80–81° (12 mm.), $n^{25}D$ 1.4395; lit.[16] b.p. 82–83° (12 mm.), $n^{25}D$ 1.4396.

Ethyl α-methyldihydrocinnamate was prepared from α-methyldihydrocinnamic acid [b.p. 103° (0.5 mm.), $n^{23}D$ 1.5143; lit.[17] b.p. 152° (10 mm.), $n^{25}D$ 1.5135] by Fischer esterification[14] with ethanol; b.p. 68° (0.6 mm.), lit.[18] b.p. 130–131° (17 mm.).

Ethyl 1-methylcyclohexanecarboxylate was prepared from 1-methylcyclohexanecarboxylic acid [b.p. 63° (1 mm.), $n^{23}D$ 1.4921; lit.[19] b.p. 132.5° (20 mm.)] by Fischer esterification[15] with ethanol; b.p. 77–79° (10 mm.), $n^{25}D$ 1.4406; lit.[16] b.p. 82–83° (12 mm.), $n^{28}D$ 1.4430.

Ethyl cyclohexanedimethylacetate was prepared in 64% yield from cyclohexanedimethylacetic acid [b.p. 98° (0.5 mm.), lit.[19] b.p. 146° (10 mm.)] *via* the interaction of the silver salt with ethyl bromide; b.p. 64° (0.6 mm.), $n^{25}D$ 1.4500.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.80; H, 11.25. Found: C, 72.80; H, 11.42.

Ethyl β,β-dimethyldihydrocinnamate was prepared from β,β-dimethyldihydrocinnamic acid (m.p. 57–58°, lit.[20] m.p. 57.5–58°) by Fischer esterification[15] with ethanol; b.p. 89° (0.4 mm.), $n^{25}D$ 1.4916.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.65; H, 8.80. Found: C 75.41; H, 8.72.

Rate Measurements.—The kinetic experiments were carried out using both ester and sodium hydroxide in equal concentrations (about 0.05 *M*). The ester was weighed out in a volumetric flask, rapidly brought up to volume with the appropriate solvent mixture (pre-equilibrated to the reaction temperature, zero time was recorded as the time when one-half the solvent had been added), and placed in a constant temperature bath (accurate to ±0.1°.). Aliquots were removed periodically; the reaction was quenched by addition to an excess of hydrochloric acid of known normality and finally back-titrated with standardized sodium hydroxide to a bromthymol blue end point. The values of k_2 were calculated from the second-order reaction rate equation

$$k_2 = x/at(a - x)$$

where a is the initial concentration of each reactant and $(a - x)$ is the concentration of each reactant at time t. All of the measured reactions followed strictly second-order kinetic law with the exception of the first 10% conversion of ethyl cyclohexanedimethylacetate. This deviation was corrected for by assuming "0" reaction time at 10% conversion.

Treatment of the Kinetic Data.—The multiple regression analyses were performed through the courtesy of the Computer Center, Louisiana Polytechnic Institute, employing an IBM 1620 computer.

(16) M. S. Newman and H. M. Walborsky, *J. Am. Chem. Soc.*, **72**, 4296 (1950).
(17) K. B. Wiberg and T. W. Hutton, *ibid.*, **78**, 1640 (1956).
(18) S. M. McElvin and H. F. McShane, *ibid.*, **74**, 2662 (1952).
(19) H. Koch and W. Haaf, *Ann.*, **618**, 251 (1958).
(20) J. F. Dippy and J. T. Young, *J. Chem. Soc.*, 3919 (1955).

1H-2,1,3-Benzothiadiazin-4(3H)-one 2-Oxides

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Several 1-methyl-3,6-disubstituted 1H-2,1,3-benzothiadiazin-4(3H)-one 2-oxides have been prepared by the reaction of suitably substituted 2-methylaminobenzamines with thionyl chloride. Certain infrared spectral characteristics of these compounds are discussed.

In an attempt to prepare 5-chloro-N-(2-chloroethyl)-2-methylaminobenzamide by the reaction of 5-chloro-N-(2-hydroxyethyl)-2-methylaminobenzamide (Ia) with thionyl chloride, we obtained, instead, 6-chloro-3-(2-chloroethyl)-1-methyl-1H-2,1,3-benzothiadiazin-4-(3H)-one 2-oxide (IIa) (see Chart I). This new and unexpected ring closure to the benzothiadiazine with thionyl chloride was found to proceed smoothly with other suitably substituted 2-methylaminobenzamides (Ia–h, Table I). In these compounds, R = alkyl, substituted alkyl, or cycloalkyl, and X is an electronegative substituent, *e.g.*, Cl, NO_2, or $SO_2NHC_2H_5$. The correspondingly substituted benzothiadiazines (IIa–h) are given in Table II.

