[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOPE COLLEGE]

The Course of Ring Opening of Glycidyl Ethers with Nucleophilic Reagents

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RECEIVED MARCH 9, 1953

The course of ring opening of ethyl and phenyl glycidyl ethers has been studied with such representative nucleophilic reagents as ethyl malonate, ethyl ethylmalonate, ethyl cyanoacetate and ethyl acetoacetate using molar equivalents of base. In all cases, ring opening was found to occur at the primary carbon atoms to give a series of α-substituted-γ-valerolactones.

Although the literature contains frequent references to the addition to alkene oxides of such nucleophilic reagents as the respective anions of malonic ester,[1-6] substituted malonic esters,[7,8] acetoacetic ester[9-12] and cyanoacetic ester,[13] there is only one reference[14] to the addition of nucleophilic reagents (malonic ester) to glycidyl ethers. The purpose of this paper is to report on a study of the chemical reactivity of this interesting class of compounds in relation to their condensation with representative nucleophilic reagents.

Furthermore, in the light of present interest in the direction of ring opening in S_N2 attack on unsymmetrical epoxides, we have observed that in the case of the glycidyl ethers studied the attack by the nucleophilic reagent occurs preferentially at the unsubstituted or primary carbon of the terminal epoxides. Recent evidence[9] would indicate that in the condensation of phenyl glycidyl ether with the ethyl cyanoacetate or ethyl acetoacetate anion, ring opening might conceivably take place in either direction. However, we were unable to demonstrate attack at the secondary carbon in detectable amounts. This is in accord with all presently held theoretical considerations.

The recent study by Adams and VanderWerf[9] of the base-catalyzed condensation of acetoacetic ester with unsymmetrical epoxides has indicated that, in this case at least, the allylic resonance of such epoxides as styrene oxide and 3,4-epoxy-1-butene may have the effect of lowering the energy of the transition state involved in nucleophilic attack at the secondary carbon atom. In the case of 3,4-epoxy-1-butene, attack took place at both the primary and secondary carbons, apparently with equal ease. This was interpreted as evidence that the effect of the allylic resonance outweighed the steric factors which would favor attack at the primary carbon.

(1) (a) W. Traube and E. Lehmann, *Ber.*, **32**, 720 (1899); (b) **34**, 197 (1901).
(2) S. Coffee, *Rev. trav. chim.*, **42**, 387 (1923).
(3) K. G. Pakendorf, *Compt. rend. acad. sci. U. S. S. R.*, **27**, 956 (1940).
(4) M. Mousseron, *et al.*, *Bull. soc. chim. France*, 629 (1946).
(5) C. J. Cavallito, D. M. Fruehauf and J. H. Bailey, THIS JOURNAL, **70**, 3724 (1948).
(6) R. R. Russell and C. A. VanderWerf, *ibid.*, **69**, 11 (1947).
(7) E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, *ibid.*, **72**, 488 (1950).
(8) G. Van Zyl and E. E. van Tamelen, *ibid.*, **72**, 1357 (1950).
(9) R. M. Adams and C. A. VanderWerf, *ibid.*, **72**, 4368 (1950).
(10) W. Traube and E. Lehmann, *Ber.*, **34**, 1971 (1901).
(11) I. L. Knunyantz, G. V. Chelintsev and E. D. Osetrova, *Compt. rend. acad. sci. U.S.S.R.*, **1**, 315 (1934).
(12) G. V. Chelintsev and E. D. Osetrova, *J. Gen. Chem.* (*U.S.S.R*), **7**, 2373 (1937).
(13) S. A. Glickman and A. C. Cope, THIS JOURNAL, **67**, 1012 (1945).
(14) R. Rothstein and J. Ficini, *Compt. rend.*, **234**, 1293 (1952).

For the present study, two representative glycidyl ethers were selected. Ethyl glycidyl ether (I) was prepared as a typical member of the saturated type. Phenyl glycidyl ether (II) was chosen as the unsaturated representative, possessing the strong resonance energy of the benzene ring. In the latter, however, the effect of this resonance energy is limited to whatever inductive effects may be manifested across the oxygen atom of the ether linkage and the two carbons of the chain. This effect would be expected to be slight compared to the strong steric effect of the bulky phenoxy group. Adams and VanderWerf[9] found that with acetoacetic ester, although the resonance effects in styrene oxide ring opening would be stronger than in the case of 3,4-epoxy-1-butene, the difference in the steric influences of the two presumably permitted ring opening to take place at both primary and secondary carbons only in the latter. The fact that we could demonstrate attack at only the terminal carbon suggests that with phenyl glycidyl ether too, the steric factors are of relatively greater importance.

