160. *Influence of Poles and Polar Linkings on the Course pursued by Elimination Reactions. Part XXII. Wagner Rearrangement in the Hofmann Degradation.*

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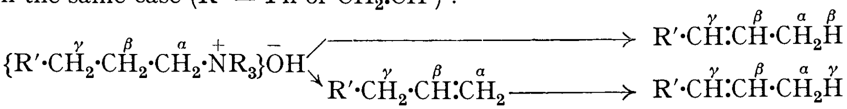
Although this series has been largely concerned with the study of β-hydrogen elimination from 'onium salts, illustrations have been given of the alternative of α-elimination with accompanying dimerisation. The remaining alternative, *viz.*, γ-elimination with an accompanying Wagner rearrangement, is now demonstrated :

$$\{R'R''CH\cdot\overset{+}{N}R_3\}\overset{-}{X} \longrightarrow (R'R''C:)_2 \qquad + HX + NR_3 \ (\alpha\text{-elimination})$$
$$\{R'R''CH\cdot CH_2\cdot\overset{+}{N}R_3\}\overset{-}{X} \longrightarrow R'R''C:CH_2 \qquad + HX + NR_3 \ (\beta\text{-} \quad ,, \quad)$$
$$\{R'R''CH\cdot CH_2\cdot CH_2\cdot\overset{+}{N}R_3\}\overset{-}{X} \longrightarrow R'R''C:CH\cdot CH_3 \quad + HX + NR_3 \ (\gamma\text{-} \quad ,, \quad)$$

β-Elimination is the normal reaction, involving neither octet disruption nor regrouping of atomic nuclei. It has been shown that α-elimination, which involves octet disruption, necessitates facilitating constitutional conditions. A similar requirement may be expected for γ-elimination, which entails atomic rearrangement.

Phenyl groups are known to activate an adjacent hydrogen atom, and γ-elimination might therefore be suspected in the decomposition of γ-phenyl-*n*-propyltrimethylammonium hydroxide, the olefin produced having the correct constitution (Senfter and Tafel, *Ber.*, 1894, **27**, 2309). On the other hand, the same olefin might also arise as the result of a β-elimination, followed by prototropic change of a type which the phenyl group is also known to promote. The formation of piperylene by the exhaustive methylation of piperidine is in the same case (R′ = Ph or $CH_2:CH\cdot$) :



$$\begin{tikzcd}
\{R'\cdot\overset{\gamma}{C}H_2\cdot\overset{\beta}{C}H_2\cdot\overset{\alpha}{C}H_2\cdot\overset{+}{N}R_3\}\overset{-}{O}H \arrow[rr] \arrow[dr] & & R'\cdot\overset{\gamma}{C}H:\overset{\beta}{C}H\cdot\overset{\alpha}{C}H_2\overset{\beta}{H} \\
& R'\cdot\overset{\gamma}{C}H_2\cdot\overset{\beta}{C}H:\overset{\alpha}{C}H_2 \arrow[r] & R'\cdot\overset{\gamma}{C}H:\overset{\beta}{C}H\cdot\overset{\alpha}{C}H_2\overset{\gamma}{H}
\end{tikzcd}$$

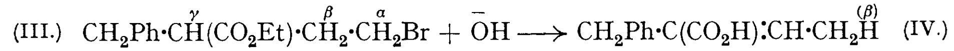
The difficulty of distinguishing between these mechanisms arises from the circumstance that the eliminated atom and the atom which migrates are both hydrogen. In the above formulæ the hydrogen atoms are labelled according to their position in the original compound, and it is seen that, whereas in one mechanism a γ-hydrogen atom is eliminated whilst a β-atom migrates, in the other the reverse is true. (Actually the position is further complicated by the presence of displaceable hydrogen in the anion, but this is not essential: the anion might have been $\cdot\overset{-}{O}Et$, $\cdot\overset{-}{O}Ph$, etc.) The site of the elimination and of the migration could, of course, be determined by an isotopic labelling of hydrogen, but the method employed in this paper is to replace one pair of hydrogen atoms by altogether different groups, which, however, like hydrogen, can undergo elimination in a positive form under the attack of a nucleophilic anion.

It is known that many substituted malonic and cyanoacetic esters, on treatment with ethoxide ions in alcohol, eliminate a carbethoxyl group as ethyl carbonate, just as substituted acetoacetic esters lose an acetyl group as ethyl acetate in the familiar retrogression of the Claisen reaction. Evidently, the reagent $Et\overset{-}{O}$, removes these groups in a positive form to give $EtO\cdot CO_2Et$ and $EtO\cdot Ac$, just as it removes the proton to give $EtO\cdot H$.

