The Chemistry of *N*-Cyanodithioimidocarbonic Acid. II. Synthesis of 3-Halo-1,2,4-thiadiazoles[1,2]

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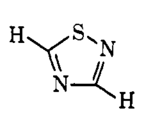
Reaction of dipotassium cyanodithioimidocarbonate ($NCN{=}CS_2K_2$) with 1 molar equiv of a variety of substituted alkyl halides has been shown to afford potassium 5-substituted cyanodithioimidocarbonate esters (monoesters). Halogenating agents (*e.g.*, Cl_2, SO_2Cl_2, Br_2, I_2) effected an oxidative cyclization of the monoesters to give a group of new 3-halo (chloro, bromo, iodo) 5-substituted thio-1,2,4-thiadiazoles. Oxidation of the external sulfur atom with 1 and 2 molar equiv of oxidizing agent yielded thiadiazole sulfoxides and sulfones, respectively. Attempted α-chlorination of a thiadiazole alkyl sulfide was unsuccessful. The 3-halo substituent proved inert to nucleophilic displacement. Discussion of infrared data on new compounds and mechanistic details of reactions are presented.

Because of the relative inaccessibility and sensitivity of the parent 1,2,4-thiadiazole molecule (1),[3] substituted 1,2,4-thiadiazoles have been constructed from appropriate acyclic parts and subsequently modified as desired by suitable transformations.[4] The history of 3-halo-1,2,4-thiadiazoles demonstrates the utility of such an approach. This class of compounds was first reported by Kurzer and Taylor[5] in 1960, who synthesized 3-chloro-5-aryl-1,2,4-thiadiazoles by a Sandmeyer–Gatterman type reaction (eq 1) and by Goerdeler and coworkers,[6] who prepared 5-amino-3-chloro-1,2,4-thiadiazole by chlorolysis of a corresponding alkyl sulfide (eq 2).



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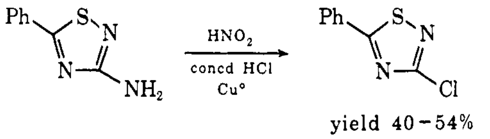
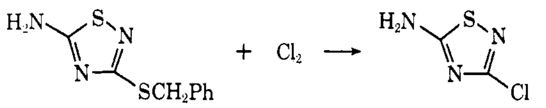


(1)



(2)

In 1967[1] we reported the first example of a direct route to 3-chloro-5-methylthio-1,2,4-thiadiazole starting from dipotassium cyanodithioimidocarbonate (2),[7,8] a compound readily obtained from cyanamide and carbon disulfide (eq 3).

$$NCNH_2 + CS_2 + 2KOH \xrightarrow{\text{alcohol}} NCN{=}C\begin{matrix}SK\\SK\end{matrix} \qquad (3)$$

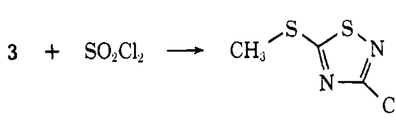
2

Alkylation of 2 with 1 molar equiv of methyl iodide proceeds stepwise to give 3 in nearly quantitative yield (eq 4).

$$2 + CH_3I \longrightarrow NCN{=}C\begin{matrix}SK\\SCH_3\end{matrix} \qquad (4)$$

3

When 3 is treated with sulfuryl chloride, an oxidative cyclization takes place to afford 4, also in high yield (eq 5).



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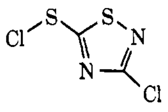
More recently Thaler and McDivitt[8] have provided convincing evidence that 2 undergoes a comparable cyclization to afford 5 in 80–100% yield.



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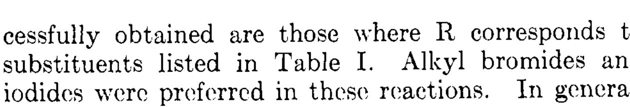
In the interval since our initial report we have investigated the scope of eq 4 and 5 and the chemical properties of the resultant 3-halo-1,2,4-thiadiazoles, and these results follow.

Results and Discussion

Monoesters of Dipotassium Cyanodithioimidocarbonate (2).—Monoalkylation of 2 was attempted with a sampling of primary, secondary, and tertiary halides in accord with eq 6.



$$NCN{=}C\begin{matrix}SK\\SK\end{matrix} + RX \longrightarrow NCN{=}C\begin{matrix}SK\\SR\end{matrix} + KX \qquad (6)$$

$X = Cl, Br, I$

The products which were successfully obtained are those where R corresponds to substituents listed in Table I. Alkyl bromides and iodides were preferred in these reactions. In general, primary alkyl halides reacted smoothly with 2 in acetone–water at reduced temperature to afford the desired monoesters in yields of 30–95%. Limited success was obtained with secondary halides and we were un-

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(1) For part I see R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967).

(2) Presented in preliminary form at the 2nd Regional Meeting of the American Chemical Society, Columbus, Ohio, June 1970.

(3) First reported by J. Goerdeler, J. Ohm, and O. Tegtmeyer, *Chem. Ber.*, **89**, 1534 (1956); J. Goerdeler and O. Tegtmeyer, *Angew. Chem.*, **67**, 302 (1955).

(4) For a current review on the synthesis and chemistry of 1,2,4-thiadiazoles see F. Kurzer, *Advan. Heterocycl. Chem.*, **5**, 119 (1965).

(5) F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 3234 (1960).

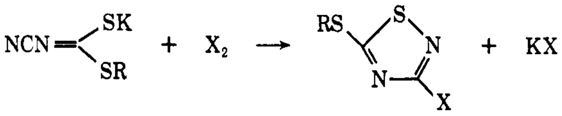
(6) J. Goerdeler and H. Rachwalsky, *Chem. Ber.*, **93**, 2190 (1960); see also J. Goerdeler and I. El Tom, *ibid.*, **98**, 1544 (1965).

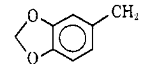
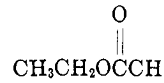
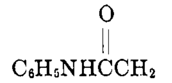
(7) Structure established by A. Hantzsch and M. Wolvekamp, *Justus Liebigs Ann. Chem.*, **331**, 265 (1904). Also accessible *via* calcium cyanamide and carbon disulfide, U. S. Patent 2,816,136.

(8) This versatile intermediate has only recently been given attention by other workers. See W. A. Thaler and J. R. McDivitt, *J. Org. Chem.*, **36**, 14 (1971), and references cited therein, for review. Also see K. A. Jensen and L. Henriksen, *Acta Chem. Scand.*, **22**, 1107 (1968).