The representative nucleophilic reagents employed in this study were the anions of ethyl malonate, ethyl ethylmalonate, ethyl acetoacetate and ethyl cyanoacetate. In all cases the condensations were carried out with molar equivalents of base. This procedure was rigidly adhered to because Glickman and Cope[13] have shown that the reaction takes a different course in the condensation of alkene oxides with cyanoacetic ester in the presence of one-tenth molar equivalent amounts of base.

The sole product isolated in the base-catalyzed condensation of phenyl glycidyl ether with malonic ester was α-carbethoxy-δ-phenoxy-γ-valerolactone (III) indicating that the attack of the malonic ester anion occurred at the primary position. The structure of III was proven by hydrolysis to an α-carboxy lactone which was identical with the α-carboxy-δ-phenoxy γ-valerolactone (XII) previously described by Fischer and Kramer.[15] Subsequent bromination yielded the known α-bromo-α-carboxy-δ-(4-bromophenoxy)-γ-valerolactone (XIII)[15] to further confirm the structure of III.

In the analogous condensation of the saturated glycidyl ether I with the malonic ester anion, only α-carbethoxy-δ-ethoxy-γ-valerolactone (IV) was obtained. The structure of IV was proven by hydrolysis and decarboxylation to the known δ-ethoxy-γ-valerolactone.[16] Synthesis of IV was also accomplished by treating malonic ester with epichlorohydrin and condensing the resulting α-carbethoxy-δ-chloro-γ-valerolactone (XX) with sodium ethylate to give α-carbethoxy-δ-ethoxy-γ-

(15) E. Fischer and A. Kramer, *Ber.*, **41**, 2733 (1908).
(16) H. Leuchs, M. Giua and J. F. Brewster, *Ber.*, **45**, 1965 (1912).

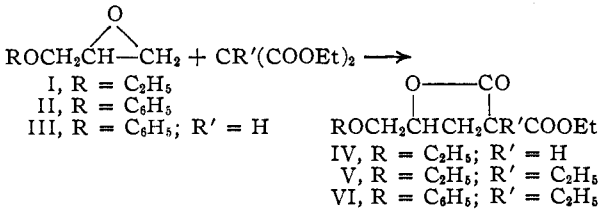
TABLE I

Nucleophilic reagent, ethyl	Product	Formula	Yield %	B.p. or m.p., °C.	Mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
PHENYL GLYCIDYL ETHER									
Malonate	III	$C_{14}H_{16}O_5$	44.2	215–217	1	63.63	63.97	6.06	6.19
Ethylmalonate	VI	$C_{16}H_{20}O_5$	42.8	198–200	2	65.73	65.65	6.90	6.66
Acetoacetate	VII	$C_{13}H_{14}O_4$	76.9	196–197	2	66.66	66.83	5.98	6.01
Cyanoacetate	XI	$C_{12}H_{11}O_3N$	54	M. 136–136.5		66.33	66.43	5.10	5.14
ETHYL GLYCIDYL ETHER									
Malonate	IV	$C_{10}H_{16}O_5$	52.1	173–176	9	55.54	55.17	7.46	7.35
Ethylmalonate	V	$C_{12}H_{20}O_5$	34.2	145–148	1	59.01	59.02	8.25	8.09
Acetoacetate	X	$C_9H_{14}O_4$	46.0	159–162	12–13	58.06	57.97	7.52	7.55
Cyanoacetate	XIV	$C_8H_{11}O_3N$	41.6	184–186	4	56.79	56.66	6.55	6.75

valerolactone. This structure of IV is reasonable in light of the work of Russell and VanderWerf,[6] who have shown that steric factors predominate in determining the direction of attack by the malonic ester anion. They have demonstrated that even in the cases of epoxides possessing allylic resonance, attack at the terminal carbon occurred exclusively with malonic ester.

In the condensation of I with ethyl ethylmalonate, the corresponding α-ethyl-α-carbethoxy-δ-ethoxy-γ-valerolactone (V) was the product. Its structure was proven by hydrolysis and decarboxylation to α-ethyl-δ-ethoxy-γ-valerolactone (XV). By treating epichlorohydrin with the ethyl ethylmalonate anion according to a known method,[17] α-ethyl-α-carbethoxy-δ-chloro-γ-valerolactone (XVI) was obtained. This compound was condensed with sodium ethylate and the product was decarboxylated to yield XV.

The analogous condensation of II with ethyl ethylmalonate yielded α-ethyl-α-carbethoxy-δ-phenoxy-γ-valerolactone (VI) the structure of which was proven by decarboxylating it to α-ethyl-δ-phenoxy-γ-valerolactone (XVII). The chlorolactone XVI reacted with sodium phenate and the product upon decarboxylation was found to be identical with XVII.



