# Studies on 2,1-Benzisoxazoles. Behaviour Towards Electrophilic Substitution and Cycloaddition Reactions



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The behaviour of 2,1-benzisoxazoles (anthranils) towards electrophilic substitutions has been studied. Nitration of 5-chloro-2,1-benzisoxazole (VII) exclusively gives 4-nitro-5-chloro-2,1-benzisoxazole (XII). However, 5-chloro-3-phenyl-2,1-benzisoxazole (VIII) gives dinitrated products XIII, one nitro group entering at position $C_7$ instead of $C_4$ of the carbocyclic ring and the other at the 4' position of the 3-aryl ring. When 6-nitro-3-carbalkoxy-2,1-benzisoxazoles (X and XI) are nitrated, 4-nitroisomers XV and XVI are obtained exclusively. The substituents already present in the carbocyclic ring exert decisive directing influence. While the parent 2,1-benzisoxazole (Ia) fails to react with dimethyl acetylenedicarboxylate, 6-nitro-2,1-benzisoxazole (XVII) and 5-chloro-2,1-benzisoxazole (VII) react to give 1,4-cycloadducts XIX and XX, respectively. These results suggest that 2,1-benzisoxazoles possess benzenoid as well as *ortho*-quinonoid character.

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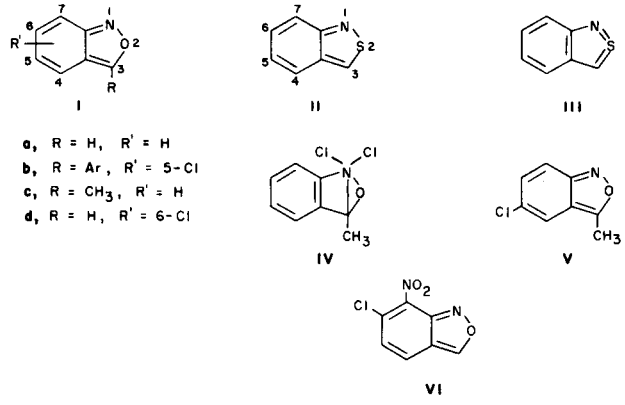
The facile reductive cleavage of 2,1-benzisoxazole (Ia) has attracted considerable attention since the aminobenzophenone thus produced from its 3-aryl derivative (Ib) is a key intermediate in the synthesis of biologically active molecules such as quinazolinones (1) and 1,4-benzodiazepines (2). However, a systematic chemical investigation of this heterocycle (I) has not been made. Davis and White (3) studied the electrophilic substitution and cycloaddition reaction (4) in a related system 2,1-benzisothiazole (II). Their study proved more of benzenoid character (III) present in this thio analogue. Halogenation of 3-methyl-2,1-benzisoxazole (Ic) was attempted as early as 1909 by Bamberger and Lublin (5), who assigned structure IV to the dichloride thus obtained. This was reinvestigated and the assignment was revised by Boulton and Altaf-ur-Rahman (6a) who observed that chlorination of Ic gave an addition product at the $C_4$-$C_5$ double bond which on treatment with dilute base or on steam distillation eliminated one molecule of hydrogen chloride to form 5-chloro-3-methyl-2,1-benzisoxazole (V). Nitration (6a) of Ia gave 5- and 7-nitro isomers, but 6-chloro-2,1-benzisoxazole (Id) was reported (6b) to give the 7-nitro isomer VI. Unlike its thio analogue II, Ia reacts with *N*-phenylmaleimide (7). Conflicting reports exist for the cycloaddition of Ia with maleic anhydride. Schonberg and Mostafa (8) claimed the formation of 1:1 adduct from maleic anhydride with Ia, whereas Acheson and Poulter (9) reported negative results. Also dimethylacetylene dicarboxylate failed (9) to react with Ia. Evidently, more investigation seemed necessary to understand the basic behaviour of this molecule, compound I. In this paper we report the results of our studies on substituted-2,1-benzisoxazoles towards a) electrophilic substitution and b) 1,4-cycloaddition reaction employing dimethylacetylenedicarboxylate as the dienophile.