TABLE I

3-HALO-1,2,4-THIADIAZOLE SULFIDES[a]

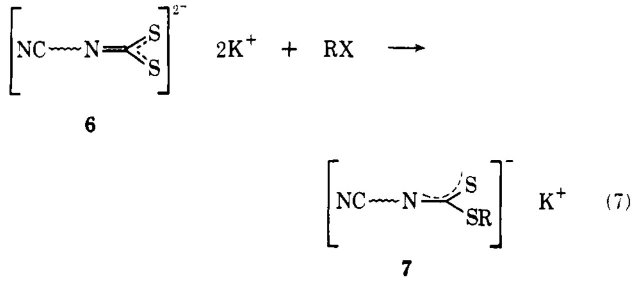


Compd	R	X	Yield, %[b]	Mp, °C	Bp, °C (mm)	Ir (ring), cm⁻¹
4	CH_3	Cl	70	54–55		1425, 1228
10	CH_3	Br	54	57–58		1404, 1202
11	CH_3	I	46	86.5–88.5		1381, 1175
12	CH_3CH_2	Cl	66		66 (0.25)	1429, 1215
13	$CH_3(CH_2)_2CH_2$	Cl	82		94–96 (0.45)	1420, 1212
14	$CH_3(CH_2)_4CH_2$	Cl	86		110–113 (0.24)	1429, 1220
15	$CH_3(CH_2)_8CH_2$	Cl	80		149–151 (0.20)	1425, 1214
16	$(CH_3)_2CH$	Cl	84		66–68 (0.15)	1422, 1214
17	$(CH_3)_2CH$	Br	67		66–67 (0.20)	1425, 1210
18	$(CH_3)_2CHCH_2$	Cl	83		82 (0.05)	1437, 1222
19	$(CH_3)(CH_3CH_2)CH$	Cl	43		64–65 (0.23)	1427, 1214
20	$C_6H_5CH_2$	Cl	85		144–147 (0.25)	1427, 1218
21	p-$NO_2C_6H_4CH_2$	Cl	59	94–97		1435, 1224
22	$C_6F_5CH_2$	Cl	72		109 (0.15)	1427, 1218
23		Cl	85	57–58		1431, 1232
24	$CH_2{=}CHCH_2$	Cl	22		81–85 (0.50)	1425, 1214
25	$CH_2{=}CClCH_2$	Cl	62		Oil[c]	1429, 1220
26	$CH_3CH_2OCH_2CH_2$	Cl	54		81–87 (0.06–0.07)	1441, 1227
27	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2$	Cl	50		56 (0.3)[d]	1433, 1222
28	$NCCH_2$	Cl	40	89.5–91.5		1433, 1225
29	 $H_2N\overset{O}{\overset{\|}{C}}CH_2$	Cl	71	137–139		1435, 1215
30	 $C_6H_5NH\overset{O}{\overset{\|}{C}}CH_2$	Cl	50	105–106.5		1439, 1220

[a] Satisfactory analyses (±0.4% for C, H, N, or S) were reported for all new compounds listed in the table. [b] Crude yields. [c] Boiling point not determined. [d] Falling film distillation.

able to characterize a comparable ester from tertiary halides.[9]

Because of their hygroscopic nature, the monoesters were difficult to obtain in an analytically pure state.[10] Thus, in many cases spectral data and subsequent characterization of the cyclized products were relied upon for structure proofs. The infrared spectra were particularly instructive, since 2 exhibits a strong band at 1322 cm^{-1} (C=N stretch) which shifts to 1340–1380 cm^{-1} in the monoesters.[11]



The disposition of 2 to undergo stepwise alkylation[12] may be represented by eq 7, wherein dianion 6 rapidly undergoes monoalkylation to give monoanion 7, which does not favorably compete with 6 for substrate giving rise to selective monoalkylation.[13]

Acylation of 2 was not thoroughly studied, but reaction with 1 molar equiv of ethyl chloroformate in refluxing acetonitrile gave back 75% of 2 with no other characterizable product. A similar experiment with 2 molar equiv of ethyl chloroformate under more forcing conditions afforded two products assigned

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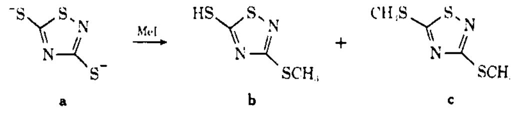
(9) Varying yields of potassium thiocyanate were obtained in those experiments which failed to give the desired monoesters [*e.g.*, $(C_6H_5)_2CHCl$, $(CH_3)_3CBr$, $C_6H_{11}I$, 2,4-dinitrochlorobenzene, CF_3CH_2I]. A more thorough product study in these cases was not undertaken, but could prove helpful in determining the origin of the potassium thiocyanate.

(10) Synthetically this presented no problem because it was unnecessary to purify these prior to cyclization.

(11) Complete removal of charge by dialkylation results in a more noticeable shift to 1466–1490 cm^{-1}.[1]

(12) R. Seltzer, *J. Org. Chem.*, **34**, 2562 (1969), has reported that a somewhat related molecule, a, reacts with 1 molar equiv of methyl iodide to afford 28% b and 27% c after work-up, indicating sequential alkylation with the 3 position being the more reactive site.



(13) Other dianionic heteroatom systems that could conceivably exhibit similar properties are those, for example, of trithiocarbonic acid, thiourea, and dithiolmethylene malononitrile [$(NC)_2C{=}C(SH)_2$]. Apparently none of these have been looked at with sequential alkylation in mind.

structures **8** and **9**.[14,15] These products can be rationalized on the basis of S and N attack by **2** on substrate,

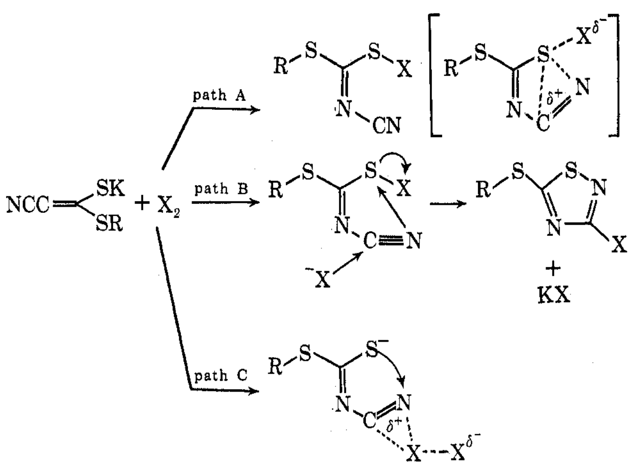
$(EtO_2C)_2S$ **8** (major) $(EtO_2C)_2NCN$ **9** (minor)

which is a predictable complication from soft–hard acid-base theory.[16] In this context, acylation of **3** also proved troublesome, although the desired S-acylated product was obtained with ethyl chloroformate.[1]