An attempt to displace the chloro group in the alkyl chain of IIa with a morpholino group was successful, but cleavage of the thiadiazine ring occurred, giving 5-chloro-2-methylamino-N-(2-morpholinoethyl)benzamide (Ii). The latter product was more easily prepared by the reaction of 5-chloro-N-methylisatoic anhydride with N-(3-aminoethyl)morpholine. Treatment of Ii with thionyl chloride in the usual manner, however, failed to give the desired benzothiadiazine.

The compounds shown in Table I were readily prepared in satisfactory yield by the reaction of a suitably substituted N-methylisatoic anhydride[1] with the appropriate amine. The previously undescribed 5-chlorosulfonyl-N-methylisatoic anhydride (III) used in the synthesis of Ih was prepared by chlorosulfonation of N-methylisatoic anhydride with chlorosulfonic acid. Treatment of the anhydride with excess aqueous ethylamine afforded Ih, which upon reaction with thionyl chloride gave the expected benzothiadiazine (IIh).

In contrast to these results, 2-methylaminobenzamide reacted with thionyl chloride to give a gummy residue which was not readily purified. The presence of a strong nitrile band at 4.54 μ in the infrared spectrum of this material indicated that dehydration of the amide group to the nitrile had occurred. Attempts to prepare the corresponding benzothiadiazines from N-ethyl-2-methylaminobenzamide and 2-amino-5-chloro-N-ethylbenzamide by reaction with thionyl chloride were unsuccessful. Similarly, 2-anilino-N-ethylbenzamide failed to give the expected ring closure. The results of these experiments make it clear that specific structural features in 2-aminobenzamides are essential for the success of the reaction. Both the amino and amido nitrogen atoms must be mono-

(1) N-Methylisatoic, 5-chloro-N-methylisatoic, 5-nitro-N-methylisatoic, and 5-chloroisatoic anhydrides were obtained from Maumee Chemical Co., Toledo, Ohio. The last three anhydrides, however, are offered by Maumee as the 6-chloro, 6-nitro, and 6-chloro derivatives, respectively, because a different numbering system was used. Since the compounds are derivatives of isatoic acid, we have numbered the substituents in accordance with the manner prescribed by *Chemical Abstracts*.

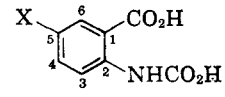
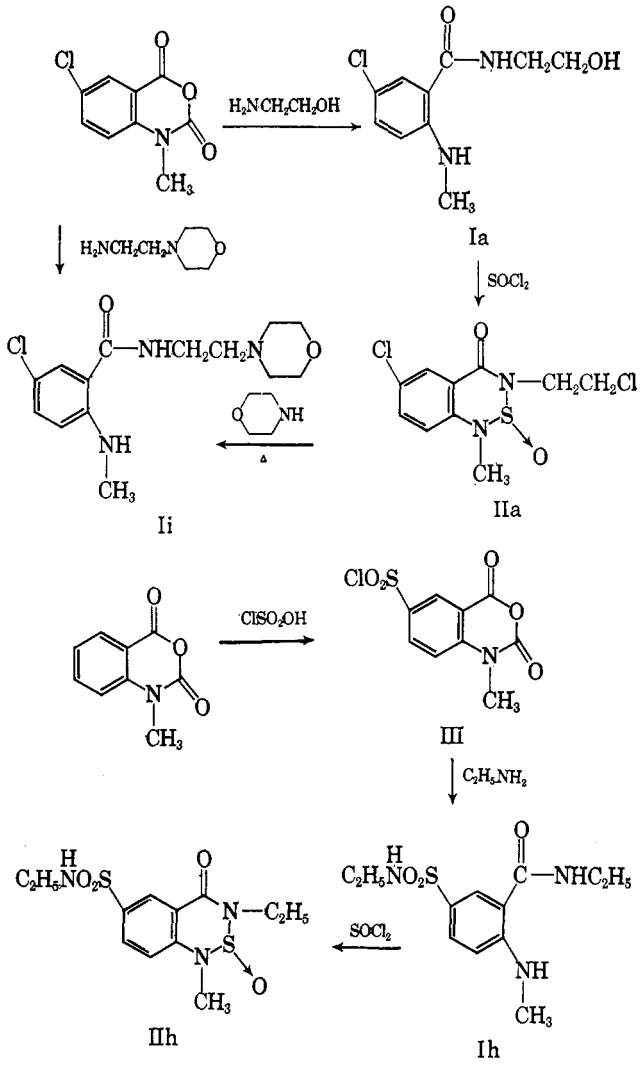


CHART I



substituted, the amino nitrogen atom by an alkyl group such as methyl and the amido nitrogen atom by an R group (Table I). In addition, the presence of an electronegative group (X) in the 5-position of the benzamide appears to be essential. The reaction has failed in those examples where any one of these conditions was not met.

