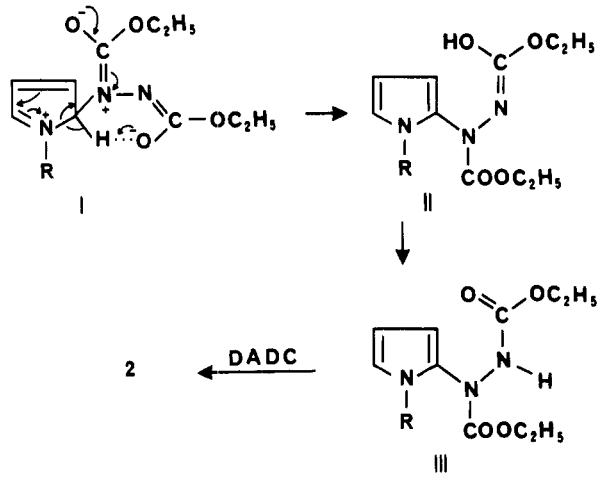
pyrroles probably forms a zwitterionic intermediate I.



Then, an α hydrogen may be transferred intramolecularly through a six-membered transition state when the reaction is carried out in the aprotic solvent. However, the facile solvation or intermolecular protonation by the protic solvent may be an explanation for the observation of increased yield.

With the exception of *p*-methoxyphenylpyrrole (**1e**), the 1-arylpyrroles did not give the adduct in aprotic solvents even after prolonged heating. The reaction did take place in the protic solvent; however, the yields were relatively low compared to those of the 1-alkyl derivatives. The relative yields of **2d–g** seem to be in line with the steric and electronic effects of the aryl groups.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-18 spectrophotometer. Ultraviolet and visible spectra were recorded on a Schimadzu double-beam spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. Mass spectra were obtained by using a Finnigan Model 3300 mass spectrometer. Elemental analyses were performed by the Institute of Physical and Chemical Research, Wako-shi, Saitama-ken, Japan.

Starting Materials. Commercial pyrroles (**1a** and **1b**) and DADC were distilled before use. Pyrroles (**1c–1g**) were prepared by literature methods.[5,6]

Typical Method of Preparation of the Adducts in Ether: 2,5-Bis(*N*,*N*'-diethoxycarbonylhydrazinyl)pyrrole (2a). A solution of pyrrole (1.34 g, 20.0 mmol) and DADC (6.96 g, 40.0 mmol) in anhydrous ether (30 mL) was refluxed for 24 h. The solvent was removed by evaporation, and the residual solid was recrystallized from ethanol (95%) to give **2a** as white powder (4.50 g, 56%): IR (KBr) 3300 (NH), 2990, 1730 (C=O), 1620, 1473, 1400, 1325, 1248, 1052 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (t, 12 H, J = 7 Hz, CH_3), 4.10 (q, 8 H, J = 7 Hz, OCH_2), 6.25 (s, 2 H, 2- and 3-H), 6.80–7.80 (br, 3 H, NH); UV (MeOH) 230 nm (ϵ 8130); mass spectrum, *m/e* (%) 415 (8, M^+), 414 (12), 255 (45), 240 (19), 179 (25), 149 (40), 94 (100).

Anal. Calcd for $C_{16}H_{25}N_5O_8$: C, 46.26; H, 6.07; N, 16.86. Found: C, 46.00; H, 5.99; N, 16.54.

Typical Method of Preparation of the Adducts in Ethanol: 2,5-Bis(*N*,*N*'-diethoxycarbonylhydrazinyl)-1-methylpyrrole (2b). A solution of 1-methylpyrrole (0.80 g, 10.0 mmol) and DADC (3.48 g, 20.0 mmol) in absolute ethanol (30 mL) was refluxed for 12 h. After the solution was cooled to room temperature, ether (10 mL) was added and the solution was kept in a refrigerator for 24 h to give precipitates. The precipitates were collected by filtration and recrystallized from ethanol–ether (1:2 v/v) to give **2b** as white prisms (2.80 g, 86%): IR (KBr) 3300 (NH), 2992, 1750 and 1715 (C=O), 1570, 1500, 1472, 1370, 1312, 1253, 1180, 1050, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (dt, 12 H, J = 7.0 Hz, CH_3), 3.48 (s, 3 H, NCH_3), 4.20 (dq, 8 H, J = 7.0 Hz, OCH_2), 6.20 (s, 2 H, 3- and 4-H), 7.00 (br, 2 H, NH); UV (EtOH) 225 nm (ϵ 13200); mass spectrum, *m/e* (%) 429 (66, M^+), 356 (24), 341 (71), 269 (100), 223 (62), 163 (43), 149 (28), 136 (33), 93 (52).