3-Halo-1,2,4-thiadiazole Sulfides.—Interaction of monoesters with chlorine, or more conveniently with sulfuryl chloride, at 0–5° resulted in an oxidative cyclization reaction furnishing the title compounds listed in Table I, where X = Cl. Similarly, treatment with bromine afforded **10** and **17**, and with iodine, **11**.[17] Chloroform, or alternatively methylene chloride, were the solvents of choice for these reactions. Rather surprisingly, water also served as solvent media for chlorine or bromine cyclizations.[18]

In the conversion of the monoesters to thiadiazole sulfides a diagnostic change was noted in the infrared spectra. To illustrate, monoesters exhibit a strong absorption at 1340–1380 cm^{-1} as described above. Cyclized products possess two strong bands ranging from 1381–1441 and 1175–1232 cm^{-1} which are assigned to ring vibrations.[19] As might be anticipated, substituents attached to the external sulfur atom do not appear to influence the position of these absorptions, but different halogen atoms at the 3 position (*i.e.*, **4**, **10** and **11**) produce a detectable red shift of both bands in the order Cl > Br > I. This phenomenon is associated with differences in atomic weight and electronic properties of the attached atoms.[20]

The mechanistic details surrounding formation of cyclized products from the monoesters have yet to be unraveled. Among the mechanisms considered, three are advanced as potential candidates.[21] In summary, path A requires formation of an intermediate sulfenyl halide, which then adds across the nitrile bond intramolecularly. In path B an intermediate sulfenyl halide is also assumed, but ring closure is assisted by halide ion attack on carbon followed by halogen displacement from sulfur with an incipient nitrogen anion in a concerted manner.[1] Electrophilic addition of elemental halogen to the nitrile bond with concomitant bond formation between sulfur and nitrogen as in path C would also lead to the observed thiadiazole. The common denominator implicit in these mechanisms is that, at some stage in the cyclization, the sp-hybridized nitrile bond is converted to sp^2, thereby enabling the heteroatoms to approach within bonding range.



As Thaler and McDivitt[8] have pointed out, sulfenyl halides do not commonly add to nitriles as required by path A. For intramolecular addition of sulfenyl halide to proceed in a manner normally associated with olefin addition,[22] a highly strained species would be required. This would appear to rule out a fast step following sulfenyl halide formation, but, if unassisted sulfenyl halide addition to nitrile is involved, the reaction is relatively fast because we have yet to isolate a sulfenyl halide precursor. Halide ion assisted ring closure (path B) appears more plausible because it avoids the strained species of path A. On the other hand, chloride ion attack in aqueous media seems unlikely, but the mechanism in water may differ in some respects from that in chloroform. Path C is attractive because of its simplicity and it circumvents the problems inherent in the two alternatives. The problem in this case is to rationalize why the nitrile band should effectively compete with a sulfur anion for oxidizing agent. In any event, experiments to rigorously establish the correct mechanism remain to be devised.

Reactions of 3-Halo-1,2,4-thiadiazole Sulfides.—Oxidation of a number of thiadiazole sulfides was carried out to yield sulfoxides and sulfones, listed in Tables II and III, respectively. Hydrogen peroxide in acetic anhydride–acetic acid solution was used effectively in preparing sulfones and a few sulfoxides. For sulfoxides and molecules containing more than one oxidizable group, *m*-chloroperbenzoic acid was the preferred oxidizing agent. All of the new sulfoxides and sulfones gave satisfactory analytical and spectral data. In addition to normal sulfoxide and sulfone bands, the infrared spectra of these derivatives also displayed the two bands attributed to thiadiazole ring vibrations, as indicated in Tables II and III. One notable feature of the thiadiazole ring absorptions in question is the rise in position of the higher frequency band relative to that of the sulfides, whereas the lower frequency band appears in about the same range.

A well-known reaction of sulfides which possess at least one hydrogen at an α-carbon atom is chlorination to give α-chloroalkyl sulfides.[23] An attempt to effect this exchange (eq 8) with 3-chloro-5-methylthio-1,2,4-

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[14] Both **8** and **9** gave consistent analytical and spectral data and their physical properties compared reasonably well with literature values (see Experimental Section).

[15] R. Seltzer, *J. Org. Chem.*, **33**, 3896 (1968), reported a reaction of **2** with Ph_3SnCl which bears some resemblance to the production of **8**.

[16] (a) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); (b) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

[17] Kurzer and Taylor[5] obtained a 3-bromo derivative in low yield by modification of their procedure (eq 1). Thaler and McDivitt also reported a 3-bromo derivative.[8] To our knowledge, examples of 3-iodo thiadiazoles have not previously appeared in the literature.

[18] Compound **4** was first prepared from **3** and perchloromethyl mercaptan in water.[1]

[19] C. N. R. Cao and R. Venkatarazhavan, *Can. J. Chem.*, **42**, 43 (1964).

[20] See L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen, Great Britain, 1968, p 33.

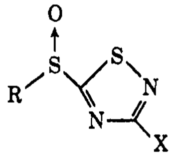
[21] See also ref 8 for discussion of mechanism.

[22] (a) N. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, Elmsford, N. Y., 1969, p 382; (b) D. R. Hogg, "Mechanisms of Reactions of Sulfur Compounds," Vol. V, Intra-Science Research Foundation, Santa Monica, Calif., 1970, p 87, and references cited therein.

[23] For review see L. A. Paquette, L. S. Wittenbrook, and K. Schreiber, *J. Org. Chem.*, **33**, 1080 (1968).

TABLE II

3-HALO-1,2,4-THIADIAZOLE SULFOXIDES[a]

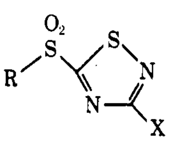


Compd	R	X	Yield, %[b]	Mp, °C	Bp, °C (mm)	Ir (ring), cm⁻¹
31	CH_3	Cl	72	99–99.5		1441, 1220
32	CH_3	Br	45	124–127		1431, 1198
33	CH_3CH_2	Cl	68		Oil[c]	1437, 1209
34	$(CH_3)_2CH$	Cl	65		Oil[c]	1439, 1214
35	$(CH_3)_2CH$	Br	82		Oil[c]	1440, 1200
36	$CH_3(CH_2)_2CH_2$	Cl	79		Oil[c]	1443, 1214
37	$CH_3(CH_2)_4CH_2$	Cl	85		Oil[c]	1441, 1214
38	$CH_3(CH_2)_8CH_2$	Cl	82		Oil[c]	1449, 1219
39	$C_6H_5CH_2$	Cl	50	92–95		1449, 1229

[a] Satisfactory analyses (±0.4% for C, H, N, or S) were reported for all new compounds listed in the table. [b] Crude yields. [c] Boiling point not determined (See Experimental Section).

