CCXVIII.—*Mobile Hydrogen Tautomerism analogous to the Wagner–Meerwein Re-arrangement. Part II. The Tautomerism of* 1 (*or* 5)-*Hydroxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-5 (*or* 1)-*one and its Derivatives.*

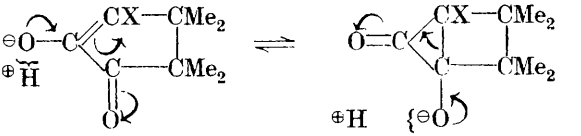
By CHARLES WILLIAM SHOPPEE.

THE two methods of electron redistribution ("inductive" and "electromeric") which have been considered in recent communications from these laboratories are characterised by the circumstance that the displaced duplets are assumed to be retained in the same octet ($\longrightarrow$C,$\overset{\curvearrowright}{\text{—C}}$), but in Part I of this series (this vol., p. 365) a general formula was given for changes such as the Wagner–Meerwein, pinacol–pinacolin, semi-pinacolic deamination, and benzil–benzilic acid, in which a duplet was assumed to pass over completely from one octet to an adjacent octet ($\overset{\curvearrowright}{\text{C—C}}$) :

$$\text{X} - \overset{\curvearrowright}{a} - \overset{\curvearrowright}{b} - c - \overset{\curvearrowright}{y} \longrightarrow \text{X}^{\oplus} + a = b - \overset{\text{R}}{\underset{|}{c}} + y^{\ominus}.$$

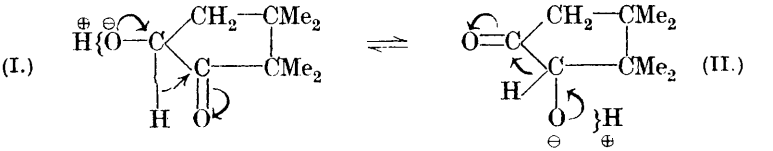
This third method of electron-redistribution may be called the "pinacolic" displacement.

In the examples of tautomerism depending on the process studied in Part I, the bonds b–R and c–R were carbon–carbon bonds, so that the duplet displaced from the octet of b to that of c was still retained in the octet of R :



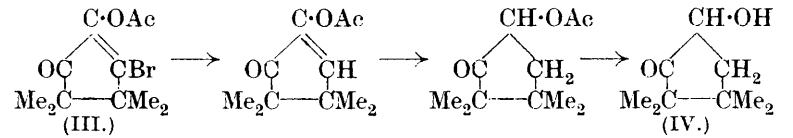
It therefore became of interest to endeavour to determine whether the octet of R was a necessary factor in the situation, and accordingly this paper reports the results of the examination of a case in which R is hydrogen.

An opportunity to test the matter arose through the preparation of the *hydroxy-ketone* named in the title. It was crystalline (m. p. 142°) and exhibited the physical behaviour of a pure substance, but, according to the foregoing hypothesis, might nevertheless exhibit tautomerism of the following kind :

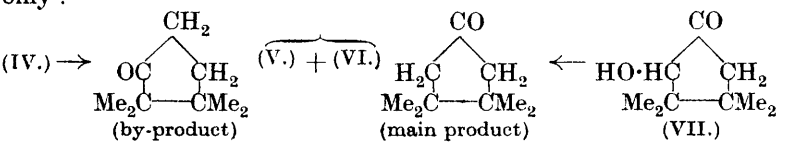


The essential change is R·CO·CH(OH)·R′ ⇌ R·CH(OH)·COR′, and for reasons now to be given is regarded as proceeding by the mechanism formulated above. Some possible alternative suggestions are considered in the sequel.