The simplest demonstration of γ-elimination becomes possible if the group which is to undergo elimination instead of hydrogen is placed in the γ-position to the ammonium residue: the stoicheiometry of the reaction reveals its character. We have used the carbethoxyl group for the elimination, with ethoxide as the attacking anion, and the result demonstrates γ-elimination with Wagner rearrangement involving migration of hydrogen :

$$(\text{I.})\ CH_2Ph\cdot C(CO_2Et)_2\cdot\overset{\beta}{C}H_2\cdot\overset{\alpha}{C}H_2\cdot\overset{+}{N}Me_3 + \overset{-}{O}Et \longrightarrow CH_2Ph\cdot C(CO_2Et):\overset{\beta}{C}H\cdot\overset{\alpha}{C}H_2\overset{\beta}{H}\ (\text{II.})$$

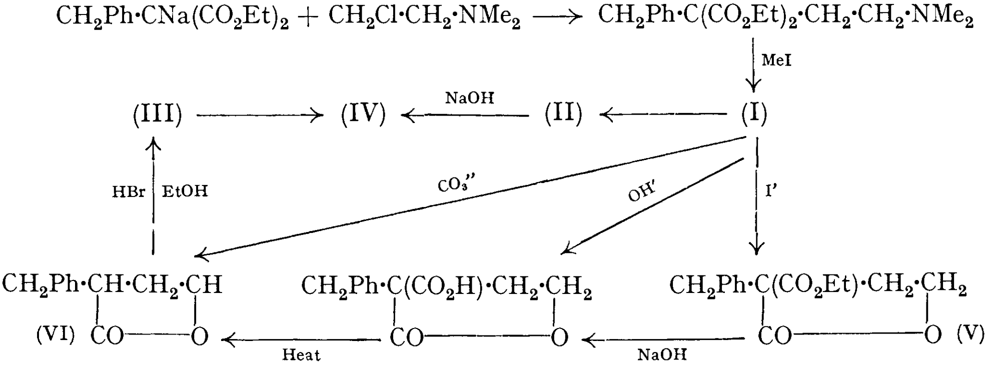
The study of this reaction assists the interpretation of another elimination that we have examined, which at first sight appears equivocal, as the removal either of γ-hydrogen with Wagner rearrangement or of β-hydrogen with prototropy could account for the structure of the product :



$$\text{(III.)}\ \mathrm{CH_2Ph{\cdot}\overset{\gamma}{C}H(CO_2Et){\cdot}\overset{\beta}{C}H_2{\cdot}\overset{\alpha}{C}H_2Br} + \overset{-}{\mathrm{O}}\mathrm{H} \longrightarrow \mathrm{CH_2Ph{\cdot}C(CO_2H){:}CH{\cdot}CH_2\overset{(\beta)}{H}}\ \text{(IV.)}$$

The following argument, however, makes it very probable that this reaction also involves γ-elimination. An acid of structure (IV) can evidently exist in two stereoisomeric forms : one of these has long been known, and the other, distinguished by the prefix *iso*-, is now described for the first time. Both the ester (II) and the acid (IV) have the *iso*-configuration. The indication of this comparison, *viz.*, that both ester and acid are produced by an analogous mechanism, is strengthened by the observation (this vol., p. 718) that when an acid of structure (IV) is actually produced by a simple prototropic change (or by a composite reaction which obviously involves one) it has its ordinary and not the *iso*-configuration. Evidently prototropy can scarcely be assumed in the reaction (III) ⟶ (IV), and the whole group of observations is interpreted consistently if it is supposed that the Wagner change in systems of the type of (I) and (III) uniformly leads to products of the *iso*-configuration.

The preparative work involved in these studies is summarised in the following scheme :



The complementary product accompanying (V), trimethylethylammonium iodide, was isolated. The constitution of (VI) was confirmed by oxidation with permanganate to benzylsuccinic acid. The constitution of the *iso*-acid (II) follows from the fact that, like the ordinary form of the acid, it gave acetaldehyde on ozonolysis.

EXPERIMENTAL.

*Formation of Ethyl Trimethyl-δ-phenyl-*n*-butylammonium-γγ-dicarboxylate Salts.*—β-Hydroxyethyldimethylamine was prepared by the following modification of the method described by Hanhart and Ingold (J., 1927, 1012). Ethylene oxide (25 g.) was slowly added with shaking and external cooling to a solution (80 g.) of dimethylamine (330 g. per l.) previously diluted with ice-water. Solid potassium hydroxide was added until a layer of amine separated, and this was then extracted with ether. The extract was dried with potassium hydroxide, the amine being distilled over barium oxide and collected within the range 125—136°. If the drying of the base with potassium hydroxide were prolonged or if sodium hydroxide were used, voluminous precipitates appeared. The compositions of these were not sufficiently constant to justify any suggestion concerning their constituents.