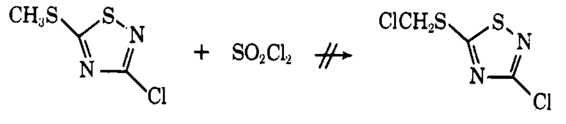
TABLE III

3-HALO-1,2,4-THIADIAZOLE SULFONES[a]



Compd	R	X	Yield, %[b]	Mp, °C	Bp, °C (mm)	Ir (ring), cm⁻¹
40	CH_3	Cl	38	82–83[c]		1447, 1232
41	CH_3	Br	59	69–71.5		1441, 1190, 1200 (sh)
42	$(CH_3)_2CH$	Cl	84	59–61		1435, 1227
43	$CH_3(CH_2)_2CH_2$	Cl	45		107 (0.55)	1441, 1217
44	$CH_3(CH_2)_4CH_2$	Cl	64		126–129 (0.20)	1447, 1220
45	$CH_3(CH_2)_8CH_2$	Cl	85	40.5–41		1437, 1206
46	$C_6H_5CH_2$	Cl	62	126.5–127		1441, 1215, 1224 (sh)
47	p-$O_2NC_6H_4CH_2$	Cl	56	137–138		1437, 1206
48	$CH_2{=}CHCH_2$	Cl	86	65–67		1433, 1224

[a] Satisfactory analyses (±0.4% for C, H, and S) were reported for all new compounds listed in the table. [b] Crude yields. [c] Reference 1.

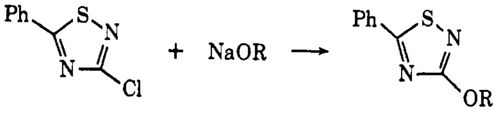


(8)

thiadiazole (**4**) under different conditions met with negative results.[24]

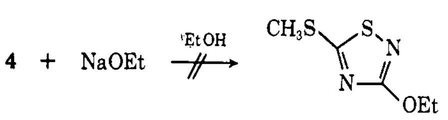
Why **4** should be so reluctant to undergo this reaction has yet to be determined.[25] Since none of the remaining compounds in Table I were subjected to similar reaction conditions, the generality of this phenomenon is an open question.

3-Halo-1,2,4-thiadiazoles are notoriously inert to nucleophilic displacement in contrast to halogen in the 5 position, which is relatively labile.[4] One of the few successful displacements has been reported by Kurzer and Taylor (eq 9).[5,26] In attempting to effect a similar displacement on **4** with sodium ethoxide in absolute ethanol, none of the desired product was obtained (eq 10). Rather, after removal of a quantitative yield of sodium chloride from the reaction mixture and further work-up, there was obtained a crude residue which exhibited prominent nitrile bands in the infrared spectrum suggesting ring opening with ejection of chloride ion. The nature of the ring-opened product(s) was not investigated further.



(9)

R = Me, benzyl



(10)

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 621 grating spectrophotometer. Spectra of liquids were taken as films between NaCl or KCl and solids as KBr pellets. The nmr spectra were recorded on a Varian Model T-60 with TMS as internal standard.

Preparation of Dipotassium Cyanodithioimidocarbonate (2).—A solution of cyanamide, 53.0 g (1.25 mol), in 100 ml of 95% ethanol was treated with 105.0 g (1.38 mol) of carbon disulfide. The mixture was cooled to 0° in an ice-salt bath and potassium hydroxide, 140.5 g (2.50 mol), in 450 ml of 95% ethanol was added dropwise while stirring rapidly with a mechanical stirrer. The temperature of the reaction mixture was maintained at or below 10°. Upon completion of the addition (4 hr), the reaction mixture was allowed to stir overnight at ambient temperature. The insoluble solid was removed by filtration, washed with 95% ethanol, and dried *in vacuo* to give 211.0 g (86% of theoretical) of **2**.

Example of Procedure for Preparing Monoesters. Potassium Allyl Cyanodithioimidocarbonate.—To a stirred solution of dipotassium cyanodithioimidocarbonate (**2**), 48.5 g (0.25 mol), in 210 ml of water and 185 ml of acetone previously cooled to 0° was added dropwise allyl bromide, 30.2 g (0.25 mol), in 90 ml of acetone. Upon completion of the addition the reaction mixture was allowed to warm to ambient temperature (approximately 21–24°) and stirred overnight. Shorter contact times down to 3 hr gave comparable results. Evaporation of the solvent on a rotary evaporator at reduced pressure (*in vacuo*) and elevated temperature afforded a solid residue which was slurried in 450 ml of acetone. The insoluble inorganic salt (in this case potassium bromide) was removed by filtration and the filtrate was evaporated *in vacuo* to furnish a solid residue. Treatment of this residue with 250 ml of ethyl acetate, in the same manner as described above for acetone, removed residual potassium bromide and any potassium thiocyanate that might have formed. Evaporation *in vacuo* of the ethyl acetate filtrate and further oven drying of the solid residue gave 47.3 g (97% of theoretical) of potassium allyl cyandithioimidocarbonate, mp 138–140°. The material prepared by this method gave the following elemental analysis.

Anal. Calcd for $C_5H_5KN_2S_2$: C, 30.59; H, 2.57; N, 14.27; K, 19.91. Found: C, 29.70; H, 2.45; N, 14.28; K, 20.30.

Recrystallization of the monoesters was not generally attempted prior to subsequent reactions, but ethyl acetate–chloroform or ethyl acetate–benzene were found to be suitable solvents for this purpose. As stated in the text, the monoesters are hygroscopic to varying degrees and, if retained for any period of time, should be stored under anhydrous conditions.

Reaction of 2 with 1 Molar Equiv of Ethyl Chloroformate.—To a stirred, refluxing solution of dipotassium cyanodithioimido-

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[24] Chlorination of **4** with chlorine in acetic acid–water did lead to 3,5-dichloro-1,2,4-thiadiazole in 85–95% yield. These results and ramifications thereof will be made available elsewhere.

[25] We had suggested[2] that a complex between **4** and sulfuryl chloride might be the culprit in preventing this reaction from taking place. Later experiments failed to clearly substantiate this theory.

[26] See also J. Goerdeler and K. H. Heller, *Ber.*, **97**, 225 (1964).

carbonate (**2**), 1.0 g (5 mmol), in 80 ml of acetonitrile under a nitrogen atmosphere was added dropwise 0.6 g (5 mmol) of ethyl chloroformate in 20 ml of acetonitrile. Upon completion of the addition, the reaction mixture was refluxed for an additional 2 hr. Heat was removed and the reaction mixture was allowed to stand overnight at ambient temperature. The insoluble solid was filtered, washed with acetonitrile, and dried to give 750 mg of material identified as **2** by comparison of infrared spectra (75% recovery). Evaporation of the filtrate *in vacuo* gave approximately 150 mg of solid residue which was triturated with ethyl acetate, filtered, and dried. The infrared spectrum of this solid contained no carbonyl absorptions anticipated for a carboethoxy group, but did contain bands characteristic for **2**.