I, R = C_2H_5
II, R = C_6H_5
III, R = C_6H_5; R′ = H

IV, R = C_2H_5; R′ = H
V, R = C_2H_5; R′ = C_2H_5
VI, R = C_6H_5; R′ = C_2H_5

Acetoacetic ester was found to condense with phenyl glycidyl ether to yield only α-acetyl-δ-phenoxy-γ-valerolactone (VII). This was isolated as a pure crystalline solid. The structure of VII was proven by decarboxylation to 1-phenoxy-5-keto-2-hexanol (VIII) followed by reduction to 1-phenoxy-2-hexanol (IX) by the Clemmensen reduction. Synthesis of IX was also accomplished by the condensation of phenol with 1,2-epoxyhexane, and the two products were shown to have identical infrared spectra. It is interesting to note here that our infrared studies provided the incidental observation that a small amount of phenol attacked the 1,2-epoxyhexane at the secondary carbon atom to yield the primary alcohol 2-phenoxy-1-hexanol, although the major portion attacked in the conventional manner to produce the secondary alcohol IX. The compound 2-phenoxy-1-hexanol could not possibly be obtained by the reaction of phenyl glycidyl ether with ethyl acetoacetate. These findings are not surprising in view of the work of Sexton and Britton[18] whose infrared studies revealed that the reaction of phenols with propylene oxide in the presence of an alkaline catalyst gives secondary alcohol ethers, and in the presence of an acid catalyst both primary and secondary ethers are obtained.

The reaction of ethyl glycidyl ether with acetoacetic ester yielded a high boiling liquid product, α-acetyl-δ-ethoxy-γ-valerolactone (X) the structure of which was proven by decarboxylation to 1-ethoxy-5-keto-2-hexanol (XVIII) which was subsequently oxidized to 1-ethoxy-2,5-hexanedione (XIX). The 2,4-dinitrophenylhydrazones of XVIII and XIX were prepared. The fact that oxidation of XVIII yielded a dione rather than a ketoacid showed that the ring opening occurred at the primary carbon atom.

The base-catalyzed condensation of phenyl glycidyl ether with cyanoacetic ester yielded only the single product, α-cyano-δ-phenoxy-γ-valerolactone (XI) which was isolated as a pure crystalline solid melting at 136–136.5° (cor.). The structure of XI was proven by alkaline hydrolysis to XII, which was shown to be identical with the α-carboxy-δ-phenoxy-γ-valerolactone described by Fischer and Kramer,[15] and also obtained by hydrolysis of III above. Further confirmation of the structure of XII was obtained by bromination to yield the known compound, α-bromo-α-carboxy-δ-(4-bromophenoxy)-γ-valerolactone (XIII).[15]

Addition of ethyl cyanoacetate to ethyl glycidyl ether yielded a high boiling liquid product, α-cyano-δ-ethoxy-γ-valerolactone (XIV). The structure of XIV was proven by hydrolysis of the cyano group followed by decarboxylation to the known δ-ethoxy-γ-valerolactone.[16]

Experimental

Ethyl Glycidyl Ether (I).—Five hundred and fifty-five grams (6 moles) of epichlorohydrin was added in portions to 1104 g. (24 moles) of absolute ethanol containing 6.6 g. (5 ml.) of anhydrous stannic chloride as a catalyst in a three-liter three-necked round-bottom flask equipped with a Friedrichs condenser, mechanical stirrer, thermometer and dropping funnel. The reaction was started at 10°, and after approximately one-half of the epichlorohydrin was added,

(17) H. Beyer and H. Hohn, *Chem. Ber.*, **83**, 14 (1950).

(18) A. R. Sexton and E. C. Britton, THIS JOURNAL, **70**, 3606 (1948).

the temperature began to rise. The reaction was controlled with an ice-bath when the mixture began to reflux. After the initial reaction subsided somewhat, the mixture was refluxed for 20–30 minutes, cooled and neutralized with ammonium hydroxide. The excess alcohol was removed by distillation under reduced pressure, and the 1-chloro-3-ethoxy-2-propanol[19] was distilled from a 20-cm. Vigreux column. Six hundred fifty-five grams of material boiling at 80–81° (16 mm.), 71° (2 mm.) was collected. The yield was 87% of theoretical.