Teufel[2] has reported the synthesis of 1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxides by cyclization reactions in *o*-sulphamidobenzoic acid derivatives. Cohen and Klarberg[3] reported a similar synthesis *via* the reaction of various anthranilic acid derivatives with sulfamoyl chloride. The compounds described in these reports bear structural resemblance to those of the current work but differ in the higher oxidation state of sulfur. We attempted to prepare 6-chloro-3-ethyl-1-methyl-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide from intermediates described in the present report. One approach, the reaction of 5-chloro-N-ethyl-2-methylaminobenzamide (Ib) with sulfuryl chloride, failed to give the desired benzothiadiazine. The product of reaction was 3,4,5,6-tetrachloro-2-chloromethylamino-N-ethylbenzamide, identified by its elemental analysis and nuclear magnetic resonance spectrum. An attempt to oxidize 6-chloro-3-ethyl-1-methyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2-oxide (IIb) to the dioxide by reaction with hydrogen peroxide in acetone resulted only in the recovery of unreacted IIb.

(2) H. Teufel, U. S. Patent 3,041,336 (1962).

(3) E. Cohen and B. Klarberg, *J. Am. Chem. Soc.*, **84**, 1994 (1962).

Infrared Spectra.—Certain infrared spectral characteristics were noted for the compounds mentioned herein. Except for IIh, the benzothiadiazines have no absorption in the NH stretching region (2.9–3.1 μ). As expected, none of these compounds has an amide II absorption band (6.4–6.5 μ) in its spectrum. This band is, however, clearly present in the spectra of benzamides Ia–h. The carbonyl stretching band at 6.12–6.16 μ in the benzamides is shifted slightly in the spectra of the benzothiadiazines (5.99–6.08 μ). Without exception, the presence of a strong band at 7.50–7.59 μ and at 8.80–8.92 μ was observed in each of the latter spectra. Cohen and Klarberg[3] reported the spectrum of 1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide to contain similar bands at 7.5 and 8.6 μ, which they assigned to the sulfonamide group. Whitehead and Traverso,[4] among others, noting bands at the same wave lengths in the spectra of several 1,2,4-benzothiadiazine 1,1-dioxides, assigned them to the SO_2 group. These absorptions have been associated with asymmetric and symmetric S–O stretching vibrations, respectively. Since these absorptions reported for the SO_2 group in compounds of the benzothiadiazine series lie in close proximity to the 7.50–7.59 and 8.80–8.92 μ bands in the spectra of IIa–h, it would be difficult on a spectral basis alone to distinguish between the monoxides and dioxides in this series. At present, therefore, these absorptions in IIa–h cannot be positively assigned. The band at 8.80–8.92 μ, however, is believed to be associated with the S–O stretching vibration and is displaced some 0.25–0.37 μ from the lower limit (9.17 μ) quoted by Colthup[5] for the S–O absorption in sulfoxides. The presence of the two electronegative nitrogen atoms bonded to the sulfur atom in IIa–h would be expected to exert a hypsochromic effect on the S–O absorption.

Experimental[6]

Procedures for preparing Ia and IIa are general and were used to prepare the other members of the series listed in Tables I and II.

5-Chloro-N-(2-hydroxyethyl)-2-methylaminobenzamide (Ia).—To a solution of 3.1 g. of 2-aminoethanol in 40 ml. of absolute ethanol was added 10.5 g. of 5-chloro-N-methylisatoic anhydride.[1] After heating the reaction mixture for 10 min. on the steam bath, the solvent was removed *in vacuo* on a rotary evaporator. The residue amounted to 5.7 g., m.p. 116–122°. Recrystallization from benzene raised the melting point to 125.5–129°; λ_{max} (C=O) 6.16, (amide II) 6.49 μ.