Reaction of 2 with 2 Molar Equiv of Ethyl Chloroformate.—A heterogeneous mixture of 9.7 g (50 mmol) of dipotassium cyanodithioimidocarbonate (**2**, rendered as anhydrous as possible by drying over phosphorus pentoxide under high vacuum at elevated temperature) and ethyl chloroformate, 10.8 g (100 mmol), 100 ml of anhydrous acetonitrile was stirred and refluxed for 20 hr under a nitrogen atmosphere. The insoluble portion of the reaction mixture was filtered, washed with acetonitrile, and dried to give 8.4 g of pale yellow solid (A), mp >280°. An infrared spectrum of A was essentially devoid of any peaks, with the exception of a weak absorption at 2185 cm^{-1} ($C\equiv N$). When solid A was stirred in water, an insoluble brown solid (B) remained which upon work-up was found to weigh 1.0 g, mp >280°. Solid B gave an infrared spectrum that appeared polymer-like with broad absorptions at 3600–2600 and 1800–1100 cm^{-1} and one relatively sharp absorption at 2185 cm^{-1}. The soluble portion of A, approximately 7.4 g, was characterized as potassium chloride (theoretical, 7.5 g).

Evaporation *in vacuo* of the acetonitrile soluble portion (filtrate from above) afforded 8.9 g of a maroon oil (C). The infrared spectrum of this displayed prominent bands at 3000 (CH), 2270 ($C\equiv N$), 2198 ($C\equiv N$), 1970 ($N=C=S$), 1832–1720 (five peaks, $C=O$), 1235, 1100, and 1010 cm^{-1}. When C was stirred in anhydrous ethyl ether, a yellow solid (D) precipitated. Solid D was separated from the ether solution by filtration and was found to weigh 1.7 g (water insoluble). This was unstable and decomposed within minutes to a maroon-colored, viscous liquid. An infrared spectrum of D taken immediately after isolation resembled that of solid B with additional carbonyl bands around 1775 cm^{-1}. The ether soluble filtrate obtained after removal of solid C was evaporated *in vacuo* to give 7.3 g of yellow liquid (E). A tlc of the yellow liquid (silica gel, elution with ethyl acetate-acetonitrile, 4:1) showed two spots at R_f 0.33 and 0.55. Removal of solid D failed to noticeably alter the infrared spectrum of E as compared to C.

Fractional distillation of liquid E under reduce pressure gave 2.0 g (center cut; total of all cuts 3.5 g) of colorless liquid (F), bp 55–56° (0.2–0.3 mm), R_f 0.55. Liquid F was assigned structure **8**, thiodiformic acid diethyl ester: bp 118° (22 mm),[27] ν_{max}^{film} 3000 (CH), 1785 ($C=O$), 1760 ($C=O$), 1720 ($C=O$), 1100, and 1010 cm^{-1}; nmr δ^{CDCl_3} 1.33 (t, 7, 3, $-OCH_2CH_3$), 4.32 (q, 7, 2, $-OCH_2CH_3$).

Anal. Calcd for $C_6H_{10}O_4S$: C, 40.44; H, 5.66; S, 17.99. Found: 40.30; H, 6.04; S, 17.66.

The pot residue which remained after removal of **8** was stirred in anhydrous ethyl ether to precipitate a small quantity of gummy yellow solid which was not investigated further. The ether portion was decanted and concentrated to lower volume on a steam bath. When cooled in a Dry Ice-acetone bath, a pale yellow solid (G) crystallized. This was filtered cold and immediately transferred to a sample bottle, where it melted at ambient temperature (crude weight 1.2 g; R_f 0.33). Recrystallization of G from ether at reduced temperature afforded pure G, mp 28–30°. Solid G was assigned structure **9**, dicarboethoxy cyanamide: mp 32.8°;[28] ν_{max}^{film} 3000 (CH), 2275 ($C\equiv N$), 2199 (w, $C\equiv N$), 1830 ($C=O$), 1805 ($C=O$), 1770 ($C=O$), 1235, 1105, and 1000 cm^{-1}; nmr $\delta_{TMS}^{CDCl_3}$ 1.40 (t, 7, 3, $-OCH_2CH_3$), 4.39 (q, 7, 2, $-OCH_2CH_3$).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.60; H, 5.68; N, 14.80.

The data from this experiment suggests that S-acylation of **2** is not likely to be successful, partly because of competition between sulfur and nitrogen anions, but also because the resultant S-monoester can further collapse by elimination of cyanoisothiocyanate to give a more stable species.[29–31]

Example of Procedure for Preparing Thiadiazole Sulfides of Table I. 3-Chloro-5-benzylthio-1,2,4-thiadiazole (20).—To a stirred slurry of potassium benzyl cyanodithioimidocarbonate, 42.0 g (0.17 mol), in 225 ml of chloroform previously cooled to 0–5° was added dropwise sulfuryl chloride, 26.8 g (0.20 mol). Upon completion of the addition the reaction mixture was stirred at 0° for 1 hr and at reflux for 3.5 hr. Removal of the insoluble white solid by filtration and evaporation of the filtrate *in vacuo* at elevated temperature afforded 34.2 g (85% of theoretical) of crude **20**. Fractional distillation of the crude product under reduced pressure furnished pure 3-chloro-5-benzylthio-1,2,4-thiadiazole, bp 144–147° (0.25 mm).

3-Chloro-5-(α-acetamidothio)-1,2,4-thiadiazole (29).—To a stirred slurry of potassium *S*-(α-acetamido)cyanodithioimidocarbonate, 2.1 g (10 mmol), in 10 ml of chloroform. Upon completion of the addition, the slurry was stirred for 24 hr at ambient temperature. Removal of the insoluble solid by filtration gave 2.4 g of crude product. Treatment of this with water to remove inorganic salt and subsequent filtration afforded 1.1 g of **29**. An additional 0.4 g of **29** (total yield was 1.4 g or 71% of theoretical) was obtained by evaporation *in vacuo* of the filtrate from the reaction mixture. Recrystallization of the product from chloroform furnished pure 3-chloro-5-(α-acetamidothio)-1,2,4-thiadiazole, mp 137–139°.

Although oxidative cyclization of the monoesters was conveniently carried out with sulfuryl chloride as demonstrated in the preceding examples, elemental chlorine was also employed to give compounds in Table I where X = Cl with comparable results. Furthermore, an excess of chlorine is not detrimental to the reaction.