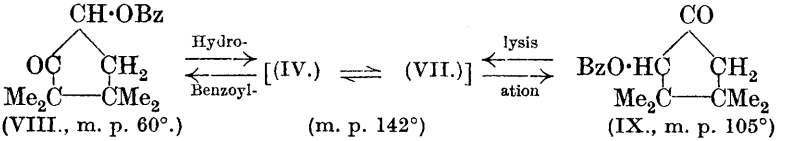
The substance was prepared from the crystalline acetoxybromo-compound (III) (Part I) in the stages represented below, and according to its method of formation should therefore have formula (IV). The presence of hydroxyl and carbonyl groups was diagnosed by the preparation of a crystalline p-*nitrobenzoyl* derivative and a p-*nitrophenylhydrazone*.



Further examination quickly revealed its dual chemical character. On treatment with acid reducing agents a mixture of isomeric tetramethyl*cyclo*pentanones (V and VI) was produced, the main isomeride in which is more easily represented as a reduction product of (VII); the ketone similarly derived from (IV) was present in small quantity only :

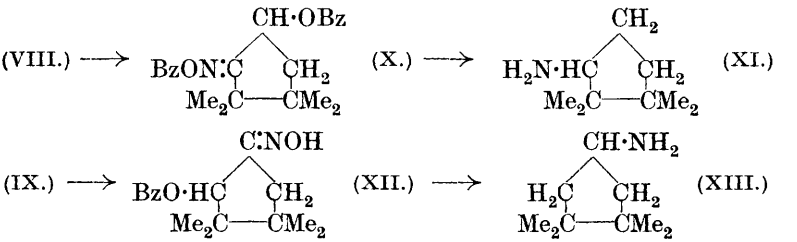


Confirmation of the view that forms (IV) and (VII) attain equilibrium in solution was forthcoming during attempts to locate the positions in which acylation and oximation occur. For the former purpose the hydroxy-ketone (m. p. 142°) was benzoylated with excess of benzoyl chloride in pyridine solution. The product was a mixture separable into two isomerides (m. p.'s 60° and 105°), to which formulæ (VIII) and (IX) have been assigned for reasons which will be given.



(VIII., m. p. 60°.) (m. p. 142°) (IX., m. p. 105°)

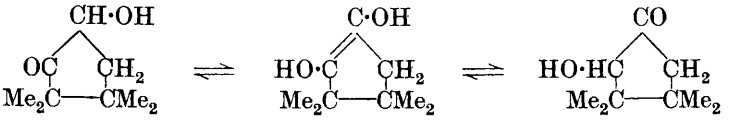
In the first place, both benzoyl derivatives on hydrolysis yield the same parent hydroxy-ketone, m. p. 142°. Secondly, the *benzoyl* derivative, m. p. 60°, on conversion into an *oxime* and complete reduction of the *benzoyl* derivative (X) of the latter, gave 2 : 2 : 3 : 3-tetramethyl*cyclo*pentylamine (XI) (compare Part I), whereas the isomeric *benzoyl* derivative, m. p. 105°, yielded an *oxime* (XII) which, when fully reduced, gave 3 : 3 : 4 : 4-tetramethyl*cyclo*pentylamine (XIII) (*loc. cit.*). Thirdly, whereas the benzoyl compound, m. p. 60°, is unaffected by bromine in chloroform or acetic acid, the isomeride, m. p. 105°, is readily brominated in chloroform solution, giving a bromination product which is under investigation. It is, of course, normal that the benzoyloxy-group should inhibit bromination on the adjacent carbon atom, whereas the carbonyl group would promote that process.



Similarly, on oximation of the substance, m. p. 142°, a mixture of oximes was obtained. They could not be separated, but the presence of both types was proved by reduction to a mixture of 2 : 2 : 3 : 3- and 3 : 3 : 4 : 4-tetramethyl*cyclo*pentylamines. Other substitution products of the parent hydroxy-ketone are described in the experimental portion.

