EXPERIMENTAL

Hippuric-carboxyl-C^{14} acid. Glycine-1-C^{14} (3.48 mC./mM.; 0.5 mC. total activity; 10.8 mg.) was dissolved in water, and diluted to 10 ml. in a 10-ml. volumetric flask. Five cubic centimeters of this solution was pipeted into a solution prepared by dissolving 5.4 g. of inactive glycine and 12.5 g. of sodium hydroxide in 75 ml. of water. Benzoyl chloride (10 g.; 8.5 ml.) was then added and the mixture shaken vigorously until solution of the benzoyl chloride was complete. The solution was then acidified, filtered with suction, washed with water, and pressed as free of water as possible. The crude mixture was thoroughly mixed in the filter with two separate portions of ethyl ether and filtered. The yield of crude hippuric acid was 10 g. (78%).

2-Phenyl-4-ethoxymethylene-5-oxazolone-5-C^{14}. The 10 g. of hippuric acid obtained in the preceding preparation was mixed with 10 g. of inactive hippuric acid, added to a flask containing 12 ml. of acetic anhydride and 20 ml. of ethyl orthoformate and treated as previously described.[4c] The yield of oxazolone was 5 g. (22%).

2-Phenyloxazole-4-carboxylic-carboxyl-C^{14} acid. The hydrolysis and rearrangement of the oxazolone were carried out according to the procedure of Cornforth and Cookson.[5] The yield of a 2-phenyloxazole-4-carboxylic acid was 1.2 g. (67%).

Decarboxylation of 2-phenyloxazole-4-carboxylic-carboxyl-C^{14} acid. The acid was decarboxylated by distilling over copper-(II) oxide (bath temperature 270–280°). The carbon dioxide was absorbed in 0.2*N* barium hydroxide solution. The precipitated barium carbonate was isolated by filtration, washed successively with distilled water, acetone and ether, dried, and then counted.

The oxazole distillate was dissolved in ether and washed with aqueous sodium bicarbonate. The ether solution was dried, the ether evaporated, and the residual 2-phenyloxazole counted. The melting point of the picrate was 115–116° and was undepressed when mixed with an authentic specimen.

Acknowledgment. The authors are grateful to the University of Wichita for a special grant for financial support of this investigation.

CHEMISTRY DEPARTMENT
UNIVERSITY OF WICHITA
WICHITA 8, KAN.

(5) J. W. Cornforth and E. Cookson, *J. Chem. Soc.*, 1086 (1952).

The Free Radical Induced Rearrangement of 2-Methoxytetrahydropyran to Methyl Valerate

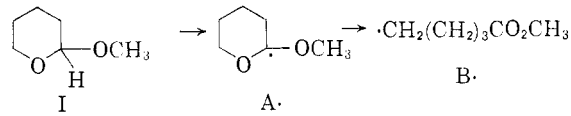
EARL S. HUYSER[1]

Received March 14, 1960

Acetals have been reported to react in a free radical chain reaction induced by alkoxy radicals yielding hydrocarbons and carbonyl-containing compounds as the main products.[2] The mechanism proposed to account for these products involves the abstraction of a hydrogen atom from the carbon atom adjacent to the oxygen producing a free radical, which undergoes decomposition into an alkyl radical and the carbonyl-containing compound.

$$R_2\dot{C}OR' \longrightarrow R_2C{=}O + R'\cdot$$

The investigation of 2-methoxytetrahydropyran (I) was undertaken to determine if this cyclic acetal could be rearranged to methyl valerate (II) *via* the following free radical chain sequence:



I A·

$$B\cdot + I \rightarrow CH_3(CH_2)_3CO_2CH_3 + A\cdot$$

II

The reaction of radical A· to form radical B· is the same type of elimination encountered in the reaction of Kuhn and Wellman. However, in the case of the cyclic radical A·, the elimination reaction amounts to a rearrangement of the radical.

Reactions in which di-*t*-butyl peroxide was thermally decomposed in the presence of 2-methoxytetrahydropyran have shown that rearrangement does in fact take place. Listed in Table I are the products obtained by heating 2-methoxytetrahydropyran with di-*t*-butyl peroxide at 120–130°.

TABLE I

PRODUCTS OBTAINED FROM THE DECOMPOSITION OF DI-*t*-BUTYL PEROXIDE IN 2-METHOXYTETRAHYDROPYRAN

	Moles	
	Run 1[a]	Run 2[b]
t-Butyl alcohol	0.21	0.18
Acetone	trace	trace
Methane	trace	trace
Methyl valerate	0.12	0.13
Residue	0.048 (m.w. 412)	(12.5 g.)
Recovered		
2-Methoxytetrahydropyran	0.08	0.25
Di-*t*-butyl peroxide	0.03	0.017

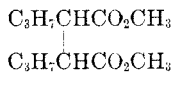
[a] 0.39 mole I, 0.15 mole di-*t*-butyl peroxide. [b] 0.48 mole I, 0.12 mole di-*t*-butyl peroxide.