## Results and Discussion.

We subjected 5-chloro-2,1-benzisoxazole (VII) to nitration with sodium nitrate in concentrated sulphuric acid at 45° over a period of 30 minutes and obtained 4-nitro-5-chloro-2,1-benzisoxazole (XII) as the sole product (10). The evidence for the formation of this isomer rests on elemental analyses and spectral data. Molecular ion peaks at m/e 198 and the loss of CO at m/e 170 followed by elimination of $NO_2$ at m/e 124, were the major mass fragmentation patterns. The nitration at $C_4$ was inferred from the pmr spectrum of XII. The proton at $C_6$ ($\delta$ 7.16) and $C_7$ ($\delta$ 7.53) showed up as AB doublet (J = 9.5 Hz) while the $C_3$ proton ($\delta$ 9.43) appeared as a singlet. Interestingly, when $C_3$ in VII is substituted by a phenyl group, the position of substitution in the carbocyclic ring shifts from $C_4$ to $C_7$. Thus the product XIII from the nitration of VIII showed $M^+$ at m/e 319 suggesting introduction of two nitro groups. The 60 MHz pmr showed a complex multiplet in the aromatic region, which was resolved in high resolution pmr (360 MHz) into two clear AA'BB' doublets at $\delta$ 8.50 (8.5 Hz) and $\delta$ 8.21 (8.5 Hz), and two meta coupled doublets at $\delta$ 8.23

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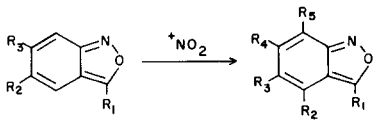
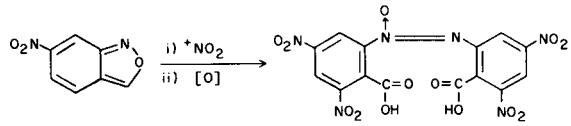


| | $R_1$ | $R_2$ | $R_3$ | | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ |
|---|---|---|---|---|---|---|---|---|---|
| VII | H | Cl | H | XII | H | $NO_2$ | Cl | H | H |
| VIII | $C_6H_5$ | Cl | H | XIII | 4'-$NO_2$-$C_6H_4$ | H | Cl | H | $NO_2$ |
| IX | $C_6H_5$ | Cl | $CH_3$ | XIV | 4'-$NO_2$-$C_6H_4$ | H | Cl | $CH_3$ | $NO_2$ |
| X | $CO_2CH_3$ | H | $NO_2$ | XV | $CO_2CH_3$ | $NO_2$ | H | $NO_2$ | H |
| XI | $CO_2C_2H_5$ | H | $NO_2$ | XVI | $CO_2C_2H_5$ | $NO_2$ | H | $NO_2$ | H |

(1.5 Hz) and δ 8.43 (1.5 Hz), showing the position of one nitro group at 4' position of 3-phenyl ring and other one at $C_7$ of the carbocyclic ring. The nitration of IX also led to a dinitro product 3-(4'-nitrophenyl)-5-chloro-6-methyl-7-nitro-2,1-benzisoxazole (XIV), the pmr spectrum at 360 MHz in deuteriochloroform showed two AA'BB' doublets at δ 8.47 (9.9 Hz) and δ 8.18 (9.9 Hz). The methyl signal in product XIV showed a clear singlet (δ 2.61) in contrast to the parent compound (IX) where $C_7$ being unsubstituted showed a doublet of methyl signal at δ 2.45 (Table 1); this fact further supported the position of one nitro group at $C_7$. The product (XV) obtained from nitration of X showed two metacoupled signals at δ 8.30 (1.0 Hz) and δ 8.66 (1.0 Hz) at 60 MHz. Interestingly, however, nitration of 6-nitro-2,1-benzisoxazole (XVII) led to scission of the isoxazole ring giving 3,3',5,5'-tetranitroazoxybenzene-2,2'-dicarboxylic acid (XVIII) arising presumably by nitration



XVII XVIII

followed by oxidation (11) of the dinitroproduct. The pmr assignments and characteristics of the nitrated products are recorded in Tables 1 and 2, respectively.

Chlorination of these substituted-2,1-benzisoxazoles (VII-XI) under the reported conditions (6a) gave no positive results in our hands with starting materials recovered unchanged in each case.