β-Chloroethyldimethylamine hydrochloride, m. p. 200°, was prepared by treatment of the hydroxy-amine with thionyl chloride in chloroform (*idem, ibid.*). Attempts to condense the chloroamine with malonic esters in the presence of alcoholic sodium ethoxide led to the formation of β-ethoxyethyldimethylamine. After removal of the sodium chloride by filtration, evaporation of most of the alcohol and addition of ether, the hydrochloride of this base was precipitated by means of dry hydrogen chloride as a white gum. From this the base was liberated and treated with methyl iodide in ether. The β-*ethoxyethyltrimethylammonium iodide*, crystallised from amyl alcohol, had m. p. 156—158° (Found : C, 32·6; H, 6·9; N, 4·7. $C_7H_{18}ONI$ requires C, 32·4; H, 6·9; N, 5·4%).

Ethyl benzylmalonate (25 g.), b. p. 168—170°/15 mm., was digested with finely divided sodium (2·2 g.) under xylene until the metal had dissolved. β-Chloroethyldimethylamine hydrochloride (11·8 g.) was purified in water, and the amine extracted with ether and dried in this solvent by shaking with potassium carbonate for ½ hour. The ether was distilled off, the last 25 c.c. being removed at the ordinary temperature in a vacuum, and xylene was added. Under these conditions polymerisation does not occur and, on mixing the solution with the xylene solution of the ester, condensation commences. The mixture was gently warmed, and then heated under reflux for 2 hours in order to polymerise any excess of chloro-amine. Water and ether were added, and the ether–xylene solution was extracted with dilute hydrochloric acid. The ethyl benzyl-β-dimethylaminoethylmalonate precipitated as an oil by basification was collected in ether. It could not be crystallised or distilled. Its *hydrochloride* crystallised from chloroform in plates, m. p. 131—132°, having a strong tendency to retain the solvent (Found: C, 59·5; H, 7·9; Cl, 12·0. $C_{18}H_{27}O_4N,HCl$ requires C, 60·3; H, 7·8; Cl, 10·0%).

The *methiodide* was prepared in nitromethane solution, and was precipitated by addition of ether as a slowly solidifying gum. This was dissolved in the minimal amount of hot chloroform, and the filtered solution was mixed, after cooling, with 5—6 volumes of benzene. The iodide then slowly crystallised in small plates, which, even after drying in a vacuum at 60°, contained benzene and had an unsharp m. p. in the range 103—130° [Found: C, 51·9, 51·7; H, 6·6, 6·6; N, 2·5; I, 25·1. $3(C_{19}H_{30}O_4NI),C_6H_6$ requires C, 51·5; H, 6·6; N, 2·8; I, 25·3%]. The iodide was more soluble in alcohol, acetone and chloroform than in water, and was appreciably soluble in benzene. The chloride was prepared from the iodide by digestion with silver chloride in aqueous alcohol. The filtered solution was evaporated to dryness, and the residue was caused to solidify by washing with ether, and then taken up in chloroform. The chloride was then caused to crystallise by the addition of benzene, and was shown to be free from iodide. Aqueous solutions of the hydroxide and carbonate were prepared from the iodide and the appropriate silver compounds. An alcoholic solution of the ethoxide was obtained from the chloride and alcoholic sodium ethoxide, the sodium chloride being removed with the aid of a centrifuge.

*Thermal Decomposition of Salts of Ethyl Trimethyl-δ-phenyl-*n*-butylammonium-γγ-dicarboxylate.*—(a) A solution of the hydroxide was evaporated to dryness and the residue was heated at 140—170° for 2 hours in a slow stream of nitrogen. The evolved trimethylamine was identified and the residue was extracted with ether, and divided into acid, basic and neutral fractions by means of aqueous hydrochloric acid and sodium carbonate. A more satisfactory preparation of the acid product is described under (b). The basic product was ethyl benzyl-β-dimethylaminoethylmalonate, identified as its methiodide. The neutral product was an oil, b. p. 180—182°/15 mm., and was identified by its properties and oxidation as *α-benzyl-γ-butyrolactone* (Found: C, 74·7; H, 6·8; *M*, Rast, 179, 182. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%; *M*, 176). The lactone is insoluble in cold dilute sodium hydroxide, and only slowly soluble in the warm reagent.