The valerate ester was detected by the appearance of a strong ester carbonyl absorption at 5.76 μ in the infrared spectrum of the fraction collected at the boiling point of 2-methoxytetrahydropyran and methyl valerate (127°). The gas-liquid partition chromatographic analysis of this fraction showed the presence of two components with retention times corresponding to methyl valerate and 2-methoxytetrahydropyran. Chemical evidence of a valerate ester was obtained by preparation of the *p*-toluidide of valeric acid from the mixture. Conversion of the methyl ester to the *n*-butyl ester through an ester exchange reaction yielded *n*-butyl valerate which could be separated by distillation.

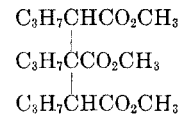
(1) Present address: Department of Chemistry, University of Kansas, Lawrence, Kan.

(2) L. P. Kuhn and C. Wellman, *J. Org. Chem.*, 22, 774 (1956).

The molecular weight of the residue obtained in Run 1 was 412. This implies that there are 3.56 methyl valerate or 2-methoxytetrahydropyran units per mole of residue. The formation of derivatives of succinic and tricarballylic acid esters by decomposition of peroxides in the presence of esters has been reported by Karasch, Jensen, and Urry.[3] This suggests that the residue in this reaction may well be formed by similar free radical reactions of methyl valerate leading to structures such as IIIa and IIIb. The infrared spectrum of the residue of

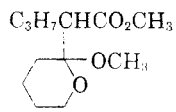


IIIa

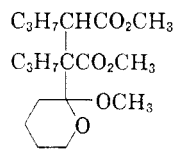


IIIb

Run 1 was very similar to that of the radical coupling product obtained from the reaction of methyl valerate and di-*t*-butyl peroxide. This spectrum does, however, contain several absorption bands (9.25, 9.45, and 9.68 μ) which are similar in wave length, intensity ratio, and band shape to 2-alkyl substituted 2-methoxytetrahydropyran. This suggests that part of the radical coupling reactions involve radical A· yielding structures such as IIIc and IIId in the residue. The molecular



IIIc

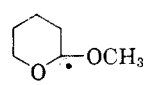


IIId

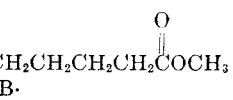
weight of the residue indicates that tetramers and probably higher molecular weight coupling products are also present.

These products and their observed distribution can be satisfactorily accounted for by the following sequence of reactions:

1) $(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO\cdot$

2) $(CH_3)_3CO\cdot + I \longrightarrow (CH_3)_3COH +$ 

A·

3) A· $\longrightarrow$ 

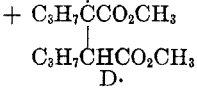
B·

4) B· + I $\longrightarrow$ II + A·

5) $(CH_3)_3CO\cdot$, A· or B· + II $\longrightarrow$ $(CH_3)_3COH$ + $CH_3CH_2CH_2\dot{C}HCO_2CH_3$

or I or II C·

6) $2C\cdot \longrightarrow$ IIIa

7) $(CH_3)_3CO\cdot$, A· or B· + IIIa $\longrightarrow$ $(CH_3)_3COH$ or I or II + 

D·

8) C· + D· $\longrightarrow$ IIIb

8b) A· + C· $\longrightarrow$ IIIc

8c) A· + D· $\longrightarrow$ IIId

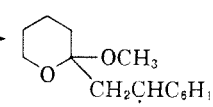
In reactions leading to radical coupling products, a relationship exists between the amount of initiator and the amount of coupling products. The stoichiometry requires one mole of initiator per mole of dimeric product and an additional mole of initiator for each additional unit in the product. The residue in Run 1, 0.047 mole of material with an average of 3.56 units per molecule, requires 0.12 mole of initiator which is in agreement with the peroxide consumed in the reaction.

The presence of radical B· in the reaction mixture was demonstrated by employing a terminal olefin, 1-octene, as the radical scavenger. Addition of radical B· to 1-octene would give the adduct radical which on chain transfer with I would yield methyl tridecanoate as the 1:1 addition product.

