4-nitrophenylmethanol matrix), positive ions at 206 ($C_{11}H_2NOS$ requires 206), 511 (($C_{11}H_{12}NOS^+)_2$ CLO_4^-, requires 511), negative ions at 99, 101 ($^{35}CLO_4$ and $^{37}CLO_4$); accurate mass: (FAB technique, using a glycerol matrix), 206.06543. Calcd. for $C_{11}H_{12}NOS$, 206.06396.

Anal. Calcd. for $C_{11}H_{12}ClNO_5S$: C, 43.21; H, 3.92; Cl, 11.62; N, 4.58; S, 10.47. Found: C, 43.33; H, 3.86; Cl, 11.93; N, 4.43; S, 10.77.

5-Amino-3-methyl-1,2-benzisothiazole (**4b**).

3-Methyl-5-nitro-1,2-benzisothiazole (0.48 g, 2.5 mmoles) [4] and iron powder (0.5 g) in acetic acid (10 ml) and water (2.5 ml) were heated at 100° for 4 hours. The mixture was diluted with water and extracted with chloroform. The extract was washed with sodium bicarbonate solution, dried and evaporated to give a dark oil which was not further purified (59%).

3-Methyl-1,2-benzisothiazole-5-carboxylic Acid (**4d**).

5-Amino-3-methyl-1,2-benzisothiazole (**4b**) (0.269 g, 1.5 mmoles) in 30% hydrochloric acid (5 ml) was diazotized at 0° with sodium nitrite (0.103 g, 1.5 mmoles) and added to a fourfold excess of freshly prepared sodium cuprocyanide in water (10 ml) at 60°. The mixture foamed and a brown precipitate formed. The mixture was allowed to stand at 60° for 1 hour and then extracted with dichloromethane. The extract was dried and evaporated to a brown oil which was heated under reflux with 50% hydrochloric acid (10 ml) for 4 hours. The aqueous solution was decanted from the tarry residue, diluted with water and extracted with chloroform. The chloroform solution was extracted with 10% sodium hydroxide solution (5 ml) and this was acidified to *p*H 7 with concentrated hydrochloric acid. The precipitate was collected and recrystallised from benzene as colorless needles, mp 235°, (41%); ^{1}H nmr: δ = 2.81 ppm (3H, s, methyl), 8.19 (1H, d, J = 8.4 Hz, H7), 8.27 (1H, d, J = 8.4 Hz, H6), 8.61 (1H, s, H4); ms: M Calcd. = 193. Found, M^+ = 193, 176 (M^+-OH), 149 (M^+-CO_2); ir: 3300 cm^{-1}, broad, (OH str), 1703 cm^{-1} (C=O str).

Anal. Calcd. for $C_9H_7NO_2S$: C, 55.96; H, 3.63; N, 7.25; S, 16.80. Found: C, 56.03; H, 3.79; N, 7.01; S, 16.80.

5-Acetyl-3-methyl-1,2-benzisothiazole (**3a**).

3-Methyl-1,2-benzisothiazole-5-carboxylic acid (**4d**) (48 mg, 0.25 mmole) in benzene (5 ml) and thionyl chloride (0.5 ml) was heated under reflux for 3 hours, then the solvent removed under reduced pressure. The oily acid chloride was dissolved in benzene (5 ml) and added to a solution of diethyl ethoxymagnesiummalonate (made from magnesium (0.24 g, 0.01 mole), and diethyl malonate (1.6 g, 0.01 mole) in benzene (10 ml)). The mixture was allowed to stand 16 hours then poured into water and extracted with chloroform. The evaporated extract was hydrolysed in a boiling mixture of acetic acid (10 ml), water (2 ml) and sulfuric acid (0.5 ml) for 6 hours, cooled and diluted with water. The chloroform extract was washed with base, dried and evaporated to give a pale yellow oil which was purified by chromatography. The ketone **3a** was obtained as a colorless oil (87%); ^{1}H nmr: δ = 2.73 ppm (3H, s, acetyl), 2.83 (3H, s, 3-methyl), 8.07, 8.09 (2H, s, H6 and H7), 8.60 (1H, s, H4); ms: M Calcd = 191. Found, M^+ = 191, 176 (M^+-CH_3), 148 (M^+-$COCH_3$); ir: 1685 cm^{-1} (C=O str).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.82; H, 4.71; N, 7.32; S, 16.75. Found: C, 62.85; H, 4.83; N, 7.06; S, 16.60.

5-Acetyl-3-methyl-6-methylthio-1,2-benzisothiazole (**3b**).

2,4-Bismethylthio-1,3-diacetylbenzene (**5a**) (0.254 g, 1.0 mmole) [1], and hydroxylamine hydrochloride (0.069 g, 1 mmole) in pyridine (10 ml) and ethanol (5 ml), were heated under reflux for 3 hours, then poured into water and extracted with dichloromethane. The extract was dried and evaporated to a pasty solid which was heated with boiling ethanol (10 ml), and filtered to remove unreacted diketone. The filtrate was evaporated and the residue was heated in a mixture of pyridine (4 ml) and acetic anhydride (2 ml) for 16 hours. This mixture was extracted with dichloromethane, which was treated with charcoal, dried and evaporated to give a yellowish oil which was purified by chromatography. It crystallised from ethanol as small yellow prisms, mp 82-83° (41%); ^{1}H nmr: δ = 2.51 ppm (3H, s, *S*-methyl), 2.75, 2.80 (two 3H, s, acetyl and 3-methyl), 7.72 (1H, s, H7), 8.83 (1H, s, H4); ms: M Calcd. = 237. Found, M^+ = 237, 222 (M^+-CH_3), 194 (M^+-$COCH_3$); ir: 1676 cm^{-1} (C=O str).