The halohydrin was converted to ethyl glycidyl ether by a known method.[20,21] Two moles of pulverized sodium hydroxide was added for every mole of the halohydrin. No solvent was used. After the sodium hydroxide was added, a spontaneous reaction set in, which was controlled with an ice-bath when the temperature reached 90°. After the reaction subsided, the mixture was allowed to cool to room temperature, and stirred for 3.5 hours without heating. It was then filtered and dried with anhydrous sodium sulfate, filtered again and distilled from the column described above to yield ethyl glycidyl ether, b.p. 123–124° (745 mm.). The yield was 73%.

Phenyl Glycidyl Ether (II).—In a one-liter three-necked round-bottom flask equipped as above, the following were added in order: 95 g. (1 mole) of phenol dissolved in 100 ml. of dioxane, 40 g. (1 mole) of sodium hydroxide, and 185 g. (2 moles) of epichlorohydrin. The mixture was stirred overnight without heating and was then heated for 8 hours at approximately 70°. The mixture was filtered, washed twice with dioxane and distilled from the above mentioned column under reduced pressure. Ninety grams of phenyl glycidyl ether was collected, b.p. 137–140° (23 mm.), yield 60%, $n^{25}D$ 1.5289.

α-Carbethoxy-δ-ethoxy-γ-valerolactone (IV).—In a 500-ml. flask equipped as above, 9.2 g. (0.4 mole) of lustrous metallic sodium was dissolved in 200 ml. of absolute ethanol. The mixture was cooled to 50° and 64 g. (0.4 mole) of ethyl malonate was added. At 35°, 40 g. (0.4 mole) of ethyl glycidyl ether was added dropwise with stirring during a period of 20 minutes. A spontaneous exothermic reaction ensued which was controlled by external cooling. The reaction mixture was maintained at 50° for 2.5 hours and allowed to stand overnight. The mixture was cooled to 15° in an ice-bath and a slight excess of chilled glacial acetic acid was added. The excess alcohol was removed under reduced pressure. About 100 ml. of water was added, the oily layer was removed, and the aqueous layer was saturated with sodium chloride and extracted with 75-ml. portions of ether. The ether and oil layers were combined, washed once with water and dried overnight over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and 45 g. of α-carbethoxy-δ-ethoxy-γ-valerolactone was obtained, b.p. 173–176° (8–9 mm.), yield 52.1%, $n^{25}D$ 1.4460.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.17; H, 7.35.

Decarboxylation of IV.—Sixteen grams of IV (0.08 mole) was added to a solution of 7 g. (0.17 mole) of sodium hydroxide in 9 ml. of water in a 200-ml. flask and refluxed for one-half hour. Twenty-five ml. of water was added and the mixture was refluxed for 15 minutes more. After cooling the solution, concentrated hydrochloric acid was added until the solution was acid to congo red paper. It was then boiled until carbon dioxide ceased to be given off. The solution was then cooled and extracted three times with 30 ml. of ether. The extracts were dried with anhydrous sodium sulfate, then distilled to yield 6 g. of δ-ethoxy-γ-valerolactone (XXI),[16] b.p. 127–129° (14 mm.), $n^{25}D$ 1.4419.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H. 8.39. Found: C, 58.37; H, 8.45.

α-Carbethoxy-δ-chloro-γ-valerolactone (XX).—In a one-liter three-neck flask equipped as above, one mole of sodium malonic ester was prepared in 500 ml. of absolute ethanol. One hundred ten grams of epichlorohydrin was added slowly at 5–10° while the reaction flask was cooled, and allowed to stir overnight. The mixture was heated to 50° and made just acid to litmus with glacial acetic acid. The excess alcohol was removed under reduced pressure and 300 ml. of water was added, and the mixture shaken. The layers were separated and the aqueous layer was extracted twice with 100 ml. of ether. The extracts were combined and dried with anhydrous sodium sulfate. Distillation yielded 43 g. of α-carbethoxy-δ-chloro-γ-valerolactone,[10] b.p. 178–182° (11–12 mm.), $n^{25}D$ 1.4659, yield 21%.

α-Carbethoxy-δ-ethoxy-γ-valerolactone from XX.—Three and one-half grams of sodium (0.15 mole) was dissolved in 100 ml. of absolute ethanol and 20.7 g. (0.10 mole) of XX was added. The mixture was refluxed seven hours and the alcohol was removed under reduced pressure. One hundred and fifty milliliters of water was added, and the mixture shaken and separated. The aqueous layer was saturated with sodium chloride and extracted with ether. Twelve grams of IV was collected, b.p. 172–176° (8–9 mm.), 85% $n^{25}D$ 1.4460.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.31; H, 7.51.