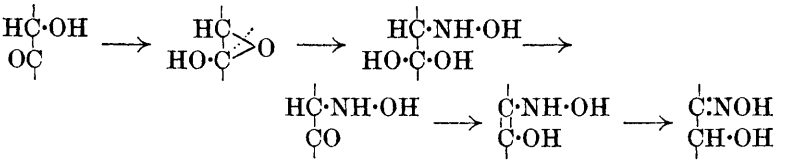
In addition to the hypothesis mentioned at the commencement of this paper, there are two other mechanisms which might be advanced

to account for the tautomerism of the substance of m. p. 142°. First, a succession of triad changes might be suggested :

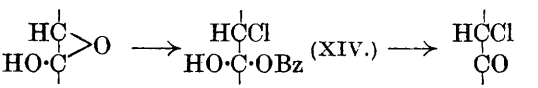


This is an intrinsically unsatisfactory hypothesis (except possibly in its application to catalysis by strong alkalis), because the hydroxyl group would work against the enolisation of the adjacent ·CH·CO group; but in any event, it is regarded as excluded by the fact that the change of structure is manifested by acylation under conditions in which the intermediate diol would be expected to appear as its diacyl derivative, further change being thus arrested. The experiment corresponds, indeed, to that whereby Thiele showed that 1·: 4-addition occurs in the reduction of benzil by reducing it in the presence of acetic anhydride and isolating diacetoxystilbene.

The second suggestion is one which has been made recently by v. Auwers and Mauss (*Biochem. Z.*, 1928, **192**, 200), whose observations on the reactions of unsymmetrical α-ketols (see also Favorski, *Bull. Soc. chim.*, 1926, **39**, 216) are evidently related to those described in this paper. Their mechanism involves keto-cyclol tautomerism with the production of an ethylene oxide, followed by fission of the oxide ring in a different direction, and then a succession of triad changes. Thus, for oximation, the process is written :

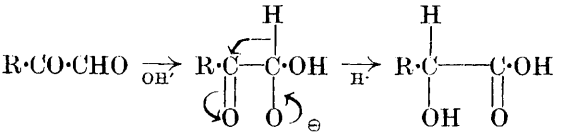


The intrinsic improbability of this is very great indeed, for the postulated ethylene oxide is not an ordinary ethylene oxide but an internal acetal of a type of which no known example exists; moreover, if it were formed, it would certainly not split in the direction suggested. Furthermore, the application of the suggestion to explain benzoylation leads to the intermediate (XIV) which, if formed, would at once yield a chloro-ketone without a change of type, not a benzoyloxy-ketone with one :



These considerations strengthen the hypothesis that the pinacolic displacement can occur with the duplet of a hydrogen atom, and as

an application it may be suggested that the general reaction whereby α-keto-aldehydes yield glycollic acid derivatives in the presence of alkalis is of this type:



It is not impossible that the sugar transformations, typified by (glucose, mannose) ⇌ fructose, which again take place in the presence of alkalis, also involve the pinacolic displacement, although in this case further evidence is naturally desirable.*

EXPERIMENTAL.

1 (*or* 5)-*Hydroxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-5 (*or* 1)-*one* (I or II).—A boiling solution of bromoacetoxyphorone (22 g.) in glacial acetic acid was treated with 35 g. of zinc dust during 6 hours. The cooled solution was filtered, the solid residue washed by decantation with fresh acetic acid, and the combined filtrates thrown into water and extracted with ether. The extract was thoroughly washed with ice-cold 5% sodium hydroxide solution, dried, evaporated, and distilled in a vacuum. A small first fraction, consisting of 5-acetoxy-2 : 2 : 3 : 3-tetramethyl-Δ^4-*cyclo*pentenone, b. p. 114°/10 mm., was followed by the main fraction, b. p. 120—121°/10 mm., which consisted of 5-acetoxy-2 : 2 : 3 : 3-tetramethyl*cyclo*pentanone (11 g.). This, on hydrolysis on the steam-bath for ½ hour with aqueous-alcoholic sodium hydroxide yielded a clear pale yellow solution, from which, after addition of water, ether extracted the *hydroxy-ketone* (5—6 g.), which was obtained as a white crystalline solid, m. p. 142° (Found: C, 69·2; H, 10·0. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

The substance closely resembles the unsaturated hydroxy-ketone (Part I) in odour, volatility, and solubility; it is extremely soluble in all organic solvents, but can be recrystallised with difficulty from ice-cold ligroin (b. p. 30—40°). It is remarkably stable to neutral permanganate in aqueous acetone solution, and but slowly oxidised by alkaline permanganate. It reduces Fehling's solution with great ease, reduction proceeding at 30°; it gives no colour with aqueous-alcoholic ferric chloride solution.