Anal. Calcd for $C_{17}H_{27}N_5O_8$: C, 47.55; H, 6.34; N, 16.31. Found: C, 47.52; H, 6.35; N, 16.29.

Acknowledgment. We thank Mr. Thomas Robison for helpful suggestions in preparing the manuscript and Mr. James Knight in the Finnigan Co. for mass spectra. C.K.L. thanks Dr. Wayland E. Noland for his kind encouragement and guidance. Financial support from the Korean Science and Engineering Foundation is gratefully acknowledged.

Registry No. 1a, 109-97-7; **1b**, 96-54-8; **1c**, 589-33-3; **1d**, 635-90-5; **1e**, 5145-71-1; **1f**, 4533-42-0; **1g**, 15898-23-4; **2a**, 73018-03-8; **2b**, 73018-04-9; **2c**, 73037-74-8; **2d**, 73018-05-0; **2e**, 73018-06-1; **2f**, 73018-07-2; **2g**, 73018-08-3; DADC, 4114-28-7.

Supplementary Material Available: Full IR, NMR, UV, and mass spectra and elemental analysis data for compounds **2c–2g** (2 pages). Ordering information is given on any current masthead page.

(5) N. Elming and N. Clauson-Kass, *Acta Chem. Scand.*, 6, 867 (1952).
(6) Y. Chiang, R. L. Hinman, S. Theodoropulos, and E. B. Whipple, *Tetrahedron*, 23, 745 (1967).

Synthesis and Identification of Isomeric Methylpyrazine Derivatives

Shoji Fujii* and Masao Matsumoto

Department of Agricultural Chemistry, Kyoto Prefectural University, Shimogamo, Kyoto 606, Japan

Hiroshi Kobatake

Kyoto General Medico Chemical Laboratory, Besshocho 95, Misasagi Yamashina, Kyoto 607, Japan

Received August 28, 1979

The condensation of an α,β-dicarbonyl compound with a 1,2-diamine is a useful method for preparation of pyrazine derivatives.[1] The procedure[2] for the condensation of biacetyl with aminomalonamide gave the best yields (93%) of 2-hydroxy-3-carboxamido-5,6-dimethylpyrazine.

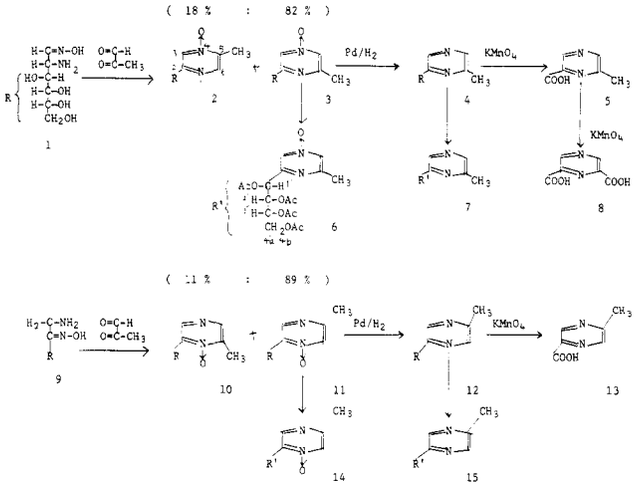
Jones claimed[2] to have obtained 2-hydroxy-3-carboxamido-5-methylpyrazine from the condensation of methylglyoxal with aminomalonamide, but later work[3] has shown that the 6-methyl isomer is formed exclusively in this reaction. The condensation of methylglyoxal bisulfite with aminomalonamide has been reported to give the 6-methylpyrazine derivative.[4] In this case, the 6-substituted isomer was the only isolable product.

We have now found that condensation of 2-amino-2-deoxy-D-glucose oxime (**1**) with methylglyoxal gives 2-(D-*arabino*-tetrahydroxybutyl)-6-methylpyrazine 4-*N*-oxide (**3**) and that condensation of 1-amino-1-deoxy-D-fructose oxime (**9**) with methylglyoxal gives 2-(D-*arabino*-tetrahydroxybutyl)-5-methylpyrazine 1-*N*-oxide (**11**) as the principal products (Scheme I). Minor amounts of an isomer were detected in each of the reaction mixtures by NMR but were not isolated.

