127. *Catalytic Influences in Three-carbon Tautomerism. Part III.*
A Review of Possible Mechanisms, and Further Examination of
Catalysis by Alkoxides.

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THE further study of the experimental conditions suitable for the occurrence of three-carbon tautomerism which is described in this and the following papers makes it clear that these tautomeric changes may occur by a number of different mechanisms according to the environment of the molecule.

(1) It is well known that the most common tautomeric changes in this system are brought about by the action of alcoholic sodium ethoxide or similar reagents. Ingold has interpreted such migrations on the basis that the mobile hydrogen is removed from the system by the alkoxide anion, leaving a tautomeric anion in which a rearrangement of electrons can occur (*Ann. Reports*, 1927, **24**, 106). The subsidiary hypothesis is that the charge in the tautomeric ion becomes localised on oxygen, *i.e.*, that a common ion of the enolate type is formed. Actually, tautomeric substances are known ranging from those in which extensive enolisation can be demonstrated (cyanoglutaconic esters) to those in which it is structurally impossible (unsaturated hydrocarbons) or very improbable (unsaturated acids). For most three-carbon tautomerides (unsaturated ketones, nitriles, etc.) enolisation or allied reaction is structurally possible but its occurrence has not been proved. The results of the experiments described in this paper, together with Kon's observations (*J.*, 1930, 775) on readily enolisable substances, show that a practical distinction can be drawn between changes in the three-carbon system in the presence of sodium alkoxide which occur through enolisation and those which do not. This distinction is that in those substances which do not enolise appreciably there is no appreciable fixation of sodium, the tautomeric change is *slow and continuous*, and acidification by all methods yields the same mixture of Δ^{α}- and Δ^{β}-isomerides; where, however, the tautomeride is a stronger ψ-acid than the alcohol of the alkoxide, the sodio-compound of the tautomeride is very rapidly formed, and acidification of such a mixture produces results depending upon the experimental conditions (Kon, *loc. cit.*).

It is not essential to assume the existence of free ions containing charged carbon in interpreting the tautomeric change of non-enolising substances : these may be represented as occurring in a cycle of interdependent processes, *e.g.*,
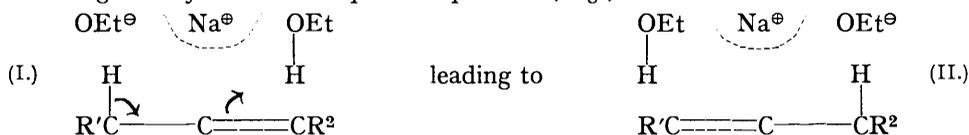
(2) If the molecule is protected from external catalysts (ions and polarised molecules) and is heated sufficiently, then a purely *intramolecular* rearrangement may occur. It is shown in the following paper that there is good reason to believe that the interconversion of Δ^{α}- and Δ^{β}-unsaturated acids at high temperatures occurs by such a mechanism. Chapman's recent studies of the intramolecular migration of aryl groups provide a parallel (J., 1930, 2458, etc.).

(3) The early explanation that tautomeric changes occur by a process of *addition and fission* of catalyst molecules may be rejected as a general interpretation, but the following facts show that it has a limited application to the three-carbon system.

Certain substances possess an *abnormally high mobility in acid solution*; *e.g.*, $\beta\beta$-dialkyl-acrylic acids (III) form γ-lactones (IV) with exceptional ease in sulphuric acid at room temperature, a reaction which involves the preliminary change of a Δ^{α}- into a Δ^{β}-acid (V) (Fichter *et al.*, *Ber.*, 1909, **42**, 4707, 4710; Linstead, J., 1932, 115; Kon, Linstead, and Wright, this vol., p. 599). The corresponding unsubstituted Δ^{α}-acids are unchanged under these conditions, although they are *more* mobile than the β-alkylated acids in alkali. This enhanced mobility in acid solution is attributed to the well-known ease with which an *as*-dialkylethylene can add on and release the elements of sulphuric acid. The following mechanism is suggested for the process :