The p-*nitrophenylhydrazone* was prepared by heating a solution of *p*-nitrophenylhydrazine hydrochloride in aqueous sodium acetate with the hydroxy-ketone for a short time. It separated from alcohol

* For another probable application, see Burton and Ingold (this vol., p. 908).

in golden-yellow needles, m. p. 223—224° (decomp.) (Found : C, 62·0; H, 7·0. $C_{15}H_{21}O_3N_3$ requires C, 61·85; H, 7·2%).

The p-*nitrobenzoyl* derivative was obtained by treating the hydroxy-ketone with *p*-nitrobenzoyl chloride in pyridine solution, and crystallised from dilute alcohol in colourless needles, m. p. 85° (Found : C, 62·5; H, 6·4. $C_{16}H_{19}O_5N$ requires C, 62·9; H, 6·3%).

Reduction of the Hydroxy-ketone to 2 : 2 : 3 : 3-*Tetramethyl*cyclo*pentanone and* 3 : 3 : 4 : 4-*Tetramethyl*cyclo*pentanone*.—(1) *With hydriodic acid.* The hydroxy-ketone (0·6 g.) was heated with 10 c.c. of hydriodic acid (*d* 1·7) in a bath at 130—140° for ½ hour, a slow stream of carbon dioxide being passed to assist sublimation of the ketones. The sublimate was dissolved in a little alcohol and treated with semicarbazide acetate (see below).

(2) *With zinc and hydrochloric acid.* The hydroxy-ketone (0·5 g.) was reduced under reflux for ½ hour, and the sublimate which formed was then washed into semicarbazide acetate solution with a little alcohol.

In both cases rapid formation of 3 : 3 : 4 : 4-tetramethyl*cyclo*pentanonesemicarbazone took place (5 mins.), and after ½ hour the solutions were diluted and filtered. Both products, on crystallisation from alcohol, separated in the characteristic form (pearly plates) and melted at 224° (decomp.); neither product depressed the melting point of a genuine specimen. The filtrates each deposited after 48 hours a small amount of a crystalline semicarbazone. Both specimens, on crystallisation from dilute methyl alcohol, separated as colourless needles, and were identified as 2 : 2 : 3 : 3-tetramethyl-*cyclo*pentanonesemicarbazone by direct comparison and by the method of mixed melting points.

Benzoylation of the Hydroxy-ketone, m. p. 142° : *Formation of* 5-*Benzoyloxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-1-*one and* 1-*Benzoyloxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-5-*one*.—The hydroxy-ketone (2·5 g.) was treated with 5 c.c. of benzoyl chloride in dry pyridine solution for 1 hour on the steam-bath. The product was poured into water and extracted with ether, and the ethereal extract washed thrice with dilute hydrochloric acid, twice with cold 5% sodium hydroxide solution, and finally with water. After drying with calcium chloride, evaporation, and evacuation the oil obtained soon crystallised.

Recrystallisation from dilute methyl alcohol yielded two fractions : (A) m. p. 85—88°, colourless needles, constituting the bulk of the product (2·0 g.), and (B) m. p. 48—50°, colourless plates (0·6 g.). (A) after two recrystallisations from ligroin (b. p. 60—80°) had m. p. 105°, unchanged by further crystallisation, and (B), twice crystallised from ligroin (b. p. 40—60°), had a constant melting point of 60°.

1-*Benzoyloxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-5-*one* (IX) crystallises well from methyl alcohol or from ligroin (b. p. 60—80°) in needles, m. p. 105°, and a mixture with the isomeride, m. p. 60°, had m. p. 52° (Found: C, 73·5; H, 7·8. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). It reduces Fehling's solution, probably owing to hyrolysis to the hydroxy-ketone.

