61. *Constitutional Factors controlling Prototropic Changes in Carbonyl Compounds. Part IV. Carbethoxyl and Allied Groups.*

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There is general agreement that the groups CO_2H and CO_2Alk cause electron-recession by the exercise of either their inductive ($-I$) or tautomeric ($-T$) effect, or of both together, and this property is made obvious by the influence of these groups upon reactions such as aromatic substitution and tautomeric change.

The prototropy of pyruvic acid (R in $CH_3{\cdot}COR = CO_2H$) has been studied by Hughes and Watson (J., 1929, 1945), and our investigation of the kinetics of the bromination of ethyl pyruvate in 75% acetic acid has now led to results similar to theirs. When the ester is in excess, the speed of reaction at first decreases and then becomes constant. Variations in the concentration of the halogen have no effect, and the initial period of greater speed, which is not observed if a small quantity of mineral acid be added, is undoubtedly to be attributed to basic catalysis, the point of minimum velocity occurring at about the same acid concentration as in the case of bromoacetone (Part II; J., 1932, 1207). The constancy of the velocity ultimately attained shows that the catalytic effect of the acid produced during bromination is insignificant; larger quantities of acid accelerate the change, though not powerfully. The influence of carbethoxyl here observed is characteristic of groups having a $-I$ effect (preceding paper).

The carbethoxyacetones (acetoacetic and acetonedicarboxylic esters) provide well-established examples of keto-enol tautomerism, and have long been known to react with halogens in their enolic forms. In the former it is the α-hydrogen which is ionisable, since bromination yields α-bromoacetoacetic ester (Conrad and Schmidt, *Ber.*, 1896, **29**, 1042), the production of the γ-brominated derivative in anhydrous media (Hantzsch, *Ber.*, 1894, **27**, 355, 3168; Epprecht, *Annalen*, 1894, **278**, 69; Conrad and Schmidt, *loc. cit.*; Smith, *J. Amer. Chem. Soc.*, 1922, **44**, 216) doubtless involving anionotropic change (compare Robinson, *Ann. Reports*, 1922, 100). The velocity of the prototropic change of acetoacetic ester at 0° has been measured by Meyer (*Annalen*, 1911, **380**, 212), who found that it is relatively fast, and accelerated by acids. Our fuller investigation of the kinetics of bromination of acetoacetic and acetonedicarboxylic esters in 75% acetic acid at 25° has shown that the introduction of the second carbethoxyl group leads to a still more rapid reaction in absence of added mineral acid, but less powerful catalysis by acids (compare the brominated acetones; Part II). In both cases, however, the speed of the prototropic change is vastly greater than that observed for acetone and its halogenated derivatives, and there is no indication of basic catalysis. An additional peculiarity of these compounds is the existence of a measurable quantity of the enolic modification under ordinary conditions.

The $-T$ and $-I$ effects of carbethoxyl will co-operate in conferring mobility upon the α-proton of the substituted acetone, and in view of the known powerful influence of tautomeric disturbances it is not surprising that the removal of this proton should be facilitated to such an extent that rapid reaction proceeds even under the influence of so weak an acid catalyst as water. Further, in the series of changes constituting the " basic mechanism," the first step (complete removal of proton to give the ketonic ion) results in the development of a negative charge at the α-carbon atom; the carbethoxyl group will then tend to stabilise this ion by absorbing the negative charge, and the second step (rearrangement of the ion) will be retarded. The rapid reaction catalysed by acids and the absence of basic catalysis under the conditions of our experiments thus receive a possible interpretation in the light of the polar effects usually ascribed to carbethoxyl. It may here be pointed out that in a γ-ketonic acid such as lævulic acid (Hughes and Watson, *loc. cit.*) the inductive effect of carboxyl will be damped by the intervening methylene group, while no suitable path is available for transmission of the tautomeric effect. The influence of carboxyl is thus small, and the observations are not very different from those relating to unsubstituted acetone.

The special characteristics associated with β-diketones and β-ketonic esters disappear when the second carbonyl group (or possibly phenyl, to which a $-T$ effect is also ascribed) is not attached directly to the carbon atom which carries the mobile hydrogen. Perhaps the presence of such a group in this position is necessary to render enolisation sufficiently rapid for the proportion of enol at equilibrium to be measurable. It is significant, however, that all stable enols appear to contain a system of alternate single and double bonds, and both the " additional element of stability " associated with such a system (" Thiele Factor," Lapworth and Manske, J., 1928, 2535; 1930, 1979; Linstead, J., 1929, 2501) and the formation of cyclic structures (Lowry and Burgess, J., 1923, **123**, 2114; Sidgwick, J., 1925, **127**, 907) may play an important part in stabilising these enols and in rendering the keto-enol change unusually rapid.