6-Chloro-3-(2-chloroethyl)-1-methyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2-Oxide (IIa).—A solution of 17 g. of Ia in 50 ml. of thionyl chloride was heated under reflux for 1.5 hr. The excess thionyl chloride was removed *in vacuo* on a rotary evaporator. The solid residual product amounted to 12.3 g., m.p. 151–154°. Recrystallization from ethanol gave an analytical sample with m.p. 153–154°; λ_{max} (C=O) 6.04, (S—O) 8.92 μ.

5-Chlorosulfonyl-N-methylisatoic Anhydride (III).—To 88.5 g. of N-methylisatoic anhydride was added, with occasional

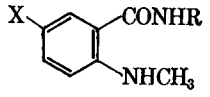
(4) C. W. Whitehead and J. J. Traverso, *J. Org. Chem.*, **27**, 951 (1962).

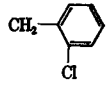
(5) N. B. Colthup, *J. Opt. Soc. Am.*, **40**, 397 (1950).

(6) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were determined in potassium bromide pellets on a Perkin-Elmer Model 21 spectrophotometer. The n.m.r. spectrum was obtained on a Varian A60 spectrometer, using a 10% solution of sample in deuteriochloroform and tetramethylsilane as the internal standard.

TABLE I

SUBSTITUTED 2-METHYLAMINOBENZAMIDES

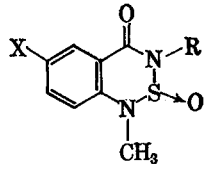


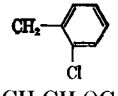
Compd. I	R	X	Yield, %	Recrystn. solvent[a]	M.p., °C.	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
a	CH_2CH_2OH	Cl	58	A	125.5–129	$C_{10}H_{13}ClN_2O_2$	52.53	5.73	12.25	15.51	52.60	5.51	12.53	15.51
b	CH_2CH_3	Cl	98	B	95–96.5	$C_{10}H_{13}ClN_2O$	56.47	6.16	13.17	16.67	56.58	6.01	13.30	16.4
c		Cl	64	C	137.5–139	$C_{15}H_{14}Cl_2N_2O$	58.27	4.56	9.06	22.93	58.54	4.41	8.77	22.5
d	$CH_2CH_2OC_2H_5$	Cl	73	B	73–74	$C_{12}H_{17}ClN_2O_2$	56.14	6.67	10.91	13.81	55.90	6.47	11.05	13.86
e	$CH_2CH_2C_6H_5$	Cl	74	A	132–134	$C_{16}H_{17}ClN_2O$	66.54	5.93	9.70	12.27	66.41	5.90	9.73	12.3
f	cyclo-C_5H_9	Cl	54	B	153–155	$C_{13}H_{17}ClN_2O$	61.77	6.78	11.08	14.03	61.50	6.74	11.36	13.9
g	CH_2CH_2OH	NO_2	75	D	173–174	$C_{10}H_{13}N_3O_4$	50.20	5.45	15.57		49.94	5.42	15.70	
h	CH_2CH_3	$SO_2NHC_2H_5$	72	E–C	118–120	$C_{12}H_{19}N_3SO_3$	50.51	6.71	14.72	11.24	50.31	6.47	14.76	11.4
i		Cl	66	C	130–132	$C_{14}H_{20}ClN_3O_2$	56.47	6.77	14.11	11.91	56.16	6.61	14.00	11.81
j	CH_2CH_3	H	86	B	87.5–89	$C_{10}H_{14}N_2O$	67.38	7.92	15.72		67.33	7.77	15.98	

[a] A = benzene, B = cyclohexane, C = ethanol, D = ethyl acetate, and E = water.