Treatment with aqueous-alcoholic sodium hydroxide at 100° for ½ hour yielded the parent hydroxy-ketone, m. p. 141—142°, mixed m. p. 142°, and identity was confirmed by preparation of the *p*-nitrophenylhydrazone, m. p. and mixed m. p. 223—224°.

A single crystalline *oxime* was formed by the action of hydroxylamine acetate in boiling absolute alcohol. After 2 hours the product from 1·1 g. of the derivative, 0·3 g. of hydroxylamine hydrochloride, and 0·4 g. of anhydrous sodium acetate was poured into water and extracted with ether: from the extract, a thick oil was obtained which crystallised on being rubbed with ligroin and then separated from ligroin (b. p. 60—80°) in colourless prisms, m. p. 115° (yield, 1 g.) (Found: C, 69·6; H, 8·0. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·7%). The oxime gave no colour with ferric chloride, and reduced Fehling's solution on boiling. On treatment with benzoyl chloride in dry pyridine solution, it yielded a *benzoyl-oximino*-derivative, which after two crystallisations from ligroin (b. p. 80—100°) formed stellate clusters of prisms, m. p. 135° (Found: C, 72·9; H, 6·75. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6%).

Reduction of the oxime (*m. p.* 115°). The oxime (0·7 g.), dissolved in a little alcohol at 60°, was reduced with 50 g. of 2·5% sodium amalgam with the continuous addition of glacial acetic acid. The product was diluted with water and extracted with ether twice; the aqueous solution was basified and extracted with ether, and the ethereal extract dried with anhydrous potassium carbonate and evaporated under a column. The resulting 3 : 3 : 4 : 4-tetramethyl-*cyclo*pentylamine crystallised readily, and after being washed with cold ligroin had m. p. 100°, mixed m. p. 100—101° with a genuine specimen. The picrate, prepared in alcoholic solution, had m. p. 250—252° (decomp.), and its identity was established by direct comparison and mixed melting point. The acetyl derivative, prepared from the amine and acetyl chloride in dry pyridine, had m. p. 94—95° after crystallisation from ligroin (b. p. 40—60°), and did not depress the melting point of a genuine specimen.

The benzoyl derivative reacts readily, after a short induction period, with bromine (1 mol.) in chloroform to yield hydrogen bromide and a complicated product, containing free benzoic acid, which is being further investigated.

5-*Benzoyloxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-1-*one* (VIII) cryst-

allises from ligroin (b. p. 40—60°) or methyl alcohol in lustrous plates having m. p. 60°, which is unchanged by further crystallisation (Found : C, 73·5; H, 8·1. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%).

Hydrolysis with aqueous-alcoholic sodium hydroxide for 1 hour at 100° yielded the hydroxy-ketone, m. p. 142°, mixed m. p. 142°. This identity was confirmed by conversion into the *p*-nitrophenylhydrazone.

An oily *oxime* was obtained when 1 g. of the derivative, 1 g. of hydroxylamine hydrochloride, and 1·2 g. of anhydrous sodium acetate were heated together in absolute-alcoholic solution on the steam-bath for 3 hours. As the oil could not be induced to crystallise, it was converted into the *benzoyl-oximino*-derivative with benzoyl chloride in dry pyridine solution. This substance was obtained as an oil, b. p. 200—215°/15 mm. (Found : C, 73·8; H, 6·4. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6%).

Reduction of the benzoyloximino-derivative, b. p. 200—215°/15 mm. This was carried out with 2·5% sodium amalgam and glacial acetic acid, as in the previous case. The product was oily, probably containing much 5-hydroxy-2 : 2 : 3 : 3-tetramethyl*cyclo*pentylamine; it was therefore reduced with hydriodic acid and phosphorus for 2 hours, and the liquid made alkaline and steam-distilled. The amine obtained on extraction of the distillate with ether was identified as 2 : 2 : 3 : 3-tetramethyl*cyclo*pentylamine by means of its picrate, m. p. 236—238° (decomp.); mixed m. p. with a genuine specimen 238° (decomp.).