Contacting monoesters in chloroform or methylene chloride with bromine in the same manner as described above afforded the 3-bromo thiadiazoles listed in Table II. Treatment of **3** with iodine was not a clean reaction and a representative experiment is presented below. This was the only iodo derivative that was attempted.

3-Iodo-5-methylthio-1,2,4-thiadiazole (11).—To a stirred slurry of potassium methyl cyanodithioimidocarbonate (**3**), 3.4 g (20 mmol), in 50 ml of chloroform at ambient temperature was added dropwise 5.1 g (20 mmol) of iodine in 300 ml of chloroform. After completion of the addition, the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then transferred to a separatory funnel and washed successively with water, 10% aqueous sodium bisulfite solution, and again with water. The organic portion was dried over sodium sulfate, filtered, and evaporated *in vacuo* to afford 3.0 g of orange semisolid which exhibited characteristic thiadiazole bands in the infrared spectrum. Attempts to recrystallize the crude product were unsuccessful and it was necessary to chromatograph the material (80 g of Woelm alumina, activity I, elution with benzene followed by 3:1 benzene–chloroform). There was obtained 2.3 g of **11** as a colorless, crystalline solid (46% of theoretical), mp 86.5–88.5°, and 30 mg of yellow oil (eluted last). The yellow oil was not characterized, but spectral data was in line with a disulfide.

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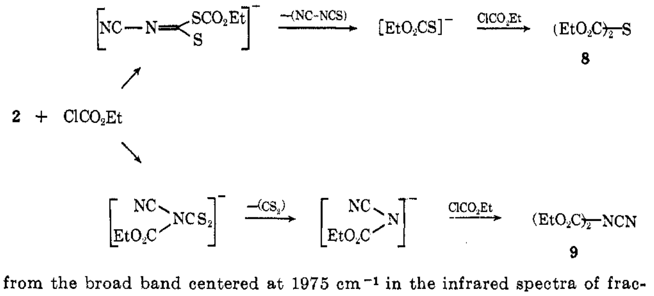
[27] *Beilstein*, **3**, 133.

[28] *Beilstein*, **3**, 82.

[29] A proposed sequence of events to explain formation of **8** and **9** is shown below. Evidence for the production of cyanoisothiocyanate obtains from the broad band centered at 1975 cm^{-1} in the infrared spectra of fractions C and E.[30,31] The lack of good material balance in this experiment (17.3 g recovered from 20.5 g) could be partly accounted for by loss of carbon disulfide from the reaction mixture.



[30] The isothiocyanate band for $EtO_2C–NCS$ has been reported to occur at 1960–1990 cm^{-1}: A. Takamizawa, *et al.*, *Bull. Chem. Soc. Jap.*, **36**, 1219 (1963).

[31] Cyanoisothiocyanate has been reported to be an unstable material (ref 7).

Water could also be employed as a solvent media in the cyclization reaction and an example procedure follows.

3-Bromo-5-methylthio-1,2,4-thiadiazole (10).—Bromine, 8.8 g (60 mmol), was added dropwise to a stirred solution of potassium methyl cyanodithioimidocarbonate (**3**), 8.5 g (50 mmol), in 100 ml of water previously cooled to 5°. The resultant slurry was stirred for 1 hr at 5° and 2.5 hr at ambient temperature. Sufficient sodium thiosulfate was added to destroy any excess bromine. Extraction of the solution with chloroform and routine work-up of the organic portion gave 5.7 g (54% of theoretical) of crude **10** as a pale yellow semisolid. Recrystallization from pentane furnished pure **10**, mp 57–58°.

In a like manner chlorine gas was introduced into an aqueous solution of **3** to afford a 60% yield of crude **4** (same work-up method as above).

Example of Procedures for Preparing Thiadiazole Sulfoxides and Sulfones of Tables II and III. 3-Chloro-5-methylsulfinyl-1,2,4-thiadiazole (31)..—To a stirred solution of 3-chloro-5-methylthio-1,2,4-thiadiazole, 16.6 g (0.1 mol), in 25 ml of acetic acid and 25 ml of acetic anhydride cooled to 0° was added dropwise 12.3 g (0.1 mol) of 30% hydrogen peroxide solution. The mixture was stirred at 0° for 1 hr and 2 days at ambient temperature. Any unreacted hydrogen peroxide was decomposed with a small amount of manganese dioxide. Filtration and evaporation of the filtrate under reduced pressure at 80° gave a semisolid residue which was treated with water followed by solid sodium bicarbonate. Extraction with chloroform and routine work-up of the organic portion afforded 13.0 g (72% of theoretical) of crude **31** as a white solid. Recrystallization of this from methanol afforded pure **31** as a white, crystalline solid, mp 99–99.5°.

Reaction of thiadiazole sulfides with 1 molar equiv of *m*-chloroperbenzoic acid in chloroform also afforded sulfoxides in a state of high purity with minimal difficulty. An example procedure is given below for sulfone **47** which is applicable to the sulfoxides with appropriate modification of stoichiometry. A major portion of the sulfoxides selected for this investigation were found to be oils that were difficult to distill without decomposition. However, the products were all obtained in state of purity sufficient enough to give acceptable analytical results.

3-Chloro-5-(4′-nitrobenzylsulfonyl)-1,2,4-thiadiazole (47).—A 30% hydrogen peroxide solution, 24.5 g (0.22 mol), was added dropwise to a stirred solution of 3-chloro-5-(4′-nitrobenzylthio)-1,2,4-thiadiazole, 24.4 g (0.08 mol), in 25 ml of glacial acetic acid and 25 ml of acetic anhydride previously cooled to 0°. Upon completion of the addition, the reaction mixture was stirred at 0° for 2 hr and 2 days at ambient temperature. A solid precipitated during this period. The reaction mixture was diluted with 20 ml of glacial acetic acid and cooled to 0°, and sufficient manganese dioxide was added to decompose excess hydrogen peroxide. The insoluble solid was separated by filtration, washed with glacial acetic acid, and dried under high vacuum. (Work-up procedure was altered accordingly when the product was soluble in acetic acid–acetic anhydride solution. For example, evaporation of the solution *in vacuo* gave the crude product in these cases.) Further purification of crude product was effected by taking the residue up in chloroform and washing with aqueous 5% sodium bicarbonate solution. The chloroform portion was then dried over sodium sulfate or magnesium sulfate, filtered, and evaporated *in vacuo* to give 15.1 g (56% yield) of **47**. Recrystallization of this material from methanol afforded pure **47**, mp 137–138°.

For thiadiazole sulfides which contained another oxidizable group, *m*-chloroperbenzoic acid gave cleaner product and better yields over hydrogen peroxide. The following example will illustrate the use of *m*-chloroperbenzoic acid.