TABLE II

1-METHYL-3,6-DISUBSTITUTED 1H-2,1,3-BENZOTHIADIAZIN-4(3H)-ONE 2-OXIDES



Compd. II	R	X	Yield, %	Recrystn. solvent[a]	M.p., °C.	Formula	Calcd., % C	H	N	Cl	S	Found, % C	H	N	Cl	S
a	CH_2CH_2Cl	Cl	80	C	153–154	$C_{10}H_{10}N_2Cl_2O_2S$	40.97	3.44	9.56	24.19	10.94	40.98	3.36	9.61	23.9	10.8
b	CH_2CH_3	Cl	94	C	95–96.5	$C_{10}H_{11}N_2ClO_2S$	46.42	4.28	10.83	13.70	12.39	46.62	4.43	10.73	13.7	12.3
c		Cl	85	C	148–149.5	$C_{15}H_{12}N_2Cl_2O_2S$	50.71	3.40	7.89	19.96	9.03	50.85	3.49	7.89	19.7	8.8
d	$CH_2CH_2OC_2H_5$	Cl	62	B	73–74	$C_{12}H_{15}N_2ClO_3S$	47.60	4.99	9.25	11.71	10.59	47.38	4.98	9.32	11.71	10.2
e	$CH_2CH_2C_6H_5$	Cl	60	C	127–128.5	$C_{16}H_{15}N_2ClO_2S$	57.57	4.23	8.39	10.62	9.60	57.50	4.45	8.21	10.82	9.53
f	cyclo-C_5H_9	Cl	33	B	127–129	$C_{13}H_{15}N_2ClO_2S$	52.25	5.05	9.38	11.87	10.73	52.49	5.12	9.32	11.84	10.8
g	CH_2CH_2Cl	NO_2	67	A	161–162	$C_{10}H_{10}N_3ClO_4S$	39.54	3.32	13.84	11.67	10.56	39.69	3.25	13.68	11.85	10.1
h	CH_2CH_3	$SO_2NHC_2H_5$	83	D	150–152	$C_{12}H_{17}N_3O_4S_2$	43.39	5.17	12.68		19.35	43.27	5.00	12.75		18.9

[a] A = 2-ethoxyethanol, B = cyclohexane, C = ethanol, and D = methanol.

shaking, 300 ml. of chlorosulfonic acid. The reaction mixture was heated on the steam bath for 2 hr., then poured onto 500 g. of ice. The yellow, powdery solid which was deposited was removed by filtration, washed with water, and dried over potassium hydroxide in a desiccator. The product amounted to 103 g., m.p. 142–146°. Recrystallization from benzene afforded the analytical sample, m.p. 147–149°; λ_{max} (anhydride C=O) 5.62, 5.77, (SO_2) 7.68, 8.58 μ.

Anal. Calcd. for $C_9H_6ClNO_5S$: C, 39.21; H, 2.19; Cl, 12.86; N, 5.08; S, 11.63. Found: C, 39.47; H, 2.28; Cl, 12.7; N, 5.42; S, 11.5.

5-Chloro-2-methylamino-N-(2-morpholinoethyl)benzamide (Ii). Method A.—To a solution of 6.5 g. of N-(β-aminoethyl)morpholine in 40 ml. of absolute ethanol was added 10.5 g. of 5-chloro-N-methylisatoic anhydride. After the evolution of carbon dioxide had abated, the reaction mixture was heated for 10 min. on the steam bath. The solvent was removed *in vacuo* on a rotary evaporator. The residual oil crystallized on cooling to afford 9.8 g. of product, m.p. 129–132°. Recrystallization from ethanol gave 8.7 g. of analytically pure material, m.p. 130–132°, λ_{max} (C=O) 6.15 μ.

Method B.—A solution of 2 g. of IIa in 5 ml. of morpholine was heated under reflux for 1 hr. The excess morpholine was then removed *in vacuo* on a rotary evaporator. The residual oil was washed with water. Upon the addition of a few drops of methanol to the residue, crystallization resulted. There was obtained 0.6 g. of Ii, m.p. 130–133.5°, whose identity was confirmed by a mixture melting point and infrared spectral comparison with an authentic sample.

2-Amino-5-chloro-N-ethylbenzamide was prepared from 5-chloroisatoic anhydride and 33% aqueous ethylamine. Recrystallization from aqueous ethanol afforded a sample with m.p. 118–120°; λ_{max} (C=O) 6.14, (amide II) 6.45 μ.

Anal. Calcd. for $C_9H_{11}ClN_2O$: C, 54.41; H, 5.58; Cl, 17.85; N, 14.10. Found: C, 54.55; H, 5.53; Cl, 17.9; N, 13.82.

N-Phenylisatoic Anhydride.—A solution of 5 g. of N-phenylanthranilic acid[7] in 20 ml. of ethyl chloroformate was heated under reflux for 10 hr. The excess ethyl chloroformate was removed *in vacuo* on a rotary evaporator. The residual solid amounted to 3.6 g., m.p. 172–179°. Recrystallization of the product from ethanol raised the melting point to 177–179°; λ_{max} (anhydride C=O) 5.64, 5.76 μ.

Anal. Calcd. for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.21; H, 3.83; N, 5.65.

2-Anilino-N-ethylbenzamide was prepared from N-phenylisatoic anhydride and 33% aqueous ethylamine. After recrystallization from cyclohexane, the analytical sample had m.p. 73–75°; λ_{max} (C=O) 6.14, (amide II) 6.48 μ.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.86; H, 6.85; N, 11.74.