$$\underset{R \cdot CH_2}{\overset{R'}{>}} C:CH \cdot CO_2H \underset{(III.)}{\overset{+H_2SO_4}{\underset{-H_2SO_4}{\rightleftharpoons}}} \underset{R \cdot CH_2}{\overset{R'}{>}} \underset{\underset{HSO_4}{|}}{C} \cdot CH_2 \cdot CO_2H \overset{-H_2SO_4}{\underset{+H_2SO_4}{\rightleftharpoons}}$$

$$\underset{R \cdot CH}{\overset{R'}{>}} C \cdot CH_2 \cdot CO_2H \longrightarrow \underset{\underset{O-}{\overset{|}{R \cdot CH}}}{\overset{R'}{>}} \underset{-CO}{\overset{|}{CH \cdot CH_2}}$$

$$\text{(V.)} \qquad\qquad\qquad \text{(IV.)}$$
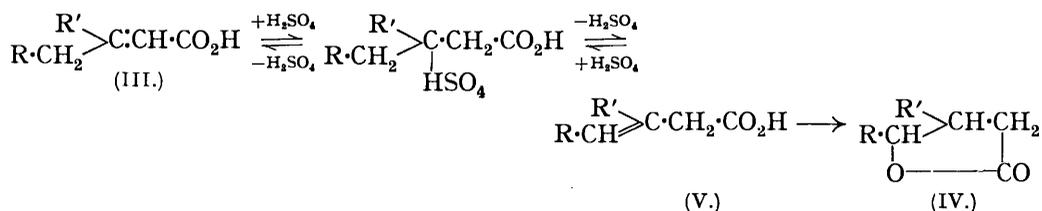
[The reaction proceeds from left to right by virtue of the one irreversible process. The possibility of the intervention of a β-hydroxy-acid (the hydrolysis product of the addition product shown above) and of the addition of sulphuric acid to the $\beta\gamma$-double bond in the reverse sense are neglected for the sake of simplicity.]

This explanation is similar to that advanced by Butleroff and by Lowry for the tautomeric change of the di*iso*butylenes. It must be emphasised that the tautomerism of unsaturated acids in alkaline media does *not* involve an additive mechanism (J., 1927, 362) : there is little addition to such double bonds in alkali, and the $\beta\beta$-dialkylacrylic acids show no enhanced mobility.

Kon and Nargund (this vol., p. 623) have observed a similar abnormal mobility of the esters of $\beta\beta$-dialkylacrylic acids in alcoholic solutions of mineral acids, although they are comparatively inert in alcoholic ethoxide (Kon, Linstead, and Maclennan, J., 1932, 2454). We attribute this to the double substitution of the β-carbon atom which facilitates the addition of acids to yield an unstable tertiary halide (or similar substance) which can then pass into either the Δ^{α}- or the Δ^{β}-unsaturated ester. Whether such a composite process can be looked upon as " tautomeric " at all is a matter of definition, but it is clear that the reactions which occur produce an *effect* of tautomeric change.

A three-carbon system in tending to attain thermodynamic equilibrium may therefore utilise one of several mechanisms, that chosen depending upon the surroundings of the " migrating " atom, both within and without the molecule. This probable diversity of mechanism indicates the need of caution in the use of a term such as " prototropy," which assumes that the migrating hydrogen passes into the ionic state. It also emphasises the necessity for retaining the classification based on the formal system (" three-carbon ") rather than adopting one involving an assumption of mechanism (compare J., 1929, 1269)

EXPERIMENTAL.

A representative selection of tautomerides detailed below has been examined from two points of view : (i) the effect of concentration of tautomeride and catalyst on the velocity of interconversion, and (ii) the fate of the former in alcoholic sodium methoxide. For this purpose

the partition of the tautomeride between a hydrocarbon solvent (*cyclo*hexane) and methyl alcohol has been determined before and after the addition of sodium; if enolisation occurs, the addition of the sodium should alter the partition coefficient in favour of the alcoholic layer. Such an increase occurred in experiments with unsaturated ketones but not with unsaturated esters or nitriles. The last two groups showed, if anything, the reverse effect; *i.e.*, there was some " salting out " of the tautomeride into the hydrocarbon.