2,1-Benzisoxazole (Ia) did not react with dimethyl acetylenedicarboxylate (DMAD) even on prolonged reflux in xylene for 72 hours. However, when XVII was treated with dimethyl acetylenedicarboxylate in boiling xylene for 20 hours, it smoothly reacted to yield 2,3-dicarbomethoxy-7-nitro-1,4-epoxy-1,4-dihydroquinoline (XIX) in 50% yield.

Table 1

$^1$H-NMR Data of Substituted-2,1-Benzisoxazoles and its Nitrated Products

| Compound No. | Solvent | Chemical Shift ppm $H_3$ | $H_4$ | $H_5$ | $H_6$ | $H_7$ | Other Chemical Shifts and Coupling Constants |
|---|---|---|---|---|---|---|---|
| VII | Deuteriochloroform | 9.06s | 7.53d | Cl | 7.20dd | 7.60d | $J_{6,7}$ = 10.00 Hz; $J_{4,6}$ = 1.0 Hz |
| VIII | " | - | - | - | - | - | 7.40-8.24 (m, 8H) |
| IX | " | - | 7.84s | Cl | $CH_3$ | 7.45q | 2.45 (d, 3H); $J_{H_7,CH_3}$ = 1.0 Hz |
| X | Perdeuteriobenzene | - | 7.30d | 7.43d | $NO_2$ | 8.06s | 3.35 (s, 3H); $J_{4,6}$ = 10.00 Hz |
| XI | " | - | 7.00d | 6.77d | $NO_2$ | 7.53s | 3.50 (q, 2H); 0.50 (t, 3H), $J_{4,6}$ = 10.00 Hz |
| XII | Perdeuterioacetone | 9.43s | $NO_2$ | Cl | 7.16d | 7.53d | $J_{6,7}$ = 9.50 Hz |
| XIII | Deuteriochloroform | - | 8.23d | Cl | 8.43d | $NO_2$ | 8.50 (d, 2H); 8.21 (d, 2H); $J_{4,6}$ = 1.5 Hz; $J_{2',3'}$ = 8.5 Hz |
| XIV | " | - | 8.11s | Cl | $CH_3$ | $NO_2$ | 2.61 (s, 3H); 8.47 (d, 2H); 8.18 (d, 2H); $J_{2',3'}$ = 9.9 Hz |
| XV | " | - | $NO_2$ | 8.30d | $NO_2$ | 8.66d | 4.13 (s, 3H); $J_{5,7}$ = 1.0 Hz |
| XVI | " | - | $NO_2$ | 8.28d | $NO_2$ | 8.53d | 4.52 (q, 2H); 2.43 (t, 3H); $J_{5,7}$ = 1.0 Hz |

s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet.

Table 2

Physical and Analytical Data for Compounds XII-XVI

| Compound No. | Yield % | Mp °C | Solvent of Crystallisation | Molecular Formula | Analysis Calculated C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| XII | 69 | 116.0 | Ethanol | $C_7H_3ClN_2O_3$ | 42.42 | 1.52 | 14.14 | 42.24 | 1.39 | 14.28 |
| XIII | 65 | 248.0 | Dimethylsulfoxide | $C_{13}H_6ClN_3O_5$ | 48.90 | 1.88 | 13.17 | 48.75 | 1.73 | 13.35 |
| XIV | 75 | 187.0 | Acetone | $C_{14}H_8ClN_3O_5$ | 50.45 | 2.40 | 12.61 | 50.49 | 2.48 | 12.87 |
| XV | 80 | 98.5 | Methanol | $C_9H_5N_3O_7$ | 40.45 | 1.87 | 15.72 | 40.40 | 1.81 | 15.65 |
| XVI | 72 | 70.0 | Ethanol-water | $C_{10}H_7N_3O_7$ | 42.70 | 2.49 | 14.95 | 42.62 | 2.42 | 14.79 |