3-Chloro-5-(allylsulfonyl)-1,2,4-thiadiazole (48).—To a stirred solution of 3-chloro-5-(allylthio)-1,2,4-thiadiazole, 14.1 g (0.07 mol), dissolved in 225 ml of chloroform previously cooled to 0° was added dropwise 25 g (0.21 mol) of 80–85% *m*-chloroperbenzoic acid also dissolved in chloroform. After the addition was complete, the reaction mixture was stirred for 1 hr at 0° and 3 hr at ambient temperature. Removal of the white, insoluble solid (*m*-chlorobenzoic acid) by filtration gave a chloroform solution which was repeatedly washed with aqueous 5% sodium bicarbonate solution (this treatment removed any chlorobenzoic acid still dissolved in the chloroform), dried over magnesium sulfate, filtered, and evaporated to afford 14.0 g (86% of theoretical) of **48** as a colorless oil. The oil crystallized on standing, however, and could be recrystallized from methanol to give pure **48**, mp 65–67°.

Attempted Preparation of α-Chloroalkyl Sulfides.—The following experiments describe attempts to chlorinate 3-chloro-5-methylthio-1,2,4-thiadiazole (**4**) with sulfuryl chloride. Evidence from the first experiment below directed attention to a possible complex between sulfuryl chloride and **4** which might be preventing the desired reaction. Although this is not an unreasonable concept, later experiments failed to confirm this possibility.

Reaction of 4 with Excess Sulfuryl Chloride.—A solution of **4**, 2.0 g (12 mmol), in 20 ml of sulfuryl chloride was heated (50°) and stirred for 24 hr. The excess sulfuryl chloride was removed at 40° *in vacuo* to give a yellow liquid residue which was further exposed to a high vacuum overnight. This treatment afforded 2.6 g of oil. An infrared spectrum of this oil was substantially featureless, but resembled that of sulfuric acid. When the oil was added to water, a solid separated. After work-up, there was obtained 1.5 g of solid material identified as **4** by comparison of infrared spectra. The aqueous phase was neutralized with sodium hydroxide solution and evaporated to dryness to give a white solid identified as mainly sodium sulfate, also by infrared comparison.

Since no precautions were taken to exclude water in the above experiment, it was repeated with appropriate modifications.

Reaction of 4 with Excess Sulfuryl Chloride (Anhydrous).—A 2.0-g (12 mmol) quantity of analytically pure **4** was heated at 50–55° in 20 ml of freshly distilled sulfuryl chloride under a blanket of nitrogen (drying tube exit) in the dark for 3 hr. Despite a very low positive nitrogen pressure and use of an efficient condenser, the volume of solution decreased during the heating period. Sulfur dioxide was detected (odor) in the effluent gases. The solution was cooled and excess sulfuryl chloride was removed *in vacuo* at 20° to give 2.4 g of yellow oil. An infrared spectrum of the oil compared with that of **4** in solution (CCl_4) with no peaks evident at 1410 and 1190 cm^{-1} (SO_2) expected for sulfuryl chloride. When the oil was poured over ice, an aqueous acidic solution developed and another oil separated. This was removed by extraction with ether and the organic layer was washed with water, dried over magnesium sulfate, filtered, and evaporated to afford 1.7 g (85% recovery) of tacky yellow solid which was characterized as **4**. A tlc (silica gel, elution with ether) of the crude **4** showed one spot at R_f 0.52 (uv) which compared with authentic **4**, but a noticeable spot remained at the origin.

Thus, by carefully excluding water from the reaction the result obtained in the previous experiment was not realized.

Reaction of 4 with 1 Molar Equiv of Sulfuryl Chloride.—To a stirred solution of analytically pure **4**, 2.5 g (15 mmol), in reagent grade carbon tetrachloride (15 ml) warmed to 35° under a nitrogen atmosphere was added dropwise 2.0 g (15 mmol) of freshly distilled sulfuryl chloride in 15 ml of carbon tetrachloride over a period of 15 min. The solution was brought to reflux and refluxed for 3 hr. The reaction mixture was cooled and volatile materials were removed *in vacuo* at 20° to give a white solid residue. This was found to weigh 2.45 g (98% recovery), mp 52–54°. An infrared spectrum of this material was superimposable upon that of authentic **4**.

The above experiment was typical of several experiments to chlorinate **4** under what might be termed "standard conditions" for preparing α-chloroalkyl sulfides. All of these ended with the same result as above.

Reaction of 3-Chloro-5-methylthio-1,2,4-thiadiazole (4) with Sodium Ethoxide.—To a stirred solution of sodium ethoxide in anhydrous ethanol (prepared from 1.8 g-atoms of sodium metal and 50 ml of ethanol) at 35° was added 3-chloro-5-methylthio-1,2,4-thiadiazole, 3.3 g (20 mmol), through a Gooch tube. Initially the thiadiazole dissolved, but a precipitate formed as the addition was continued. Upon completion of the addition the reaction mixture was stirred at ambient temperature for 5 hr. The white, insoluble solid was removed by filtration, washed with ether, and dried *in vacuo* to give 1.5 g of material, mp >280°, which was completely water soluble. This was readily determined to be primarily sodium chloride (1.2 g is theoretical if all of **4** is degraded), apparently contaminated with about 300 mg of organic salt which displayed nitrile bands at 2170 and 2185 cm^{-1} in the infrared spectrum (very weak spectrum because of sodium chloride dilution). Other absorptions occurred at 1620 and 1572 cm^{-1} indicative of C=O or C=N. Removal of solvent from the above filtrate afforded a residue which was taken up in water. Neutralization of this solution with 5 *N* hydrochloric acid separated a small quantity of oil. This was removed by extraction with ether and further treatment to give 200 mg of yellow semisolid residue (strong odor). The infrared of this material contained bands at 2260 (C≡N) and 1775 cm^{-1} (C=O), but in general the peaks were quite broad. The neutralized, aqueous portion was evaporated *in vacuo* and the residue was dried to give 4.0 g of white solid, mp 60–65° (wet), 175° (bubbled), >300°. Although this residue was largely sodium chloride, an infrared spectrum again displayed a weak nitrile peak at 2175 cm^{-1}. None of the different fractions possessed peaks characteristic of a thiadiazole ring in the infrared spectra, but all displayed quartet-triplet combinations in the nmr indicative of ethoxy groups.