(1) G. W. H. Cheeseman and E. S. G. Werstiuk, *Adv. Heterocycl. Chem.*, 14, 99 (1972).
(2) P. G. Jones, *J. Am. Chem. Soc.*, 71, 78 (1949).
(3) G. P. G. Dick and H. C. S. Wood, *J. Chem. Soc.*, 1379 (1955).
(4) F. L. Muehlman and A. R. Day, *J. Am. Chem. Soc.*, 78, 242 (1956).

0022-3263/80/1945-1693$01.00/0

Scheme I



The position of the methyl substituent in each of these pyrazines was established by deoxygenation of the *N*-oxide followed by oxidation of the tetrahydroxybutyl side chain. Thus **3** was converted to the known 6-methylpyrazine-2-carboxylic acid (**5**) and **11** to the known 5-methylpyrazine-2-carboxylic acid (**13**).

NMR spectra of the reaction mixtures that gave compounds **3** and **11** (after removal of excess methylglyoxal) indicated the presence of minor amounts of their isomers, **2** and **10**, respectively. The ratios of the isomers to the principal products were estimated from the areas under the NMR singlet CH_3 peaks (**3**, δ 2.58; **11**, δ 2.55; **2** and **10**, δ 2.40) by using the procedure of Abushanab and Alteri.[5] The predominant component in the mixture was identified from the CH_3-group chemical shift of a pure sample, and is also consistent with the report of Gumprecht[6] that the NMR chemical shift of the CH_3 protons in 3-methylpyrazine *N*-oxide is shifted downfield more than that of CH_3 protons in 2-methylpyrazine *N*-oxide.

The tendency of the reaction to form **2** and **10** appears to be inhibited by steric hindrance between the acetyl group of methylglyoxal and the oximino group of the sugar oximes.

Tetraacetyl derivatives of **3**, **4**, **11**, and **12** were prepared, and their NMR spectra (Table I) confirm the same extended planar zigzag conformation of the tetraacetoxybutyl side chain that has been established for analogous derivatives of quinoxaline[7] and pyrazine *N*-oxides.[8,9]

Experimental Section

All melting points are uncorrected. Infrared spectra were obtained on a Shimadzu Model IR-27C. NMR spectra were obtained by using a Varian A-60 spectrometer. Tetramethylsilane and the sodium salt of 2-(trimethylsilyl)propanesulfonic acid were used as internal standards. Acetylations were carried out with pyridine and acetic anhydride as described previously.[8]

2-(D-*arabino*-Tetrahydroxybutyl)-6-methylpyrazine 4-*N*-Oxide (3). To a solution of 19.4 g of 2-amino-2-deoxy-D-glucose oxime[8] (**1**) in 100 mL of water was added 24.1 g of a 30% aqueous solution of methylglyoxal (pyruvaldehyde). After the mixture was stirred for 1 h at room temperature and kept in a refrigerator overnight, the resulting crystals were collected by filtration. Recrystallization from hot water afforded 10.1 g of **3**: $[\alpha]^{25}_D$ −58.9° (*c* 1.0, water); mp 207–209 °C; NMR (D_2O) δ 2.53 (s, 3 H, CH_3).

Table I. NMR Data on the Tetraacetyl Derivatives

	chemical shifts[a]			
proton	**6**	**7**	**14**	**15**
1'-OAc	2.20 (3 H, s)	2.19 (3 H, s)	2.20 (3 H, s)	2.18 (3 H, s)
2'-OAc	2.10 (3 H, s)	2.09 (3 H, s)	2.12 (3 H, s)	2.09 (3 H, s)
3'-OAc	2.07 (3 H, s)	2.05 (3 H, s)	2.05 (3 H, s)	2.03 (3 H, s)
4'-OAc	1.97 (3 H, s)	1.93 (3 H, s)	1.95 (3 H, s)	1.93 (3 H, s)
CH_3	2.50 (3 H, s)	2.57 (3 H, s)	2.49 (3 H, s)	2.57 (3 H, s)
H-1'	6.05 (1 H, d)	6.09 (1 H, d)	6.53 (1 H, d)	6.11 (1 H, d)
H-2'	5.70 (1 H, q)	5.65 (1 H, q)	5.71 (1 H, q)	5.67 (1 H, q)
H-3'	5.25 (1 H, m)	5.30 (1 H, m)	5.32 (1 H, m)	5.28 (1 H, m)
H-4'a,4'b	4.26 (2 H, m)	4.19 (2 H, m)	4.25 (2 H, m)	4.21 (2 H, m)
H-5	7.88 (2 H, s)	8.33 (2 H, s)	7.98 (1 H, s)	8.38 (2 H, s)
H-3				
H-6			8.22 (1 H, s)	