Materials.—Ethyl Δ^α- and Δ^β-*n*-hexenoates, prepared from the silver salts of the acids (Kon, Linstead, and Maclennan, *loc. cit.*), were almost identical in physical properties with the previous preparations. The Δ^α-ester had J 1·5%,* and the Δ^β-ester J 83%, the previous reference curve (*loc. cit.*) being exactly confirmed.

Methyl *cyclo*pentylideneacetate, prepared by the action of methyl iodide on the silver salt of the acid (15 hours), had b. p. 75°/8 mm., n 1·4756, d 1·0083, J 0·5%. Methyl Δ^1-*cyclo*pentenyl-acetate, similarly prepared, had b. p. 62°/8 mm., n 1·4569, d 1·0016, J 85%. Mixtures of the esters had the following iodine additions :

Δ^α-, %	100	90	80	60	40	20	10	0
J, %	0·5	11·3	21·9	43·5	62·4	76·2	81	85·2

Δ^1-*cyclo*Hexenylacetone (Jupp, Kon, and Lockton, J., 1928, 1638) was purified by removal of the $\alpha\beta$-isomeride with aluminium amalgam and regeneration through the semicarbazone (m. p. 143°) (Kon, J., 1930, 1616). The properties of the ketone before and after regeneration are given below, together with those reported in the literature :

	B. p./mm.	$n_D^{t°}$.	$d_4^{t°}$.	t.	J, %.
Fractionated	90°/16	1·4706	0·9360	20°	84
Regenerated	94 /20	1·4726	0·9381	20	84
Kon (*loc. cit.*)	80 /15	1·4730	0·9390	18·4	84·9
Dickins, Hugh, and Kon (J., 1928, 1636)	83 /12	1·4731	0·9375	18·6	83·7

These figures indicate that the b. p. more recently given by Kon is too low. The agreement of the other figures is satisfactory.

*cyclo*Hexylideneacetone (Dickens, Hugh, and Kon, *loc. cit.*) had the following properties after fractionation : b. p. 80°/9 mm., n 1·4912, d 0·9514, J 17·9% (Kon gives b. p. 83°/9 mm., n 1·4922, d 0·9459, J 13·4% for the pure ketone).

*iso*Pulegone (Tiemann and Schmidt, *Ber.*, 1896, **29**, 917; Hugh, Kon, and Linstead, J., 1927, 2585) was regenerated from its semicarbazone by Kon's method. Its properties and those recorded for the two pure isomerides are tabulated below :

	B. p./mm.	$n_D^{t°}$.	$d_4^{t°}$.	t.	J, %.
*iso*Pulegone (authors)	100°/18	1·4675	0·9198	20°	65·0
*iso*Pulegone (Kon, *loc. cit.*)	100·5/18	1·4672	0·9197	21	66·0
Pulegone (Kon, *loc. cit.*)	109/19	1·4881	0·9381	16·9	10·6

Effect of Concentration on Mobility.—The tautomeride was treated at 25° with a solution of sodium alkoxide of the desired concentration. At the end of the required time the product was worked up in the manner described by Kon and Linstead (J., 1929, 1278), the mixture of tautomerides distilled, and its physical properties and iodine addition measured.

Ethyl Δ^β-n-hexenoate + sodium ethoxide.

Time, mins.	Concn. of reactants.		Properties of product.			Compn. of product.	
	Ester, N.	NaOEt, N.	d.	n.	J, %.	Δ^β-Ester, %.	Ethoxy-ester, %.*
60	1·0	0·05	0·8955	1·4255	81	96	nil
60	1·0	0·25	0·8960	1·4262	74	85	nil
60	1·0	0·5	0·8968	1·4270	65	71	4·5
60	1·0	0·75	0·8980	1·4272	54	56	11
60	1·0	0·95	0·8991	1·4267	47	47	17·5
20	1·0	1·0	0·8973	1·4267	64·5	70	7·5
20	0·5	1·0	0·8976	1·4264	65	71	9
20	0·25	1·0	0·8973	1·4267	66	72	8
20	2·0	2·0	0·8998	1·4261	48	48	21

* The amount of ethyl β-ethoxyhexoate in the product was calculated from the physical properties, linear relationships being assumed (compare Kon, Linstead, and Maclennan, *loc. cit.*, p. 2457).