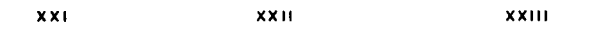
The mass spectrum showed $M^+$ at m/e 306 and ir showed two carbonyl absorptions at 1740 and 1720 $cm^{-1}$. The pmr (90 MHz, deuteriochloroform) showed a sharp singlet at $\delta$ 4.68 which accounts for $C_4$ proton. Two *ortho* coupled protons at $\delta$ 7.90 (8.2 Hz) and $\delta$ 8.37 (8.2 Hz), where the latter is further metacoupled (2.3 Hz) are assigned to $H_5$ and $H_6$, respectively. The *meta* coupled signal at $\delta$ 8.73 (2.3 Hz) is accounted for by the proton at $C_8$. 5-Chloro-2,1-benzisoxazole (VII) also produced a 1:1 Diels-Alder adduct XX

| | $R_1$ | $R_2$ |
|---|---|---|
| XVII | H | $NO_2$ |
| VII | Cl | H |

| | $R_1$ | $R_2$ |
|---|---|---|
| XIX | H | $NO_2$ |
| XX | Cl | H |

when refluxed with dimethyl acetylenedicarboxylate in toluene. 3-Substituted-2,1-benzisoxazoles (VIII-XI) failed to react with dimethyl acetylenedicarboxylate.

In the parent compound (Ia), the positions 5 and 7 are the electrophilic centres (6a), explainable by the resonating structures, XXI ←→ XXII ←→ XXIII. When a substituent is present in the carbocyclic ring (for example VII, X and XI), orientation is determined by the prior substituent. The shift of position of nitration from $C_4$ to $C_7$ in compound VIII and IX is explained by the hindrance of the bulky aryl group at $C_4$ and thereby increasing the contribution of resonating structure XXIII. The electrophilic substitution pattern reveals the aromatic character.



XXI XXII XXIII

The parent 2,1-benzisoxazole (Ia) did not react with dimethyl acetylenedicarboxylate, but the presence of an electron withdrawing substituent in the carbocyclic ring favours the cycloaddition. Our results with Diels-Alder reaction support the *ortho*-quinonoid structure. From these facts it is reasonable to conclude that 2,1-benzisoxazole is a unique system exhibiting both aromatic and orthoquinonoid characters.

## EXPERIMENTAL

Melting points are uncorrected and were taken in a Buchi apparatus. The nmr spectra were recorded on Varian T-60, Varian 90 MHz or Bruker 360 MHz spectrometer and chemical shifts values are recorded in $\delta$ units parts per million, relative to internal standard (tetramethylsilane). Ir spectra were determined on potassium bromide discs, recorded with a Perkin-Elmer 237B spectrometer. Mass spectra were determined on a AEI MS 30 instrument.

6-Nitro-2,1-benzisoxazole (XVII) and its 3-carbalkoxy esters (X and XI) were prepared by the pyrolysis of 2,4-dinitrophenylacetic acid in concentrated sulphuric acid (12). 3-Aryl-2,1-benzisoxazoles (VIII and IX) were prepared by employing the standard procedures of Davis and Pizzini (13).

5-Chloro-2,1-benzisoxoazole (VII).

A solution of 5-chloro-2-nitrobenzaldehyde (2.5 g) in stirred glacial acetic acid (40 ml) was reduced with tin foil (3.0 g) at 45-60° over a period of 30 minutes. The reaction mixture was steam distilled; after the first fraction of distillate (mainly acetic acid) an oily organic compound started distilling and it solidified to a white substance in the receiving flask. The distillate along with the solid was extracted with ether, washed with water and dried over sodium sulfate. Removal of solvent gave a solid which was crystallised from light petroleum to give 1.5 g (73%) of VII, mp 78°; ir (potassium bromide): 1625 (C=N), 1370, 1480, 1075 ($cm^{-1}$); ms: 153 (100%) $M^+$, 155 (50%), 125 (83%), 98 (25%), 63 (49%).

*Anal.* Calcd. for $C_7H_4ClNO$: C, 54.91; H, 2.61; N, 9.1. Found: C, 54.61; H, 2.41; N, 8.9.

Nitration of 5-Chloro-2,1-benzisoxazole (VII).