Saturated Monocarboxylic Acids and Acid Bromides.—The peculiarity of acetic acid and its homologues in exhibiting no perceptible tendency to undergo prototropic change (Watson, J., 1925, 2067) is obviously one expression of the failure of the carboxyl group to show normal carbonyl reactivity, a characteristic which has been attributed (Rây and Robinson, J., 1925, **127**, 1619) to the compensating effects of processes *a* and *b* in $\mathrm{H}\overset{\curvearrowright^{b}}{\mathrm{O}{-}}\underset{|}{\mathrm{C}}\overset{\curvearrowright^{a}}{=}\mathrm{O}$. If the demand of the carbonyl carbon atom (due to process *a*) is in this way supplied from the lone electrons of the hydroxylic oxygen ($+T$; process *b*), there will be no incipient ionisation of an α-proton, and prototropic change will not occur (compare Orton, Watson, and Hughes, J., 1927, 2460). It is obvious, however, that in the cases referred to above (where CO_2H or CO_2Et has a $-I$ and sometimes also a $-T$ effect) the demand set up by process *a* is supplied, at least to a large extent, from outside the group, *i.e.*, from the attached benzene nucleus or prototropic system, and it would appear that carboxyl and carbethoxyl are " self-contained " only when linked to an atom having an electronic system which is free from other disturbing influences.

An allied problem is presented in the halogenation of acyl halides, for in these compounds also the carbonyl group is attached to an atom capable of supplying electrons by tautomeric displacements. Acetyl bromide reacts with bromine at a rate which is proportional to the concentration of the latter (Watson, *loc. cit.*, p. 2073; J., 1928, 1137), and Orton, Watson, and Hughes (*loc. cit.*) suggested that *rapid* prototropic change might be followed by halogenation at *measurable* speed. It is difficult to understand, however, why bromine should cause so complete a reversal of the normal state of affairs, while carbethoxyl (similar $-I$ effect; compare % of *m*-derivative in nitration of $Ph{\cdot}CH_2Br$ and $Ph{\cdot}CH_2{\cdot}CO_2Et$; Flürscheim and Holmes, J., 1928, 1607; Baker and Ingold, J., 1927, 832) has no such drastic influence. Again, a substance which passes so easily into its enolic form would be expected to exist very largely in this form under ordinary conditions, and there is nothing to indicate that such is the case in acetyl bromide. It appears more reasonable to regard the bromination of the acid bromide as a direct reaction of the halogen with the ketonic form.

The sequence $C<O<Hal$ for increasing $-I$ effect leads to the anticipated order acetone>acetic acid>acetyl bromide for co-ordination at carbonyl oxygen. Although, therefore, co-ordination of esters with acid catalysts has been demonstrated (Baker and Hey, J., 1932, 1226), acyl halides may not co-ordinate to any appreciable extent (compare deactivation of the nucleus in halogenobenzenes). In acetyl bromide, the deficiency of electrons at carbonyl carbon (created by process *a*) can be made good from the unshared electrons of the bromine atom; the α-proton will then not be incipiently ionised (compare acetic acid), and the system will not be " predisposed " (Baker, J., 1932, 2634) towards prototropic change. But, in absence of the increased polarisation brought about elsewhere by co-ordination, the tautomeric effect is perhaps, in this process, not demanded to its fullest extent, and may therefore still be available for transmission to C_α (through three-co-ordinated carbon) at the demand of a reagent such as the polarised bromine molecule. In homologous bromides the effect will not pass beyond C_α, and this may account for the exclusive α-bromination of carboxylic acids, since in this process the halogen reacts with the acyl halide and not with the acid itself.

The interpretation here presented is by no means free from difficulties. For instance, in bromoacetyl bromide the tautomeric effect of the substituent halogen would appear to be available for further activation of the α-carbon atom, but only deactivation ($-I$ of Br) occurs, for this acid bromide is relatively inert towards substituting agents (Gal, *Compt. rend.*, 1863, **56**, 1259), and this is analogous to the fact that, in the halogenobenzenes, the activity of the *o*- and *p*-positions is below the standard of unsubstituted benzene. Further, if phenyl is capable of initiating tautomeric displacements of either sign, acetophenone should resemble acetic acid and acetyl bromide, but such is not the case. These remarks emphasise still further the difficulty of forecasting whether, in any given circumstances, the tautomeric effect is likely to operate (compare preceding paper), and in the present unsatisfactory state of our knowledge of the polar influences of groups the above suggestions must be regarded as an attempt to indicate the lines along which an explanation of the varied behaviour of carbonyl compounds may ultimately be found.

EXPERIMENTAL.