α-Carbethoxy-δ-phenoxy-γ-valerolactone (III).—Sodium malonic ester (0.22 mole) was prepared in 125 ml. of absolute alcohol contained in a 500-ml. three-neck flask equipped as described above. Thirty-three grams (0.22 mole) of phenyl glycidyl ether was added dropwise at 35° over a period of about 30 minutes. A spontaneous reaction ensued which brought the solution to its boiling point. After refluxing for three hours it was allowed to stand overnight. The solution was then cooled to 15° and a slight excess of chilled glacial acetic acid was added. The mixture was worked up in the manner previously described and distilled from a modified Claisen flask. Twenty-seven grams of III was obtained; b.p. 215–217° (1 mm.), yield 44%.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.06. Found: C, 63.97; H, 6.19.

α-Carboxy-δ-phenoxy-γ-valerolactone (XII).—Five grams of III was saponified by refluxing with a solution of 2.5 g. of 85% potassium hydroxide in 3 ml. of water for 45 minutes. The resulting solution was cooled to 0°, and 5 ml. of cold water was added, and made acid to congo red with cold, concentrated hydrochloric acid. The oil which separated upon standing in the cold was removed and dried at 45–50° for a day. Upon rubbing with benzene–petroleum ether, solidification occurred. The acid was recrystallized from the same solvents, yield 2.6 g. (59%), m.p. 92.5–94° dec. A second recrystallization gave material sintering at 93–95° with decomposition. Fischer and Kramer[15] reported sintering at 93–96° with subsequent decomposition. Bromination yielded α-bromo-α-carboxy-δ-(4-bromphenoxy)-γ-valerolactone, XIII, m.p. 156° dec., yield 58%. The m.p. in the literature[15] is 157° dec., cor.

α-Ethyl-α-carbethoxy-δ-ethoxy-γ-valerolactone (V).—Sodium malonic ester (0.36 mole) was prepared in 175 ml. of absolute alcohol contained in a 500-ml. three-necked flask equipped as described above. Thirty-seven and two-tenths grams (0.36 mole) of ethyl glycidyl ether was added dropwise at 35° during about 30 minutes with external cooling. A spontaneous reaction ensued, but was controlled at 40° for 2 hours. The reaction mixture was cooled to 15° and worked up in the manner previously described. Thirty grams of V boiling 145–148° (1 mm.) was obtained, yield 34.2%, $n^{25}D$ 1.4462.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.01; H, 8.25. Found: C, 59.02; H. 8.04.

α-Ethyl-δ-ethoxy-γ-valerolactone (XV).—Seventy-six grams (0.30 mole) of V was decarboxylated in the same manner as was described in the decarboxylation of IV. Thirty-five grams of XV was collected boiling at 159° (20 mm.), $n^{25}D$ 1.4411.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.44; H, 9.15.

α-Ethyl-α-carbethoxy-δ-chloro-γ-valerolactone (XVI).—This compound was prepared by the method of Beyer and Hohn,[17] b.p. 170–175° (10 mm.), $n^{25}D$ 1.4518. The b.p. reported by Beyer and Hohn was 170–175° (10 mm.). One-tenth mole of XVI was condensed with sodium ethylate, in the same way that XX was. The product spontaneously decarboxylated to give 10 g. of XV, b.p. 159° (20 mm.), $n^{25}D$ 1.4410, yield 58%.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.85; H, 9.31.

(19) E. Fourneau and I. Ribas, *Bull. soc. chim. France*, [4] **39**, 1586 (1926).

(20) Nef, *Ann.*, **335**, 240 (1904).

(21) The above procedure represents a modification of the general method of preparation as outlined by the Shell Chemical Company.

α-Ethyl-α-carbethoxy-δ-phenoxy-γ-valerolactone (VI).—Thirty-three grams (0.22 mole) of phenyl glycidyl ether was added to a solution of 0.25 mole of sodium ethyl ethylmalonate and the mixture was maintained at 40° for 16 hours. The reaction was carried out and worked up as above. Twenty seven and one-half grams of VI was obtained, b.p. 198–200° (2 mm.), $n^{25}D$ 1.5187, yield 42.8%.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.73; H, 6.90. Found: C, 65.65; H, 6.66.

Decarboxylation of VI was carried out in the same manner as the decarboxylation of the other carbethoxy compounds to give α-ethyl-δ-phenoxy-γ-valerolactone (XVII), b.p. 177–180° (3 mm.), m.p. 38–39°. The over-all yield was 45%.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.06; H, 7.56.

α-Ethyl-δ-phenoxy-γ-valerolactone also was prepared by condensing XVI with phenol in the presence of sodium, then decarboxylating the resulting α-carbethoxy compound as in the above procedures, yield 53%.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.53; H, 7.57.