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* Iodine additions were carried out at 20° throughout. Values of n and d are for $n_D^{20°}$ and $d_4^{20°}$ throughout unless otherwise stated.

The first five experiments showed that the change of Δ^β-ester into Δ^α- and ethoxy-esters was dependent on the concentration of the catalyst, and the next three indicated that it was independent of the concentration of the tautomeride. To test this more accurately in a system in which there was no addition of alcohol, similar experiments were carried out (1 hour at 20°) on methyl Δ^1-*cyclo*pentenylacetate :

Methyl Δ^1-cyclopentenylacetate + sodium methoxide.

Concn. of reactants.		Properties of product.			Δ^α-Ester formed, %.
Ester, N.	NaOMe, N.	d.	n.	J, %.	
{ 0·25	1·0	1·0033	1·4641	60·6	42
{ 0·25	1·0	1·0036	1·4642	60·8	42
0·50	1·0	1·0030	1·4640	62·0	41
{ 1·0	1·0	1·0030	1·4637	61·5	41·5
{ 1·0	1·0	1·0032	1·4638	61·8	41
2·0	1·0	1·0030	1·4630	64·5	37·5
1·0	0·5	1·0020	1·4605	76·6	20

The first six experiments show that the rate of change is the same over a wide range of ester concentration; the last experiment shows the dependence on the concentration of alkoxide. The point of equilibrium in the system was determined by a separate experiment (4 hours at 25°) to be 65% Δ^α-ester, resembling that of the corresponding ethyl esters.

Similar experiments were carried out on the action of sodium methoxide on *cyclo*hexylideneacetone and Δ^1-*cyclo*hexenylacetone. The results confirmed those reported above but are not given in detail as the reaction was complicated by the formation of methoxy-ketone, and the mobility of the system was too low for accurate work. In experiments with *iso*pulegone, on the other hand, the mobility was so high that complete equilibration to pulegone occurred at all but very low concentrations of alkoxide.

The last five experiments in the following table show that the change was again independent of the concentration of tautomeride :

isoPulegone + sodium methoxide at 25°.

Time, mins.	Concn. of reagents.		Properties of product.			Δ^α-Ketone formed, %.
	isoPulegone, N.	NaOMe, N.	d.	n.	J, %.	
10	1·0	1·0	0·9373	1·4832	16	100
5	1·0	1·0	0·9356	1·4826	17	99
2	1·0	1·0	0·9244	1·4826	19	97
10	0·2	0·2	0·9329	1·4827	22·5	93
10	0·1	0·1	0·9314	1·4800	31·5	79
5	0·4	0·2	0·9341	1·4803	31·5	79
5	0·27	0·2	0·9334	1·4801	31·5	79
5	0·2	0·2	0·9334	1·4801	31	79·5
5	0·13	0·2	0·9333	1·4799	30	81
5	0·1	0·2	0·9326	1·4797	31	79

The same result was obtained in experiments kindly carried out by Dr. R. A. Letch on α-Δ^1-*cyclo*hexenylbutyronitrile, of b. p. 112°/12 mm., d 0·9216, n 1·4750, J 55%.*

α-Δ^1-cycloHexenylbutyronitrile + sodium ethoxide (3 hours at 25°).

Concn. of reagents.		Properties of product.			Δ^α-Nitrile formed, %.
Nitrile, N.	NaOEt, N.	d.	n.	J, % (2 hrs.).	
4·0	1·0	0·9168	1·4846	31·7	52
2·0	1·0	0·9165	1·4831	32·4	50
1·0	1·0	0·9168	1·4851	31·0	55
0·5	1·0	0·9170	1·4843	31·8	52
0·25	1·0	0·9167	1·4846	31·0	55
0·25	1·0	0·9170	1·4846	31·0	55
1·0	2·0	0·9164	1·4908	12·5	86
1·0	2·0	0·9160	1·4905	12·8	85·5
1·0	0·5	0·9173	1·4809	43·5	23
1·0	0·25	0·9164	1·4782	51·0	6