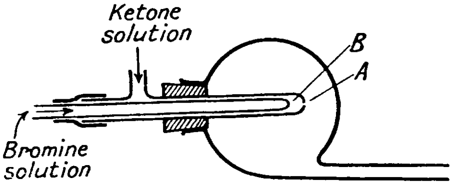
Ethyl pyruvate was prepared by esterification of pyruvic acid (b. p. 78°/27 mm.) with dry EtOH at 50°. B. p. 63°/23 mm., 149—150°/760 mm. The velocities were measured by the usual titration method. Expts. in which a known quantity of Br was added indicated absence of measurable quantity of enol. In the table the results are expressed as fall in $N/10\text{-}Na_2S_2O_3$ titre of 25 c.c. of $0{\cdot}5M$-solutions in 75% AcOH at 25°. It was necessary to carry out the measurements within 2 hr. of distillation.

		Fall in titre after (min.).			
HCl (*M*).	Initial titre.	30.	60.	120.	300.
0·00	7·20	0·50	0·92	1·60	3·22
0·00	22·30	0·55	1·00	1·65	3·22
0·01	3·42	0·30	0·55	1·08	2·70
0·10	10·25	0·25	0·50	1·05	2·48
0·50	6·00	0·85	1·70	3·38	—
1·00	8·52	2·55	5·05	—	—

Acetoacetic and acetonedicarboxylic esters were purified by distillation under reduced press. Sufficient time was allowed before use for equilibrium to be attained, but solutions were used immediately after making up, owing to slow hydrolysis. For these fast reactions, accuracy exceeding 10% cannot be claimed. The measurements on acetoacetic ester were carried out by the " colour " method (Part II); 25 c.c. of $0{\cdot}5M$-solutions of the ester in 75% AcOH were employed, and the velocities (v) are expressed as fall in $N/10$-$Na_2S_2O_3$ titre per hr., subsequent to the initial instantaneous fall v_0 (obtained by extrapolation to $t = 0$). For comparison, the velocities for acetone are given in the same units.

HCl(M)	0	0·01	0·10	0·50	1·0
v_0	4·45	4·35	4·10	1·20	0·0
v	240	270	410	2120	5180
$v_{acetone}$	0·90	—	—	45·0	134

The very rapid bromination of acetonedicarboxylic ester rendered this method of measurement unsuitable, since the time necessary for mixing was comparable with the complete time of reaction. A " flow method " similar to that of Hartridge and Roughton (*Proc. Roy. Soc.*, 1923, **104**, 376) was therefore adopted. Solutions of Br and ester, maintained at const. temp. in a thermostat, were forced by const. hydrostatic press. through two jets into a small mixing chamber (see fig.), and the liquid subsequently flowed away through a horizontal tube of length 100 cm. The distance traversed by the mixed liquid before the colour of Br disappears is a measure of the time of the reaction. The sizes of the jets were adjusted so that the resultant concns. of ester and Br were as desired, and the concn. of Br was varied by changing that of the initial solution. Solutions containing equiv. quantities of acid and alkali showed neutrality to phenolphthalein after flowing through less than 5 cm.



Cross-section of tube = 0·1324 sq. cm. The solutions flowed at the following rates (time per 100 c.c.) : Br, 630 sec.; ester, 78·5 sec.; mixed, 69·2 sec. = 10 cm. of tube in 1·17 sec. Hence vol. of Br solution/vol. of ester solution = 78·5/630 = 0·125. Concn. of ester solution used = 0·567M, and hence ester in reaction mixture = 0·5M (C_E).

C_0 = concn. of Br solution used. C_{Br} = concn. of Br in reaction mixture. l = distance the mixture flows before it becomes colourless, and the corresponding time (t) = 1·17l/10 sec.

v_0 = instantaneous fall in Br, calc. as c.c. of $N/10$-solution. v = fall in Br concn. ($N/10$) per hr. subsequent to this, for 25 c.c. of the reaction mixture.

HCl(M).	C_0.	C_{Br}/C_E.	C_{Br}.	l.	t.	v_0.	v.
0·0	0·884	0·211	0·105	20	2·35	25·0	2480
0·0	0·916	0·229	0·114	50	5·85	25·0	2350
0·1	0·784	0·196	0·098	10	1·17	23·5	3420
0·1	0·868	0·217	0·108	33	3·80	23·5	3300
0·1	0·920	0·230	0·115	50	5·85	23·5	3000
1·0	0·336	0·084	0·420	15	1·83	9·5	4160
1·0	0·464	0·116	0·580	40	4·68	9·5	4380

The percentages of enol present in 75% AcOH medium with varying concns. of HCl are given below. They are calculated from the above values of v_0. In a number of cases they were checked by Meyer's indirect Br process, *m*-cresol (which leads to more consistent values) being used instead of β-naphthol. The figures in parentheses were obtained by Meyer's method. The smaller enol content in presence of acid, observed by Meyer, is confirmed.

HCl(M)	0	0·01	0·10	0·50	1·00
Enol, %, in					
acetoacetic ester	1·80 (2·05)	1·75 (2·00)	1·70 (1·90)	0·50 (1·10)	0·00
acetonedicarboxylic ester	9·70 (11·0)	—	9·30	—	3·20

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