3,4,5,6-Tetrachloro-2-chloromethylamino-N-ethylbenzamide.—A solution of 4 g. of Ib in 30 ml. of sulfuryl chloride was heated under reflux for 1 hr. The excess sulfuryl chloride was removed *in vacuo* on a rotary evaporator. The residue was recrystallized from benzene–petroleum ether (b.p. 30–60°) affording 2.1 g. of product, m.p. 130–131.5°; λ_{max} (C=O doublet) 5.96, 6.06, (amide II) 6.58 μ.

The expected hydrogen ratio of 3:2:2 in the n.m.r. spectrum was confirmed by the following resonance signals (in δ-values): triplet centered at 1.15 ($-CH_3$), multiplet centered at 3.32 ($-CH_2$), and a singlet at 3.42 ($-CH_2Cl$).

Anal. Calcd. for $C_{10}H_9Cl_5N_2O$: C, 34.27; H, 2.59; Cl, 50.59; N, 7.99. Found: C, 34.19; H, 3.16; Cl, 50.0; N, 7.96.

Acknowledgment.—The authors are indebted to Ronald D. Stewart for his technical assistance, to Dr. Gordon Ellis and staff for the spectral and microanalytical results, and to Mr. Bruce Hofmann for his helpful comments concerning the infrared spectra.

(7) N-Phenylanthranilic acid is available from Aldrich Chemical Co., Inc., Milwaukee, Wis.

Reactions of Mixed Acetals with Di-*t*-butyl Peroxide[1]

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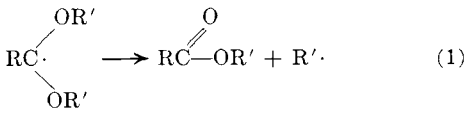
Received March 24, 1964

The mixed acetals of acetaldehyde undergo extensive fragmentation in reactions induced by di-*t*-butyl peroxide at 130°. The products of these reactions—namely, aldehydes, ketones, acetate esters, and hydrocarbons—can be explained in terms of β-elimination reactions of alkyl radicals from α-alkoxyalkyl free radicals. A comparison of the amounts of the acetate esters formed in these reactions gives the relative ease of β-elimination of alkyl radicals from the acetal-derived radicals $CH_3\dot{C}OR(OR')$. The relative β-elimination rates of various alkyl radicals from such acetal-derived radicals are discussed in terms of resonance and steric and polar factors.

Acetals have been shown to undergo rather extensive fragmentation in reactions induced by the thermal decomposition of di-*t*-butyl peroxide. In most cases, the major product of the reaction is an ester which results from the β-elimination of an alkyl radical from an α,α-dialkoxyalkyl radical as shown in eq. 1. For



(1)

example, ethyl butyrate was obtained from the reaction of diethyl-*n*-butyral and di-*t*-butyl peroxide.[3] Similar reactions of cyclic acetals yield esters which are rearrangement products of the acetal as evidenced by the formation of methyl valerate from 2-methoxytetrahydropyran,[4] benzoate esters in the reactions of the cyclic acetals obtained from benzaldehyde and 1,2-glycols and 1,3-glycols,[5] and ethyl alkanoates in the photochemically induced reactions of the acetals obtained from ethylene glycol with various aldehydes.[6] The formation of aldehydes and ketones as products in these reactions results from similar fragmentation reactions of radicals formed by the abstraction of α-hydrogens from the alcohol moieties of the acetal.

The present study is concerned with the reactions of di-*t*-butyl peroxide with acetals of acetaldehyde having two different alkyl groups. Such mixed acetals are readily prepared by the acid-catalyzed reaction of a vinyl ether with an alcohol. Table I lists the mixed acetals used for our studies which were prepared in 40–

(1) This work was supported by a grant from the National Science Foundation.

(2) Phillips Petroleum Research Fellow, 1963–1964. Taken from the thesis submitted by D. T. W. in partial fulfillment of the requirements for the Ph.D. degree from the University of Kansas, 1964.

(3) L. P. Kuhn and C. Wellman, *J. Org. Chem.*, **22**, 774 (1957).

(4) E. S. Huyser, *ibid.*, **25**, 1820 (1960).

(5) E. S. Huyser and Z. Garcia, *ibid.*, **27**, 2716 (1962).

(6) D. Elad and R. D. Youssefyeh, *Tetrahedron Letters*, **No. 30**, 2189 (1963).