* In view of the fact that unsaturated ketones, but *not* unsaturated esters, can be alkylated by the conventional method, it is of interest that this nitrile could *not* be prepared from the corresponding un-ethylated nitrile (Δ^1-*cyclo*hexenylacetonitrile). For instance, 6 g. of the acetonitrile were treated successively with a solution of potassium (2 g.) in ethyl alcohol (6 c.c.) and 8 g. of ethyl iodide, and the mixture heated on the water-bath (5 hours). The nitrile, isolated as usual, had b. p. 112°/25 mm., d 0·9411, n 1·4922 (Found : C, 79·1; H, 9·2. Calc. for no ethylation : C, 79·3; H, 9·1%). It had therefore merely suffered conversion into the Δ^α-isomeride without alkylation (compare Kandiah and Linstead, J., 1929, 2139).

Measurements of Partitions.*—Absolute methyl alcohol was digested twice over calcium and redistilled; *cyclo*hexane was distilled over sodium. (i) The simple partition of a given tautomeride was determined as follows : A 2*N*-solution in methyl alcohol was shaken vigorously with *cyclo*hexane (generally 5 vols.) and allowed to separate. The two layers were then distilled slowly through jacketed columns packed with glass beads, and the residual ester distilled under reduced pressure. (ii) For experiments with sodium alkoxide solutions the procedure was as follows : The tautomeride was left with an equivalent amount of 2*N*-sodium methoxide in dry methyl alcohol for the requisite period at 20° and was then extracted with *cyclo*hexane (5 vols.), the two layers being separated rapidly. The hydrocarbon layer was neutralised (phenolphthalein) with an ethereal solution of benzoic acid, the remainder of the equivalent amount of benzoic acid (generally 95—97%) being added to the alcoholic layer. The *cyclo*hexane layer was washed with water, dried, and distilled as before. The alcoholic layer was treated with water, extracted with ether, the extract washed, dried, freed from solvent, and distilled.

1. *Methyl* cyclo*pentenylacetate.* The partition of this ester was determined (*a*) in the absence of sodium, and after equilibration (with 1 equiv. of 2*N*-sodium methoxide) for (*b*) 15 secs., (*c*) 30 mins. The amounts of ester isolated from the alcoholic layer were 13, 9, and 9%, respectively. A good recovery of ester (*ca.* 90%) was obtained in each case.

For the following four substances, partitions are given in terms of the % found in the alcoholic layer (*a*) in absence of sodium and (*b*) in presence of sodium methoxide.

2. cyclo*Hexylideneacetone.* (*a*) 6% ; (*b*) 15% (after 15 mins.).

3. Δ¹-cyclo*Hexenylacetone.* Partitions were between 1 vol. of methyl alcohol and 4 vols. of *cyclo*hexane. (*a*) 11% ; (*b*) 25% (after 30 secs. and after 30 mins.).

4. iso*Pulegone.* (*a*) 6% ; (*b*) 15% (after 1 min.).

5. Δ¹-cyclo*Hexenylbutyronitrile.* (*a*) 11% ; (*b*) 12% (after 30 mins.). These values were obtained with 5 vols. of *cyclo*hexane to 1 vol. of alcohol. The following results, obtained by using less of the hydrocarbon, are given in detail as being typical of those obtained by this method :

(i) Simple partition. 10 G. of nitrile in 38·6 c.c. of methyl alcohol and 150 c.c. of *cyclo*hexane gave (α) from methyl alcohol : 2·2 g., b. p. 120—124°/20 mm., *n* 1·4738, *d* 0·9210, *J* 54·5% ; (β) from *cyclo*hexane : 6·3 g., b. p. 116—120°/18 mm., *n* 1·4748, *d* 0·9201, *J* 55%. Partition : 26% in alcohol.

(ii) Partition with sodium. 10 G. of nitrile were mixed with 38·6 c.c. of 2*N*-sodium methoxide and extracted after 30 mins. with 150 c.c. of *cyclo*hexane. There were isolated : (α) from methyl alcohol : 2·0 g., b. p. 120—122°/20 mm., *n* 1·4748, *d* 0·9194, *J* 52·5% ; (β) from *cyclo*hexane : 6·7 g., b. p. 117—120°/18 mm., *n* 1·4741, *d* 0·9250, *J* 52·5%. Partition : 23% in alcohol.