9) B· + $C_6H_{13}CH{=}CH_2 \longrightarrow C_6H_{13}CH(CH_2)_5CO_2CH_3$

10) $C_6H_{13}CH(CH_2)_5CO_2CH_3$ + I $\longrightarrow$ $C_{12}H_{25}CO_2CH_3$ + A·

The presence of methyl tridecanoate in the 1:1 addition product was confirmed by conversion of the ester to the *p*-toluidide. The infrared spectrum of the 1:1 addition product, however, indicated the presence of an undetermined amount of material containing a tetrahydropyran ring. Although it has not been specifically identified, the appearance of absorption bands at 9.25, 9.45, and 9.68 μ which are similar in wave length, intensity ratio, and band shape to those of a 2-alkyl-2-methoxytetrahydropyran, indicates that the material may be 2-octyl-2-methoxytetrahydropyran resulting from the addition of the unrearranged radical A· to the terminal olefin.

A· + $C_6H_{13}CH{=}CH_2 \longrightarrow$  11

EXPERIMENTAL[4]

The 2-methoxytetrahydropyran was prepared by a method described previously[5] and distilled at 63–64° at 85 mm.; n_D^{25} 1.4227. The di-*t*-butyl peroxide (Shell Chemical Co.) was redistilled before using; b.p. 47° at 75 mm.; n_D^{25} 1.3887. A 10-foot column packed with Dow Corning 550 Silicone Fluid on Celite with helium as the carrier gas was used for the gas-liquid partition chromatographic analysis.

(3) M. S. Karasch, E. V. Jensen, and W. H. Urry, *J. Org. Chem.*, **10**, 386 (1945).

(4) All melting points and boiling points are uncorrected. The author is indebted to Dr. W. J. Potts of the Spectroscopy Laboratory of the Dow Chemical Co. for aid in interpreting the infrared spectra.

(5) G. F. Wood and D. M. Kramer, *J. Am. Chem. Soc.*, 69, 2246 (1947).

Reaction of 2-methoxytetrahydropyran with di-t-butyl peroxide. A reaction mixture consisting of 46 g. (0.39 mole) of 2-methoxytetrahydropyran and 21.5 g. (0.15 mole) of di-*t*-butyl peroxide was heated at 120–125° for 44 hr. During the course of the heating, material boiling at 83–90° was distilled through an 8-inch Vigreux column as fast as it was formed. At the end of the heating period the reaction mixture was distilled through the same column and material boiling up to 120° was combined with the earlier cut. The combined fractions (21.0 g.) were analyzed by infrared as 0.21 mole of *t*-butyl alcohol and 0.03 mole of unchanged di-*t*-butyl peroxide. The reaction mixture was further distilled until the pot temperature reached 200° yielding 23 g. of material boiling at 120–129°. Analysis of this fraction by gas-liquid partition chromatography showed two peaks, with retention times identical to 2-methoxytetrahydropyran and methyl valerate. Infrared analysis of the mixture showed a very strong ester carbonyl absorption at 5.76 μ. Both infrared analysis and gas-liquid partition chromatography showed the ester content of the mixture to be 40%. The distillation residue amounting to 19.5 g. had a molecular weight of 412. The infrared spectrum of the residue showed it to consist mainly of a product similar to that obtained from the reaction of di-*t*-butyl peroxide and methyl valerate with additional absorption bands at 9.25, 9.45 and 9.68 μ.

p-Toluidide of valeric acid. A portion of the ester-containing mixture was added to the reaction mixture of ethylmagnesium bromide and *p*-toluidine in ether. Hydrolysis yielded the *p*-toluidide of *n*-valeric acid which after recrystallization from dilute alcohol melted at 70°; reported[6] m.p. 70°. A mixed melting point with an authentic sample showed no depression.

n-Butyl valerate. In another reaction 56 g. (0.48 mole) of 2-methoxytetrahydropyran and 17.5 g. (0.12 mole) of di-*t*-butyl peroxide were heated at 125–130° for 23 hr. During the course of the heating, 16.5 g. of material was distilled through an 8-inch Vigreux column at 82–85° which on infrared analysis proved to consist of 13.5 g. (0.18 moles) of *t*-butyl alcohol, a trace amount of acetone, and 2.5 g. of unchanged peroxide (0.017 mole). Further distillation at the end of the heating period yielded 42 g. of material boiling at 126–128° leaving a high boiling residue (pot temperature 210°) amounting to 12.5 g. Infrared analysis of the distillate showed it to consist of 32% methyl valerate (0.13 mole) and the remainder, unchanged 2-methoxytetrahydropyran. This mixture was refluxed for 6 hr. in 100 g. of *n*-butyl alcohol containing 0.025 g. of metallic sodium. During the course of the refluxing, 4.2 g. of methyl alcohol (0.13 mole) were removed by distillation through an 8 inch Vigreux column. The unchanged *n*-butyl alcohol and 2-methoxytetrahydropyran were removed by further distillation. The infrared spectrum of this mixture showed no ester carbonyl present. The remaining material was *n*-butyl valerate which distilled at 119–121° at 104 mm. (n_D^{25} 1.4143) and amounted to 17 g. (0.11 mole). The infrared spectrum of this material was identical with that of an authentic sample of *n*-butyl valerate.