The benzoyl derivative, m. p. 60° (in contrast with its isomeride, m. p. 105°) is unaffected by bromine in chloroform or in glacial acetic acid at all temperatures up to the boiling points of these solvents.

Oximation of the Hydroxy-ketone.—The hydroxy-ketone (1·5 g.), hydroxylamine hydrochloride (0·7 g.), and anhydrous sodium acetate (0·85 g.) were heated together in absolute-alcoholic solution on the steam-bath for 2 hours. The product was cooled, diluted with much water, and extracted with ether; the ethereal extract was washed with sodium hydrogen carbonate solution, dried, and evaporated. The mixture of oily oximes obtained (Found : C, 64·1; H, 9·9. $C_9H_{17}O_2N$ requires C, 63·2; H, 10·0%) could not be induced to crystallise after some weeks. Treatment with hydrogen chloride in ether at 0° yielded a small amount of a crystalline hydrochloride, m. p. 61—63° (not analysed). The oily mixture (0·3 g.), when benzoylated with excess of benzoyl chloride in dry pyridine, yielded a yellow oil, which partly crystallised after being kept in a vacuum for a week. After being drained from the residual oil and washed with and crystallised from ligroin (b. p. 80—100°), the substance was obtained in clusters of short prisms, m. p. 135°. It was identi-

fied as the benzoyl-oximino-derivative of 1-benzoyloxy-2 : 2 : 3 : 3-tetramethyl*cyclo*pentan-5-one by direct comparison and the method of mixed melting points. An oil accompanied it which probably consisted of the isomeric benzoyl-oximino-derivative, b. p. 200—215°/14 mm. (see below).

On reduction of the mixture of oily oximes with 2½% sodium amalgam in glacial acetic acid, and treatment of the product with ethereal picric acid, a mixture of 2 : 2 : 3 : 3-tetramethyl*cyclo*pentylamine and 3 : 3 : 4 : 4-tetramethyl*cyclo*pentylamine picrates was obtained, which melted at 243—245° (unchanged on recrystallisation) and depressed the melting points of both pure isomerides. Treatment with acetic anhydride and anhydrous sodium acetate yielded a mixture of *acetyltetramethyl*cyclo*pentylamines*, m. p. 79—85°. A similar mixture was obtained on oximation, reduction, and acetylation of the mixture of tetramethyl*cyclo*pentanones obtained from the hydroxy-ketone (p. 1663) (Found: C, 70·5, 70·4; H, 11·5, 11·5; N, 7·4, 7·4). $C_{11}H_{21}ON$ requires C, 72·1; H, 11·4; N, 7·6%). The mixture is much more soluble than either of the pure isomerides: a synthetic mixture of these has m. p. 83—85°.

1 (*or* 5)-*Methoxy*-2 : 2 : 3 : 3-*tetramethyl*cyclo*pentan*-5 (*or* 1)-*one*.—The hydroxy-ketone can be methylated with methyl sulphate and 10% sodium hydroxide solution by treatment on the steam-bath for 1½ hours. On fractionation, a colourless oil, b. p. 94°/14 mm., was obtained, almost the whole of the product passing over at this temperature. A small residue, which solidified, consisted of unchanged hydroxy-ketone. On redistillation, a fraction, b. p. 88—90°/10 mm., $n_D^{19°}$ 1·4574, was obtained (Found: OMe, 18·0. $C_{10}H_{18}O_2$ requires OMe, 18·2%).

On reduction with hydriodic acid 3 : 3 : 4 : 4-tetramethyl*cyclo*pentanone, isolated as the semicarbazone, m. p. 224° (decomp.), was formed. Characteristic solid derivatives could not be prepared; but treatment with hydroxylamine acetate in absolute-alcoholic solution yielded an oily *oxime*, which on reduction in the usual manner was converted into 2 : 2 : 3 : 3-tetramethyl*cyclo*pentylamine. Thus the main constituent appears to be the 5-methoxy-ketone; it cannot be asserted, however, that the isomeric 1-methoxy-ketone is not present.

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