	J values[b]			
	6	**7**	**14**	**15**
$J_{1',2'}$	3.0	3.0	2.5	3.0
$J_{2',3'}$	9.0	8.5	9.0	8.5
$J_{3',4a'}$	3.0	3.0	2.0	2.0
$J_{3',4b'}$	4.0	5.0	2.5	3.0
$J_{4a',4b'}$	12.0	12.0	13.0	12.5

[a] Chemical shifts (δ) in $CDCl_3$. [b] First-order coupling constants (Hz).

Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 46.71; H, 6.20; N, 12.17.

Tetraacetate 6: $[\alpha]^{20}_D$ −3.4° (*c* 1.0, methanol); mp 81–82 °C; for NMR data, see Table I. Anal. Calcd for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.57; N, 7.03. Found: C, 51.50; H, 5.60; N, 6.97.

Catalytic hydrogenation of **3** with palladium in methanol[9] yielded the known 2-(D-*arabino*-tetrahydroxybutyl)-6-methylpyrazine (**4**): $[\alpha]^{20}_D$ −83.2° (*c* 1.0, water) (lit. −70°,[10] −74°[11]]; mp 168–170 °C (lit.[10,11] mp 170 °C).

Tetraacetate 7: $[\alpha]^{20}_D$ −9.28° (*c* 1.0, methanol); mp 86–87 °C; for NMR data, see Table I. Anal. Calcd for $C_{17}H_{22}N_2O_8$: C, 53.40; H, 5.80; N, 7.33. Found: C, 53.63; H, 5.96; N, 7.34.

6-Methylpyrazine-2-carboxylic Acid (5). Oxidation of 3 g of 2-(D-*arabino*-tetrahydroxybutyl)-6-methylpyrazine (**4**) at 60–70 °C[12] gave 120 mg of 6-methylpyrazine-2-carboxylic acid (**5**), mp 198–201 °C (lit.[13] mp 201–202 °C). The product analyzed correctly and conformed with an authentic sample[13] in IR spectrum, R_f value, and color development with ferrous sulfate[14] in descending paper chromatography with the solvent systems *n*-butyl alcohol/pyridine/water (6:4:3) and isoamyl alcohol/pyridine/water (7:8:6). When the oxidation was carried out at 80–90 °C, the product was a mixture of **5** and pyrazine-2,6-dicarboxylic acid (**8**), as confirmed by the R_f values of an authentic mixture in the same chromatographic system.

2-(D-*arabino*-Tetrahydroxybutyl)-5-methylpyrazine 1-*N*-Oxide (11). 1-Amino-1-deoxy-D-fructose oxime (**9**), prepared[9] from 23 g of 1-amino-1-deoxy-D-fructose acetate[15] and hydroxylamine, was dissolved in 80 mL of water. To this solution was

(5) E. Abushanab and N. D. Alteri, Jr., *J. Org. Chem.*, **40**, 157 (1975).
(6) W. H. Gumprecht, T. E. Benkelmann, and R. Paju, *J. Org. Chem.*, **29**, 2477 (1964).
(7) D. Horton and M. J. Miller, *J. Org. Chem.*, **30**, 2457 (1965).
(8) S. Fujii and H. Kobatake, *J. Org. Chem.*, **34**, 3842 (1969).
(9) S. Fujii and H. Kobatake, *J. Org. Chem.*, **37**, 2635 (1972).
(10) M. I. Taha, *J. Chem. Soc.*, 2468 (1961).
(11) L. Hough, J. K. N. Jones and E. L. Richman, *J. Chem. Soc.*, 3854 (1952).
(12) H. I. X. Mager and W. Berends, *Recl. Trav. Chim. Pays-Bas*, **77**, 829 (1958).
(13) D. Pittre, S. Boveri, and E. B. Grabitz, *Chem. Ber.*, **99**, 364 (1966).
(14) P. Dietrich and D. Mercier, *J. Chromatogr.*, **1**, 67 (1958).
(15) R. Kuhn and H. J. Haas, *Justus Liebigs Ann. Chem.*, **600**, 148 (1956).