α-Acetyl-δ-phenoxy-γ-valerolactone (VII).—Fifty grams (0.3 mole) of phenyl glycidyl ether was added dropwise with stirring to a solution of 0.3 mole of sodium acetoacetate at 35° over a period of 20 minutes. The reaction mixture was maintained at 50° for 18 hours, cooled and worked up in the manner described above for the α-carbethoxy-γ-valerolactones. Fifty-four grams (76.9%) of VII was obtained, b.p. 196–197° (2 mm.).

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 5.98. Found: C, 66.83; H, 6.01.

α-Acetyl-δ-ethoxy-γ-valerolactone (X).—Thirty and six-tenths grams (0.3 mole) of ethyl glycidyl ether was added dropwise with stirring to a solution of 0.3 mole of sodium acetoacetate at 35°. The reaction mixture was maintained at 50° for 18 hours, cooled to 15° and worked up in the usual manner. Twenty-five and seven-tenths grams (46.0%) of X was obtained, b.p. 159–162° (12–13 mm.), $n^{25}D$ 1.4566.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.52. Found: C, 57.97; H, 7.55.

1-Ethoxy-5-keto-2-hexanol (XVIII).—This compound was prepared by decarboxylation of X using the method described by Adams and VanderWerf[9] for the decarboxylation of α-acetolactones. XVIII boiled at 124–126° (12–13 mm.), $n^{25}D$ 1.4412, 70%.

Anal. Calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.00; H, 10.06.

The 2,4-dinitrophenylhydrazone was prepared, m.p. 99–100° (uncor.).

Anal. Calcd. for $C_{14}H_{20}O_6N_4$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.60; H, 5.78; N, 16.63.

1-Ethoxy-2,5-hexanedione (XIX).—Sixty grams of ice and 85 ml. of 12 *N* sulfuric acid were mixed, cooled and added slowly to 64 g. (0.4 mole) of XVIII. The resulting mixture was added dropwise to 45 g. of sodium dichromate in a 500-ml. three-neck flask. After the initial reaction had subsided, the mixture was warmed on a steam-bath to 90° and allowed to stand overnight. The mixture was then neutralized with sodium carbonate and saturated with potassium carbonate. The saturated solution was extracted several times with ether and the extracts were dried and distilled. Twenty-six and one-half grams of 1-ethoxy-2,5-hexanedione was collected, b.p. 114° (16–17 mm.), $n^{25}D$ 1.4378, yield 42%.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.79; H, 9.00.

The di-(2,4-dinitrophenylhydrazone) was prepared, m.p. 210.8–211.5° (uncor.).

Anal. Calcd. for $C_{20}H_{22}O_9N_8$: C, 46.33; H, 4.28; N, 21.62. Found: C, 46.44; H, 4.34; N, 21.58.

1-Phenoxy-5-keto-2-hexanol (VIII).—Twenty-three and four-tenths grams (0.1 mole) of VII was added to 5 ml. of hydrochloric acid diluted to 10 ml. and heated at 50–60° until evolution of carbon dioxide ceased. The solution was cooled in an ice-bath and solid sodium hydroxide was added with stirring to almost neutralize the hydrochloric acid. The solution was saturated with potassium carbonate, and 1-phenoxy-5-keto-2-hexanol (VIII) separated as an oil. The mixture was extracted twice with ether, and the product distilled under reduced pressure. Twelve and one-half grams of VIII was recovered, b.p. 139–142° (24 mm.).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74. Found: C, 69.60; H, 7.54.

The 2,4-dinitrophenylhydrazone derivative was prepared, m.p. 136.5–137.5° (uncor.).

Anal. Calcd. for $C_{18}H_{19}N_4O_6$: C, 55.81; H, 4.83; N, 14.39. Found: C, 55.85; H, 4.87; N, 14.44.

1-Phenoxy-2-hexanol (IX).—Ten and four-tenths grams of VIII was reduced according to the Clemmensen method essentially as described in "Organic Reactions" (Vol. 1, p. 164). Three and six-tenths grams of the product, 1-phenoxy-2-hexanol (IX), was obtained, b.p. 153–157° (17 mm.).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.22; H, 9.34. Found: C, 74.32; H, 9.15.

1-Chloro-2-hexanol.—Hypochlorous acid was prepared according to the method described in reference 22. In a 5-liter round-bottom flask equipped with a sealed stirrer was placed 126 g. (1.5 moles), of hexene-1, and about one-fourth the calculated amount of hypochlorous acid solution. The mixture was stirred vigorously, and the temperature maintained at 15–20° until a 1-ml. test portion gave no color with hydriodic acid solution. When the first portion had reacted, a second was added and the process repeated. When the process was completed, the solution was saturated with sodium chloride and steam distilled. About 2.5 g. of distillate was collected, from which an oil separated when saturated with sodium chloride. The aqueous layer was extracted once with 250 ml. of ether. The extract and oil were combined and dried overnight with anhydrous sodium sulfate. The product was distilled under reduced pressure, yield 99 g. (48%), b.p. 78–83° (20 mm.).