To an ice-cooled stirred solution of VII (1.0 g) in concentrated sulphuric acid (20 ml) was slowly added a solution of sodium nitrate (1.0 g) in concentrated sulphuric acid (20 ml). The mixture was vigorously stirred at 0° for 15 minutes and then kept 45° for 30 minutes. The mixture was poured into crushed ice (100 g), the solid was filtered, washed with cold water and crystallised from rectified spirit to afford 0.9 g (69%) of straw crystals of 4-nitro-5-chloro-2,1-benzisoxazole (XII), mp 116°; ir (potassium bromide): 1629 (C=N), 1520 ($NO_2$) 1320 ($NO_2$) ($cm^{-1}$); ms: 198 (30%) $M^+$, 182 (5%); 170 (8%), 168 (18%), 152 (5%), 126 (50%), 124 (100%), 97 (50%), 88 (55%).

Nitration of 3-Phenyl-5-chloro-2,1-benzisoxazole (VIII).

A solution of VIII (1.0 g) in concentrated sulphuric acid (40 ml) was nitrated at 65-70° for 45 minutes and worked up as for VII to obtain 0.9 g (65%) of 3-(4'-nitrophenyl)-5-chloro-7-nitro-2,1-benzisoxazole (XIII), mp 248°; ir (potassium bromide): 1625 (C=N), 1590, 1515, 1330, 1100 ($cm^{-1}$); ms: 319 (25%) $M^+$, 303 (15%), 286 (100%), 273 (25%), 150 (90%).

Nitration of 3-Carbomethoxy-6-nitro-2,1-benzisoxazole (X).

A solution of X (1.0 g) in concentrated sulphuric acid (40 ml) was nitrated at 60-65° for 45 minutes. On pouring over crushed ice (100 g) a sticky red material was obtained, which was washed several times with cold water and then triturated with ethanol to obtain a solid. Recrystallisation from methanol gave 0.96 g (80%) of 3-carbomethoxy-4,6-dinitro-2,1-benzisoxazole (XV) as brick-red crystals, mp 98.5°; ir (potassium bromide): 3100, 1725 (C=O), 1630 (C=N), 1560 ($NO_2$), 1530 ($NO_2$), 1370 ($NO_2$), 1350 ($NO_2$), 1115 ($cm^{-1}$); ms: 267 (100%) $M^+$, 250 (40%), 236 (38%), 222 (70%), 209 (62%), 191 (85%), 144 (95%).

Nitration of 6-Nitro-2,1-benzisoxazole (XVII).

A solution of XVII (0.5 g) in concentrated sulphuric acid (40 ml) was nitrated as above at 60° over 50 minutes. The product obtained after discharging the mixture in ice-cold water was filtered, washed and crystallised from water to give 0.28 g of 3,3',5,5'-tetranitroazoxybenzene-2,2'-dicarboxylic acid (XVIII), mp 225° dec; ir (potassium bromide): 3075, 3025, 1700, 1540, 1110 ($cm^{-1}$); nmr (60 MHz, perdeuteriodimethylsulfoxide): $\delta$ 7.90-8.60 (m, 6H); ms: 466 (2%) $M^+$, 422 (35%), 376 (50%), 332 (45%), 250 (60%), 233 (100%).

*Anal.* Calcd. for $C_{14}H_6N_6O_{13}$: C, 36.05, H, 1.29; N, 18.03. Found: C, 35.78; H, 1.45; N, 17.82.

Chlorination of 5-Chloro-2,1-benzisoxazole (VII).

To a cooled solution of VII (2.0 g) in concentrated hydrochloric acid (40 ml) chlorine gas was passed slowly for 2 hours and then allowed to stand for 4 hours at room temperature. Work up for the reaction mixture gave the starting material.

Reaction of 2,1-Benzisoxazole (Ia) with Dimethyl Acetylenedicarboxylate.

To a solution of Ia (1.0 g) in dry xylene (50 ml) was added dimethyl acetylenedicarboxylate (0.75 g) and the solution was refluxed for 72 hours. Evaporation of the solvent gave back the unreacted starting material (Ia).

Reaction of 6-Nitro-2,1-benzisoxazole (XVII) with Dimethyl Acetylenedicarboxylate.