added 24 g of a 30% aqueous solution of methylglyoxal. After keeping the reaction mixture at room temperature, the solution was treated with 500 mL of Amberlite IR-120 (H^+), and the resin was eluted with 10 L of water. Evaporation of water left white crystals, 7.5 g (yield 32.5%). Recrystallization was carried out in water to yield 6.7 g of white needles: $[\alpha]^{16}_D$ −131.95° (c 1.2, water); mp 202–203 °C; NMR (D_2O) δ 2.55 (s, 3 H, CH_3). Anal. Calcd for $C_9H_{14}N_2O_5$: C, 46.95; H, 6.13; N, 12.17. Found: C, 47.06; H, 6.03; N, 12.10.

Tetraacetate 14: $[\alpha]^{21}_D$ −23.75° (c 1.0, methanol); mp 110 °C; for NMR data, see Table I. Anal. Calcd for $C_{17}H_{22}N_2O_9$: C, 51.25; H, 5.57; N, 7.03. Found: C, 51.11; H, 5.49; N, 6.99.

Catalytic hydrogenation of **11** with palladium in methanol yielded the known 2-(D-*arabino*-tetrahydroxybutyl)-5-methylpyrazine (**12**): $[\alpha]^{21}_D$ −61.19° (c 1.0, water) (lit.[11] $[\alpha]^{13}_D$ −62.4°); mp 198 °C (lit.[11] mp 196 °C).

Tetraacetate 15: mp 103–104 °C; for NMR data, see Table I. Anal. Calcd for $C_{17}H_{22}N_2O_8$: C, 53.40; H, 5.80; N, 7.33. Found: C, 54.21; H, 5.85; N, 7.44.

5-Methylpyrazine-2-carboxylic Acid (13). By the procedure described for **5**, 1.2 g of **12** afforded 230 mg of crystalline **13**, mp 164–165 °C (lit.[13] mp 166–167 °C).

Determination of Isomers 2 and 3 and Isomers 10 and 11. A small amount of the reaction mixture, after 1 h of reaction, was lyophilized and analyzed after being dissolved in D_2O with the sodium salt of 2-(trimethylsilyl)propanesulfonic acid as internal standard.

Registry No. 1, 21537-55-3; 2, 72938-69-3; 3, 32077-79-5; 4, 13440-26-1; 5, 5521-61-9; 6, 72938-70-6; 7, 72938-71-7; 8, 940-07-8; 9, 72938-72-8; 10, 72938-73-9; 11, 72938-74-0; 12, 13532-06-4; 13, 5521-55-1; 14, 72938-75-1; 15, 72938-76-2; methylglyoxal, 78-98-8.

2*H*-Cyclopenta[*d*]pyridazines. Polyhalogenation Studies. Evidence for a Radical Substitution with *N*-Chlorosuccinimide[1]

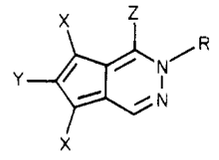
Arthur G. Anderson, Jr.,* and Taran Y. Tober[2]

Department of Chemistry, University of Washington, Seattle, Washington 98195

Received October 30, 1979

Previous results showed that the 2*H*-cyclopenta[*d*]-pyridazine system, a π-excessive heteroanalogue of azulene, underwent electrophilic substitution, including halogenation with *N*-halosuccinimides, readily at the 5- and 7-positions and more slowly at the 6-position.[3-5] We now report the reactions of 5,6,7-trichloro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (**1**) with NCS and also the preparation of several other new polyhalogen derivatives.

The parallels in reactivities, positions of substitution, and yields in the reactions of azulene and its π-excessive heteroanalogues with established electrophiles and with *N*-halosuccinimides[3-6] have demonstrated that the latter act as electrophilic reagents in effecting ring halogenation. Substitution of halogen for a benzylic hydrogen is known to proceed by a radical mechanism in nonpolar solvents with benzenoid compounds, however, and this provided a possible method for the preparation of chloromethyl derivatives in this nonbenzenoid series as intermediates for the formation of new functional substituents. Accordingly, this was investigated for the 2-methyl group in **1**.