1,2-Epoxyhexane.—In a 1-liter round-bottom flask fitted with a mechanical stirrer was placed a solution of 30 g. (0.75 mole) of sodium hydroxide in 175 ml. of water. To this solution was then added 99 g. (0.72 mole) of 1-chloro-2-hexanol. The mixture was stirred vigorously for about one hour. The stirring was stopped and the oily upper layer was separated and fractionated, b.p. 34–39° (21 mm.), yield 35.7 g. (50%), $n^{27}D$ 1.4053. The literature[23] reported b.p. 123–124° (atm.), $n^{19.5}D$ 1.4093.

1-Phenoxy-2-hexanol from 1,2-Epoxyhexane.—One-tenth mole (10 g.) of 1,2-epoxyhexane was added slowly to an ice-cooled solution of 0.45 g. of boron trifluoride (1 ml. of 45% solution) and 0.4 mole of phenol (37.6 g.) in 80 ml. of benzene with stirring. After 30 minutes the boron trifluoride was decomposed with water and the excess benzene and phenol was distilled off. Six and four-tenths grams of 1-phenoxy-2-hexanol (b.p. 152–155° (16 mm.)) was collected, yield 34%.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.22; H, 9.34. Found: C, 74.27; H, 9.13.

α-Cyano-δ-ethoxy-γ-valerolactone (XIV).—In a 500-ml. flask equipped as described above, 5.75 g. of metallic sodium (0.25 mole) was dissolved in 100 ml. of ethanol and cooled to 10°. Twenty-eight and three-tenths grams (0.25 mole) of ethyl cyanoacetate was added dropwise with stirring during ten minutes. The ice-bath was removed and the temperature was allowed to rise to 50° during one hour. At 50° sodium cyanoacetate dissolved and a vigorous exothermic reaction occurred which was controlled by external cooling. The resulting solution was heated at 60° for 16 hours. Most of the alcohol was removed under reduced pressure. Benzene (50 ml.) was added to the residue, followed by a mixture of 50 ml. of ice and water, and 25 ml. of 12 *N* hydrochloric acid. The benzene layer was separated, and the red aqueous layer extracted with benzene. The combined benzene solutions were washed successively with water, twice with saturated sodium bicarbonate and finally with water. After drying over anhydrous sodium sulfate, the benzene solution was concentrated and the product XIV was distilled under reduced pressure. The yield was 17.6 g. (41.6%), b.p. 184–186° (4 mm.), $n^{25}D$ 1.4531.

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.79; H, 6.55. Found: C, 56.66; H, 6.75.

(22) G. H. Coleman and H. F. Johnstone, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. 1, p. 158.

(23) B. Rothstein, *Bull. soc. chim.*, [5] **2**, 1936 (1935).

δ-Ethoxy-γ-valerolactone (XIX).—Twenty-five grams (0.15 mole) of XIV was refluxed with 42 g. of sodium hydroxide, dissolved in 350 ml. of water, for 24 hours. During this time ammonia was given off. The solution was then acidified with concentrated hydrochloric acid and refluxed for five hours more. The mixture was then filtered and extracted three times with ether, dried and distilled to yield 8 g. of δ-ethoxy-γ-valerolactone, b.p. 127–129° (14 mm.), $n^{25}D$ 1.4419, yield 36%.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.39; H, 8.45.

α-Cyano-δ-phenoxy-γ-valerolactone (XI).—In a 500-ml. flask equipped as above, 0.25 mole of sodium cyanoacetate was prepared and cooled to 10°. Thirty-seven and five-tenths grams (0.25 mole) of phenyl glycidyl ether was added and the reaction run as above. Most of the alcohol was removed under reduced pressure. Benzene (50 ml.) was added followed by a mixture of 50 ml. of ice and water and 25 ml. of 12 *N* hydrochloric acid. A copious, red precipitate came down which was filtered, washed with benzene and then with water to yield 51.5 g. (53.9%) of fine white crystals, XI, m.p. 136–136.5°.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.33; H, 5.10; N, 6.44. Found: C, 66.43; H, 5.14; N, 6.47.