Dimethyl acetylenedicarboxylate (0.5 g) was added to a solution of XVII (0.75 g) in dry xylene (50 ml) and refluxed for 20 hours. The solvent was removed by distillation under reduced pressure. Crystallization of the residue from ethanol gave 0.47 g (50%) of 2,3-dicarbomethoxy-7-nitro-1,4-epoxy-1,4-dihydroquinoline (XIX), mp 170°; ir (potassium bromide): 2950, 1740 (C=O), 1720 (C=O), 1550 ($NO_2$) 1325 ($NO_2$) ($cm^{-1}$); nmr (60 MHz, deuteriochloroform): $\delta$ 4.68 (s, 1H), $\delta$ 7.90 (d, 1H), $\delta$ 8.37 (dd, 1H), 8.73 (d, 1H), $\delta$ 4.04 (s, 3H), $\delta$ 3.91 (s, 3H), $J_{5,6}$ = 8.2 Hz, $J_{6,8}$ = 2.3 Hz; ms: 306 (40%) $M^+$, 290 (5%), 275 (20%), 260 (24%), 248 (20%), 247 (15%), 174 (100%).

*Anal.* Calcd. for $C_{13}H_{10}N_2O_7$: C, 50.98; H, 3.27; N, 9.15. Found: C, 51.14; H, 3.32; N, 8.90.

Reaction of 5-Chloro-2,1-benzisoxazole (VII) with Dimethyl Acetylenedicarboxylate.

Dimethyl acetylenedicarboxylate (1.0 g) was added to a solution of VII (1.2 g) in dry toluene (100 ml) and the mixture was refluxed for 15 hours. Distillation followed by crystallisation of the residue from light petroleum gave 0.95 g (49%) of 2,3-dicarbomethoxy-6-chloro-1,4-epoxy-1,4-dihydroquinoline (XX), mp 113°; ir (potassium bromide): 2945, 1745 (C=O), 1590, 1150 ($cm^{-1}$); nmr (60 MHz, deuteriochloroform): $\delta$ 4.50 (s, 1H), $\delta$ 7.60 (d, 1H), $\delta$ 7.50 (dd, 1H), $\delta$ 7.76 (d, 1H), $\delta$ 4.00 (s, 3H), $\delta$ 3.84 (s, 3H), $J_{5,7}$ = 2.0 Hz; ms: 295 (100%) $M^+$, 278 (56%), 264 (72%), 236 (40%), 235 (60%).

*Anal.* Calcd. for $C_{13}H_{10}ClNO_5$: C, 52.88; H, 3.39; N, 4.75. Found: C, 52.80; H, 3.25; N, 4.85.

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## REFERENCES AND NOTES

(1) G. E. Hardtmann and N. J. Florham, U. S. Patent 3,642,897 (1972); *Chem. Abstr.*, **76**, 153341f (1972).

(2a) R. C. Boruah, J. S. Sandhu and G. Thyagarajan, *J. Heterocyclic Chem.*, **16**, 1087 (1979); (b) K. W. Gopinath, J. S. Sandhu, D. Mago and A. K. Sharma, British Patent 1,460,141 (1975); *Chem. Abstr.*, **87**, 22781d (1977).

(3) M. Davis and A. W. White, *J. Chem Soc., (C)*, 2189 (1969).

(4) M. Davis and K. S. L. Srivastava, *J. Chem. Soc., Perkin Trans. I*, 935 (1972).

(5) E. Bamberger and J. Lublin, *Chem. Ber.*, **42**, 1676 (1909).

(6a) Altaf-ur-Rahman and A. J. Boulton, *Tetrahedron*, **7**, 49 (1966); (b) A. J. Boulton and R. C. Brown, *J. Org. Chem.*, **35**, 1662 (1970).

(7) E. C. Taylor, D. R. Eckroth and J. Bartulin, *ibid.*, **32**, 1899 (1967).

(8) A. Schonberg and A. Mostafa, *J. Chem. Soc.*, 654 (1943).

(9) R. M. Acheson and P. W. Poulter, *ibid.*, 2138 (1960).

(10) Also independently observed by A. J. Boulton (personal communication).

(11a) G. Heller, *J. Prakt. Chem.*, **77**, 145 (1908); (b) M. C. Garg, *J. Org. Chem.*, **27**, 3683 (1962).

(12) R. C. Boruah, P. Devi and J. S. Sandhu, *J. Heterocyclic Chem.*, **16**, 1555 (1979).

(13) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).