The reaction of 2-methoxytetrahydropyran and 1-octene. Over a period of 24 hr. a solution consisting of 1-octene (33.6 g., 0.30 mole) and di-*t*-butyl peroxide (8.8 g., 0.06 mole) was slowly added to 2-methoxytetrahydropyran (150 g., 1.29 moles) heated to reflux temperature (127°). On distillation through an 8 inch Vigreux column, the reaction mixture yielded about 6 g. of *t*-butyl alcohol and 124 g. of unchanged 2-methoxytetrahydropyran. The residue was distilled through a 12-inch Holzmann column and yielded a fraction amounting to 6.0 g. (b.p. 90–110° at 0.7 mm., n_D^{25} 1.4430) which on infrared examination was found to consist mainly of methyl tridecanoate. Absorptions at 9.25, 9.45, and 9.68 μ in the infrared spectrum of the sample indicate the presence of a pyran ring but are different from those of 2-methoxytetrahydropyran. Reaction of a portion of the 1:1 addition product with the reaction mixture obtained from ethylmagnesium bromide and *p*-toluidine yielded the *p*-toluidide of *n*-tridecanoic acid; m.p. 87–88°, reported[7] m.p. 87°. A high boiling residue amounting to 30 g. remained after distillation of the 1:1 addition product (pot temperature 150°), presumably telomeric products.

E. C. Britton Research Laboratory
The Dow Chemical Co.
Midland, Mich.

(6) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 222.

(7) W. H. Urry and E. S. Huyser, *J. Am. Chem. Soc.*, **75**, 4876 (1953).

Adducts with *N*-Substituted Acrylamides[1]

Irwin L. Honigberg[2] and Walter H. Hartung[3]

Received February 23, 1960

Acrylamides, especially the *N*-substituted products, appear as attractive reagents for the synthesis of isomers and analogs of amino acids and peptide-like compounds. The reactions which come under consideration may be summarized as in Fig. 1. Reactions of type (c) are adaptations of the Michael reaction[4] and of type (b) have been employed by Mattocks and Hartung.[5]

EXPERIMENTAL

Acrylamides. By allowing acrylyl chloride[6] to react with an appropriate amine, the following *N*-substituted acrylamides were obtained: Acrylanilide[7] (I), m.p. 105–106°; *p*-acrylotoluidide[8] (II), m.p. 140–141°; diethyl acrylamidomalonate[9] (III), $C_{10}H_{15}NO_5$, yield 56%, m.p. 106–107°; ethyl acrylamidoacetate[10] (IV); diethyl acrylamidobenzylmalonate[11,12] (V), $C_{17}H_{21}NO_5$, yield 62%, m.p. 84–86°.

From cinnamyl chloride[13] and diethyl aminomalonate was

(1) No. 21 in Amino Acid Series. For No. 20 see L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **24**, 1943 (1959). Work done at the University of North Carolina.

(2) Supported in part by funds from the Sterling-Winthrop Research Foundation and in part by the American Foundation for Pharmaceutical Education. This assistance is gratefully acknowledged. Present address: Midwest Research Institute, Kansas City, Missouri.

(3) Present address: Medical College of Virginia, Richmond, Virginia.

(4) *Cf.* C. S. Marvel and M. P. Stoddard, *J. Org. Chem.*, **3**, 198 (1938); J. R. Shekelton and C. D. Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

(5) A. M. Mattocks and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 2018 (1946).

(6) Prepared by the procedure of H. C. Brown, *J. Am. Chem. Soc.*, **60**, 1325 (1938), and C. H. Stempel, *et al.*, *J. Am. Chem. Soc.*, **72**, 2299 (1950), in yields of 70–80%.

(7) M. Moureu, *Bull. soc. chim. France* [3] 421 (1893).

(8) M. Moureu, *Bull. soc. chim. France* [3] 422 (1893).

(9) Calcd.: N, 6.11. Found: N, 5.95, 6.13.

(10) See under compound IX below.

(11) Calcd.: N, 4.37. Found: N, 4.24, 4.14.

(12) The intermediate is described by J. H. R. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc.*, **41**, 578 (1952).

(13) H. Meyer, Sitzber., *Akad. Wiss. Wien, Math. naturiv. Kl. Abt IIB;* **110**, 329 (1901).