(b) A solution of the hydroxide together with sodium hydroxide in excess of the amount necessary for the hydrolysis of the carbethoxyl groups was evaporated to dryness, and the residue heated at 140° for 2 hours. The residue was taken up with water and the filtered solution was strongly acidified with hydrochloric acid. The *α-benzyl-γ-butyrolactone-α-carboxylic acid*, precipitated as an oil, was collected in ether, and, after removal of the solvent, was kept over phosphoric oxide until solid. It crystallised from carbon tetrachloride, or from a large volume of carbon disulphide, in needles, m. p. 87—88° (Found: C, 65·3; H, 5·4; *M*, Rast, 190. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·4%; *M*, 220). The acid is soluble in water, acetone and benzene, but insoluble in ligroin. At 125—140° it evolves carbon dioxide, the residue being α-benzyl-γ-butyrolactone.

(c) A solution of the carbonate was evaporated, and the residue was decomposed at 125—150° in a slow stream of carbon dioxide. The product, taken up in ether and distilled, b. p. 186—188°/17 mm., was α-benzyl-γ-butyrolactone.

(d) The iodide was heated for 2 hours at 160—200°. The issuing gases were passed through dilute hydrochloric acid, but the amount of base thus collected was small. The residue was washed with ether, and the extract washed with dilute hydrochloric acid, which removed a small amount of ethyl benzyl-β-dimethylaminoethylmalonate. The residue obtained on removal of the ether was separated by distillation into two fractions, the more volatile of which was usually the larger in amount, although the proportions varied in the different experiments. The more volatile fraction was ethyl *iso*-α-benzylcrotonate, described under (e); the less volatile was ethyl α-benzyl-γ-butyrolactone-α-carboxylate. The esters were identified by hydrolysis with alcoholic potassium hydroxide to the corresponding acids. The residue which was insoluble in ether was a mixture of tetramethylammonium iodide (Found: C, 24·1; H, 5·9; I, 63·1. Calc.: C, 23·9; H, 6·0; I, 63·2%) and trimethylethylammonium iodide (Found: C, 27·1; H, 6·6; I, 58·3. Calc.: C, 27·9; H, 6·5; I, 59·2%), which were separated by means of chloroform, in which the former salt is insoluble; the first was crystallised from aqueous alcohol, and the second from absolute alcohol.

(e) An alcoholic solution of the ethoxide was evaporated to dryness, and the residue was heated for 2 hours at 150—210°. The product, taken up in ether and washed with dilute hydrochloric acid, yielded *ethyl* iso-*α-benzylcrotonate*, b. p. 144—148°/19 mm. (Found: C, 76·2; H, 7·7. $C_{13}H_{16}O_2$ requires C, 76·6; H, 7·8%). This was hydrolysed by means of both aqueous and aqueous-alcoholic potassium hydroxide, and on acidification iso-*α-benzylcrotonic acid* was precipitated as a rapidly solidifying oil. The acid crystallised from light petroleum in oblique prisms, m. p. 107° (Found: C, 75·0; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%. For the *silver* salt: Found: Ag, 37·9. $C_{11}H_{11}O_2Ag$ requires Ag, 38·2%), and its amide, prepared by way of the chloride, separated from benzene–ligroin in plates, m. p. 82—83°. α-Ethylcinnamic acid, m. p. 104°, was prepared for comparison: a mixture with the acid of m. p. 107° melted at about 70°.

Conversion of α-Benzyl-γ-butyrolactone into iso-*α-Benzylcrotonic Acid.*—A solution of the lactone in ethyl alcohol was saturated with hydrogen bromide. The solvent was removed by warming in a vacuum, and the residual bromo-ester was hydrolysed by boiling for several hours with 20% aqueous-alcoholic sodium hydroxide. The acid, m. p. and mixed m. p. 107°, was obtained as a precipitate on acidification.

Oxidation of α-Benzyl-γ-butyrolactone.—A solution of the lactone in sodium hydroxide was mixed with a slight excess of 3% permanganate solution. The next day the residual permanganate was destroyed with sulphur dioxide, and the solution was worked up for acids. The benzylsuccinic acid, isolated by extraction with ether, and purified by washing with benzene and crystallisation from water, had m. p. (and mixed m. p.) 159—160°.

Properties of iso-*α-Benzylcrotonic Acid.*—The acid showed no sign of any change either on heating at temperatures up to 250°, or on boiling for 8 hours with 20% aqueous potassium hydroxide. On treatment with ozonised oxygen in chloroform at 0° an ozonide was formed, which evolved acetaldehyde on warming with water. The aldehyde was identified (m. p. and mixed m. p.) as its 2 : 4-dinitrophenylhydrazone (Found: C, 43·0; H, 4·0. Calc.: C, 42·9; H, 3·6%).

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