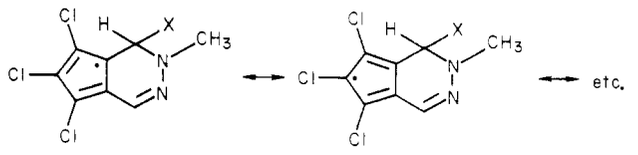


1, R = CH_3; X = Y = Cl; Z = H
2, R = CH_2Cl; X = Y = Cl; Z = H
3, R = $CHCl_2$; X = Y = Cl; Z = H
4, R = CCl_3; X = Y = Cl; Z = H
5, R = CH_2Cl; X = Y = Z = Cl
6, R = CH_3; X = Y = Cl; Z = *N*-succinimidyl
7, R = CH_3; X = Br; Y = Cl; Z = H
8, R = C_6H_5; X = Cl; Y = Br; Z = H
9, R = C_6H_5; X = Br; Y = Z = H
10, R = C_6H_5; X = Br; Y = Cl; Z = H
11, R = H; X = Br; Y = Z = H

Treatment of **1** with 1 equiv of NCS in refluxing carbon tetrachloride in the presence of air resulted in rapid decomposition. Repetition of the procedure in the absence of NCS caused decomposition but at an appreciably slower rate. Thus oxygen in the air appeared to be acting as an oxidant as well as a radical scavenger. The same reaction under a nitrogen atmosphere produced the chloromethyl derivative **2** (64%) and a trace of material spectrally identified as **3**. The NMR spectrum of **2** showed doublets at δ 8.47 and 8.61 for H-1 and H-4 and a singlet at δ 5.95 (as compared to δ 4.34 for the CH_3 in **1**) for the CH_2Cl group. Further reaction of **2** with 1 equiv of NCS under nitrogen formed **3** (77%) and a trace amount of **4**. The NMR spectrum of **3** had doublets at δ 8.59 and 8.97 (H-1, H-4) and a singlet at δ 7.78 ($CHCl_2$). Finally, longer treatment of **3** with a slight excess of NCS gave **4** (62%), the NMR spectrum of which consisted of only doublets at δ 8.74 and 9.33 (H-1, H-4).

Attempts to introduce chlorine into the remaining ring positions by the above method were unsuccessful, the hexachloro compound **4** being recovered unchanged after more than 1 week at reflux temperature.

Irradiation of **1** and 3 equiv of NCS in the absence of oxygen, however, formed a complex mixture of products (at least seven) from which small amounts of two compounds were isolated and spectrally characterized as the 1,5,6,7-tetrachloro-2-chloromethyl (**5**) and 1-succinimidyl-5,6,7-trichloro (**6**) derivatives. The NMR spectrum of **5** showed singlets at δ 8.60 (H-4) and 6.27 (CH_2Cl), and that of **6** had singlets at δ 8.66 (H-4), 4.02 (CH_3), and 3.1 (succinimidyl group) with the corresponding areas. The choice of the 1-position for the radical substitution was based on the postulate of a resonance-stabilized intermediate (**12**), which is not possible for substitution at position



12

4, and the correlation of the chemical shift of the remaining ring hydrogen with those observed in the spectra of **2**.

Additional electrophilic substitutions with *N*-halosuccinimides were also effected. Chlorination of the 5,7-

(1) Abbreviated NCS throughout this paper.
(2) From the Ph.D. Thesis of T. Y. Tober, University of Washington, 1977.
(3) Ammon, H. L.; Watts, P. H., Jr.; Anderson, A. G., Jr.; Forkey, D. M.; Grina, L. D.; Johnson, Q. *Tetrahedron* **1970**, *26*, 5707.
(4) Anderson, A. G., Jr.; Forkey, D. M.; Grina, L. D.; Hickernell, L. W.; Tober, T.; Wills, M. T. *J. Org. Chem.* **1975**, *40*, 2196.
(5) Anderson, A. G., Jr.; Forkey, D. M.; Grina, L. D. *J. Org. Chem.* **1978**, *43*, 1602. Anderson, A. G., Jr.; Grina, L. D.; Forkey, D. M. *Ibid.* **1978**, *43*, 664. Anderson, A. G., Jr.; Forkey, D. M.; Grina, L. D. *Ibid.* **1972**, *37*, 3499.
(6) Anderson, A. G., Jr.; Harrison, W. F. *J. Am. Chem. Soc.* **1964**, *86*, 708. Anderson, A. G., Jr.; Nelson, J. A.; Tazuma, J. *Ibid.* **1953**, *75*, 4980. Anderson, A. G., Jr.; Scotoni, R., Jr.; Cowles, E. J.; Fritz, C. G. *J. Org. Chem.* **1957**, *22*, 1193.

0022-3263/80/1945-1695$01.00/0