Anal. Calcd. for $C_{11}H_{11}NOS_2$: C, 55.70; H, 4.64; N, 5.91; S, 27.00. Found: C, 55.83; H, 4.70; N, 5.98; S, 27.12.

6-Acetyl-3-methyl-5-methylthio-1,2-benzisothiazole (**3c**).

This was made by the same method as for **3b** above, starting from 1,4-diacetyl-2,5-bismethylthiobenzene (**5b**) [1]. The product was recrystallised from ethanol as yellow needles, mp 131° (38%); ^{1}H nmr: δ = 2.53 ppm (3H, s, the *S*-methyl), 2.71, 2.78 (two 3H, s, acetyl and 3-methyl), 7.70 (1H, s, the 7-proton), 8.30 (1H, s, the

H6); ms: M Calcd. = 237. Found, M^+ = 237, 222 (M^+-CH_3), 194 (M^+-$COCH_3$); ir: 1674 cm^{-1}, (C=O str).

Anal. Calcd. for $C_{11}H_{11}NOS_2$: C, 55.70; H, 4.64; N, 5.91; S, 27.00. Found: C, 55.59; H, 4.83; N, 6.17; S, 26.88.

Reaction of 2-Chloro-1,3-diacetylbenzene with Hydroxylamine.

The ketone **2c** (0.588 g, 3 mmoles) and hydroxylamine hydrochloride (0.27 g, 3 mmoles) in pyridine (5 ml) were heated under reflux for 20 hours. The mixture was poured into dilute hydrochloric acid and extracted with dichloromethane (2 x 20 ml). The extract was washed with dilute hydrochloric acid and treated with charcoal. Evaporation gave an oily solid that appears to be a complex mixture. It was not further examined.

6-Acetyl-2,3-dimethylbenzo[*b*]thiophene.

This was prepared as described [7]. It had an infrared C=O absorption at 1669 cm^{-1}.

3-Phenacylidene-5-phenyl-1,2-dithiole (**9b**).

This was prepared as described [17]. Its ^{13}C spectrum exhibited a peak at 183.98 ppm.

3-Phenacylidenebenzo-1,2-dithiole (**9c**).

This was prepared as described [18]. Its ^{13}C spectrum exhibited a peak at 185.30 ppm.

Acknowledgements.

We wish to thank the Natural Sciences and Engineering Council of Canada for financial support of this work. We also wish to thank Mr. K. Marat and Mr. T. Wolowiec for the preparation of nmr spectra, and Mr. W. Buchannon for the preparation of mass spectra.

REFERENCES AND NOTES

[1] D. M. McKinnon and A. A. Abouzeid, *J. Heterocyclic Chem.*, (in press).

[2] D. M. McKinnon and A. A. Abouzeid, *J. Heterocyclic Chem.*, (in press).

[3] D. M. McKinnon and K. R. Lee, *Can. J. Chem.*, **66**, 1405 (1988).

[4] K. Clarke, B. Gleadhill and R. M. Scrowston, *J. Chem. Res. S.*, 197 (1980).

[5] P. Demersman, J-P. Lechartier, C. Pene, A. Chretien and R. Royer, *Bull. Soc. Chim. France*, 1473 (1965).

[6] J. Cooper, D. F. Ewing, R. M. Scrowston and R. Westwood, *J. Chem. Soc. (C)*, 1949 (1970).

[7] J. Cagniant and D. Cagniant, *Bull. Soc. Chim. France*, 941 (1969).

[8] E. Haddock, P. Kirby and A. W. Johnson, *J. Chem. Soc.*, 3994 (1971).

[9] N. Losac'h, *Adv. Heterocyclic Chem.*, **13**, 161 (1971).

[10] L. Capuano, B. Boschat, I. Muller, R. Zander, V. Schram and E. Hadlicke, *Chem. Ber.*, **116**, 2058 (1983).

[11] R. Benassi, U. Folli, D. Iarossi, L. Schenetti and F. Taddei, *J. Chem. Soc., Perkin Trans. II*, 911 (1983).

[12] P. Faller, *Bull. Soc. Chim. France*, 934 (1969).

[13] R. Benassi, U. Folli, D. Iarossi, L. Schenetti and F. Taddei, *J. Chem. Soc., Perkin Trans. II*, 1479 (1984).

[14] R. D. Lapper and A. J. Poole, *Tetrahedron Letters*, 2783 (1974).

[15] K. A. Thakar and B. M. Bhawal, *J. Indian Chem. Soc.*, **54**, 875 (1977).

[16] S. S. Kumari, K. S. R. Krishna Mohan Rao and N. V. Subba Rao, *Indian J. Chem.*, **11**, 541 (1973).

[17] E. Brown, D. Leaver and D. M. McKinnon, *J. Chem. Soc. (C)*, 1202 (1970).

[18] D. M. McKinnon, *Can. J. Chem.*, **61**, 1161 (1983).