Registry No.—2, 13145-41-0; 4, 10191-90-9; 8, 36955-31-4; 9, 19245-24-0; 10, 36955-33-6; 11, 36955-34-7; 12, 36955-35-8; 13, 36955-36-9; 14, 36955-37-0; 15, 36955-38-1; 16, 36955-39-2; 17, 36955-40-5; 18, 36955-41-6; 19, 36955-42-7; 20, 36598-31-9; 21, 36955-44-9; 22, 36955-45-0; 23, 36950-00-2; 24, 36950-01-3; 25, 36950-02-4; 26, 36950-03-5; 27, 36950-04-6; 28, 36994-19-1; 29, 36950-05-7; 30, 36950-06-8; 31, 36950-07-9; 32, 36950-08-0; 33, 36950-09-1; 34, 36994-20-4; 35, 36950-10-4; 36, 36950-11-5; 37, 36950-12-6; 38, 36950-13-7; 39, 36950-14-8; 40, 10191-91-0; 41, 36950-16-0; 42, 36950-17-1; 43, 36950-18-2; 44, 36950-19-3; 45, 36950-20-6; 46, 36950-21-7; 47, 36950-22-8; 48, 36950-23-9; potassium allylcyanodithioimidocarbonate, 36598-32-0.

Intermediate Neglect of Differential Overlap Theoretical Studies.[1] 2-Substituted 1,3-Dioxolan-2-ylium Ions

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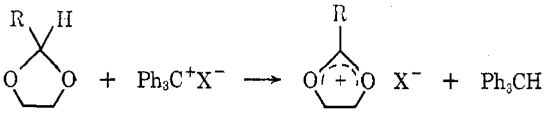
SCF–MO calculations in the INDO approximation have been performed on a series of 2-substituted 1,3-dioxolan-2-ylium cations where the 2 substituent was H (1), CH_3 (2), F (3), NH_2 (4), OH (5), and CN (6). In each of cations 1–6 a geometry search was performed to obtain the optimized geometry. The 2-cyano group was found to be a better electron donor than 2 hydrogen owing to back π_y donation to the C-2 carbon of the ring. A picture of both the π- and σ-electron distribution for this cation series was provided as a function of the 2 substituent. The NH_2 function was the best π donor followed by OH and F. However, fluorine is a better σ-electron-withdrawing function followed by OH and then NH_2, an order which parallels the electronegativity of the atom bond to C-2. This σ-withdrawal effect reduces the donor ability of fluorine to slightly less than that of a methyl function. The interrelation of σ- and π-electron framework over the ring oxygen atoms, C-2, and the 2 substituent is given. Rotational barriers are calculated. A comparison of the calculated positive charge densities on the ring methylene hydrogens is made with nmr chemical shifts for examples where spectra have been obtained.

Since the pioneering solvolytic studies of Winstein[2,3] and synthetic efforts of Meerwein,[4–6] a large body of chemistry has developed around the synthesis, reactions, structure, spectroscopy, and intermediacy (in organic reactions) of 1,3-dioxolan-2-ylium and related cations.[7] They have been isolated as stable salts[6,8–10] and shown to be stable in strong acids at high temperatures.[11] The great stability of 1,3-dioxolan-2-ylium ions is emphasized by their quantitative formation from 2-substituted 1,3-dioxolanes upon hydride abstraction by triphenylcarbonium ion salts[12] (see eq 1). Furthermore, the large rate accelerations observed in the acetolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate[13,14] and the high gas-phase stabilities of dioxonium ions relative to the methyl cation (*i.e.*, compare heats of formation: CH_3^+, 258; $(CH_3O)_2CH^+$, 101–113; $(CH_3O)_2CCH_3^+$, 146 kcal/mol)[15,16] demonstrate the inherent stability of these species. The heats of formation of a series of 2-substituted 1,3-dioxolan-2-ylium ions have been measured calorimetrically in strong acid solutions,[17,18] and a correlation between heats of formation and the nmr chemical shifts of the ring protons exists for a series of these ions with various 2-aryl substituents. Noteworthy was the fact that a 2-phenyl group destabilizes the cations, relative to a 2-methyl group. This is probably due to the relative effects of phenyl and methyl groups on the ester precursors used in the heat of formation measurements. Despite the enormous[7] number of studies on these cations, theoretical descriptions are noticeably lacking.



(1)

It is the purpose of this paper to present a SCF theoretical description in the INDO approximation[19,20] of 1,3-dioxolan-2-ylium ions, 1–6, where the substituent is varied to include H (1), CH_3 (2), F (3), NH_2 (4),

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[1] Paper V. For papers I–IV in this series, see (a) L. D. Kispert, C. Engelman, C. Dyas, and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, **93**, 6948 (1971); (b) C. U. Pittman, Jr., C. Dyas, C. Engelman, and L. D. Kispert, *J. Chem. Soc., Faraday Trans. 2*, **68**, 345 (1972); (c) L. D. Kispert, C. U. Pittman, Jr., D. L. Allison, T. B. Patterson, Jr., C. W. Gilbert, C. F. Hains, and J. Prather, *J. Amer. Chem. Soc.*, **94**, 5979 (1972); (d) C. U. Pittman, Jr., L. D. Kispert, and T. B. Patterson, Jr., *J. Phys. Chem.*, in press.

[2] S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, **64**, 2780, 2787 (1942).

[3] S. Winstein and D. Seymour, *ibid.*, **68**, 119 (1946).

[4] H. Meerwein, *Angew. Chem.*, **67**, 374 (1955).

[5] H. Meerwein and K. Wunderlich, *ibid.*, **69**, 481 (1957).

[6] H. Meerwein, H. Allendorfer, P. Beekmann, F. Kunert, H. Morschel, F. Pawellek, and K. Wunderlich, *ibid.*, **70**, 211, 630 (1958).

[7] C. U. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, **72**, 357 (1972).

[8] H. Hart and D. A. Tomalia, *Tetrahedron Lett.*, 1347 (1967).

[9] D. A. Tomalia and H. Hart, *ibid.*, 3383 (1966).

[10] D. A. Tomalia and H. Hart, *ibid.*, 3389 (1966).

[11] C. U. Pittman, Jr., and S. P. McManus, *ibid.*, 339 (1969).

[12] H. Meerwein, V. Hederich, H. Morschel, and K. Wunderlich, *Justus Liebigs Ann. Chem.*, **635**, 1 (1960).

[13] S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

[14] S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *ibid.*, **70**, 816 (1948).

[15] R. W. Taft, R. H. Martin, and F. W. Lampe, *ibid.*, **87**, 2490 (1965).

[16] R. H. Martin, F. W. Lampe, and R. W. Taft, *ibid.*, **88**, 1353 (1966).

[17] J. W. Larsen and S. Ewing, *ibid.*, **93**, 5107 (1971).

[18] J. W. Larsen and S. Ewing, *Tetrahedron Lett.*, 539 (1970).

[19] J. A. Pople, D. L. Beveridge, and P. A. Bobosh, *J. Chem. Phys.*, **47**, 2026 (1967).

[20] J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970.