α-Carboxy-δ-phenoxy-γ-valerolactone (XII).—Five grams (0.023 mole) of XI was refluxed with 50 ml. of 3 *N* sodium hydroxide for 6 hours during which time evolution of ammonia ceased. The solution was cooled and neutralized in an ice-bath with ice-cold 12 *N* hydrochloric acid. Most of the water was taken off under reduced pressure and the resulting mixture extracted twice with 30-ml. portions of benzene. The benzene extract was dried over anhydrous sodium sulfate and concentrated to about half its volume. The oil which separated crystallized upon rubbing with a benzene–petroleum ether mixture. Yield of XII was 4.2 g. (77.4%), m.p. 93–95° with decomposition.[15] Bromination yielded XIII, melting 156° dec.[15]

Acknowledgment.—The authors wish to thank the Research Corporation for a grant-in-aid supporting this project, and the Shell Chemical Corporation for a generous gift of epichlorohydrin.

HOLLAND, MICHIGAN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DEPAUW UNIVERSITY]

Trichloroaminoalcohols. II. 1,1,1-Trichloro-2-alkoxy-3-aminopropanes

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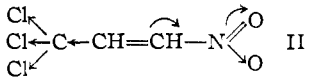
RECEIVED NOVEMBER 5, 1952

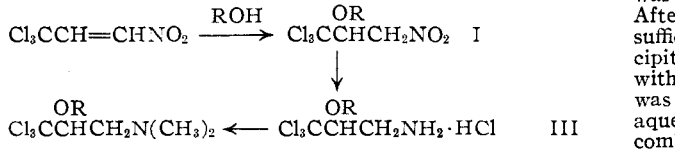
Starting with 1,1,1-trichloro-3-nitropropene, a series of 1,1,1-trichloro-2-alkoxy-3-nitropropanes, the corresponding amines and several of the dimethylamines have been prepared. A few of the latter two types of compounds show marked antispasmodic action.

Efforts to prepare 1,1,1-trichloro-2-alkoxy-3-nitropropanes (I) from a reaction between sodium alkoxides and the compound reported to be 1,1,1,2-tetrachloro-3-nitropropane have resulted in failure.[1] However, another approach has been suggested by numerous reports[2,3] of the addition of alcohols to nitroölefins in the presence of the corresponding sodium alkoxide or of the addition of the sodium alkoxide directly to the nitroölefin in an inert solvent. Hence, the previously prepared[1] 1,1,1-trichloro-3-nitropropene (II) was a potentially suitable intermediate. Since the inductive effect of the three chlorine atoms and the electromeric effect of the nitro group should make the middle



II

carbon a more positive center, it was anticipated that alcohols should add across the double bond of II with unusual ease. Indeed, this proved to be true. Warming II with an excess of various alcohols for one to four days afforded I in good yields. One thioether was also prepared.



Reduction of the nitro group of I to give the corresponding 1,1,1-trichloro-2-alkoxy-3-aminopropane hydrochloride (III) was carried out with stannous chloride and hydrochloric acid in yields of 16–65%. The desired product was not obtained from attempts to reduce the nitro group of the thioether.

Methylation of III with formaldehyde and formic acid according to the procedure of Clarke[4] gave 1,1,1-trichloro-2-alkoxy-3-dimethylaminopropane in 30–71% yields for those which were attempted.

Acknowledgment.—The authors thank Eli Lilly and Company for testing these compounds for pharmacological activity and for analysis of a number of them.

Experimental

1,1,1-Trichloro-2-alkoxy-3-nitropropanes. General Procedure.—A solution of 1,1,1-trichloro-3-nitropropene[1] (1 mole) in the alcohol (2 to 4 moles) was kept at 100–120° for 1 to 4 days. After distilling the alcohol, the product was distilled under reduced pressure. Data for these compounds are given in Table I.

1,1,1-Trichloro-2-alkoxy-3-aminopropane Hydrochloride. General Procedure.—The 1,1,1-trichloro-2-alkoxy-3-nitropropane (0.2 mole) was dissolved in 250 ml. of ethanol and heated to reflux. A solution of 292 g. of stannous chloride dihydrate (1.3 moles) in 205 ml. of concd. hydrochloric acid was then added during five minutes with good stirring. After refluxing for six hours, the mixture was cooled and sufficient concd. hydrochloric acid was added to cause precipitation, if necessary. The solid was filtered and mixed with 400 ml. of ether. A 10% solution of sodium hydroxide was added until all the tin hydroxides were dissolved. The aqueous layer was separated and extracted with ether. The combined ether layers were mixed thoroughly with excess concd. hydrochloric acid and the layers separated. The ether was evaporated. In some cases the residue was the major portion of the product. The aqueous acid layer was chilled and the solid filtered. In other cases this was the

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