27. *Optical Activity in Relation to Tautomeric Change. Part III. Constitutional and Catalytic Influences on the Rates of Racemisation of Prototropic Compounds.*

By Christopher L. Wilson.

In Part II (preceding paper) it was shown that the velocity of racemisation of a certain tautomeric substance was quantitatively equivalent to its rate of isomeric change. No other measurements are at present available to support the generalisation of this conclusion, but considerable indirect support is now adduced from existing data. It has often been concluded that the racemisation of compounds of the form R^1R^2CHX (X = COR, CN, or NO_2) is the result of prototropic change (cf. Kipping and Hunter, J., 1903, **83**, 1009; Rothe, *Ber.*, 1914, **47**, 843; McKenzie and co-workers, J., 1919, **115**, 602, *et seq.*), and the trend of the evidence to be summarised is to the effect that the speed of racemisation of such compounds is subject to exactly the same constitutional and catalytic influences as are known to affect prototropic change.

Just as in prototropy, so also in racemisation, both bases and acids play important rôles as catalysts. Basic catalysts would be expected to have an effect dependent on their strength, and thus the order $NaOAlk > NaOH > H_2O$ might be anticipated; this appears to be true, for in the hydrolysis of ethyl *l*-mandelate more racemisation occurs when alcoholic than when aqueous alkali is employed (McKenzie and Wren, J., 1919, **115**, 602), and whereas *d*-mandelonitrile racemises only slowly in the presence of methyl alcohol, it does so instantly under the influence of a trace of potassium methoxide (Smith, *Ber.*, 1931, **64**, 427). Further, in both types of change basic catalysis is in general more effective than acid catalysis; *e.g.*, with the natural proteins, alkaline hydrolysis yields amino-acids which are much more extensively racemised than when acid hydrolysing agents are used.

It is known that the order in which different groups X should affect prototropic mobility is $CO_2^{\ominus} < CONH_2 < CO_2H < CO_2R < COCl < COR < CN$ (cf., *e.g.*, Ingold, Shoppee, and Thorpe, J., 1926, 1477). This series may be compared with the following data concerning speeds of racemisation. The position of the group $CO_2^{\ominus}$ is clearly established inasmuch as many authors have observed that the alkali-metal salts of optically active acids exhibit a much higher optical stability than either the acids themselves or their other simply constituted derivatives; for instance, Ahlberg (*Ber.*, 1928, **61**, 811) found that neutralisation caused the speed of racemisation of *d*-$\alpha\alpha'$-sulpho-di-*n*-butyric acid to fall almost to zero. Concerning the amido-group, McKenzie and Smith (J., 1922, **121**, 1348) have recorded that in the partial hydrolysis by alkalis of *l*-mandelamide the residual amide is much more strongly racemised than the mandelic acid produced. According to Gadamer (*Chem.-Ztg.*, 1910, **34**, 1004), ethyl *d*-tropate is racemised by alkalis, whereas sodium *d*-tropate is optically stable. Ashley and Shriner (*J. Amer. Chem. Soc.*, 1932, **54**, 4410) have shown that the period of half-change of *l*-α-benzenesulphonylbutyric acid in alcohol at 27° is 1350 hours, whereas the corresponding time for the ester of this substance was 80 hours. Again, Kipping and Hunter (J., 1903, **83**, 1009) have observed that whilst benzylmethylacetic acid has considerable optical stability, its chloride becomes racemised with great facility. The position of the cyano-group is illustrated by a comparison of the facile racemisation of *d*-mandelonitrile (Smith, *loc. cit.*) with the well-known optical stability of the benzoins (cf., *e.g.*, McKenzie, Roger, and Wills, J., 1926, 779).

When either of the groups R^1 or R^2 is an electron attractor, the invariable result is a great increase in the optical lability of the compound. In illustration, reference may be made to dihydrocarbostyril-β-carboxylic acid (Leuchs, *Ber.*, 1921, **54**, 830), to α-cyanopropionic acid, and to ethanesulphonylsuccinic acid (Fitger, "Racemisierungserscheinungen," p. 21, Lund, 1924), each of which forms only a single salt with an appropriate alkaloid. In the case of α-cyanopropionic acid, the free acid cannot be liberated from the salt without complete racemisation. The action of the ammonium pole is exemplified by Fischer's observation (*Ber.*, 1907, **40**, 5005) of the very rapid racemisation of salts of ethyl *l*-α-trimethylammoniumpropionate. The halogens evidently exhibit a similar, though

weaker, effect, and McKenzie and Smith (*Ber.*, 1925, **58**, 906; J., 1923, **123**, 1964) record results concerning the phenyl halogenoacetic esters which establish the order Cl>Br≫OH for the effect of these groups on velocity of racemisation.

The examples of the preceding paragraph all relate to racemisation by the basic mechanism (Watson and Yates, J., 1932, 1207); but observations are available in illustration of the influence of alkyl groups on racemisation under the influence both of basic and of acid catalysts. Data referring to basic catalysis are recorded by Ahlberg (*loc. cit.*) in relation to the acids $SO_2(CHR{\cdot}CO_2H)_2$. Under comparable conditions the half-life periods are :

R	Me	Et	Pr^{β}
Half-life (hours)	1·3	2·75	50

and this shows the sequence of facilitation to be Me>Et>Pr^{β}. On the other hand, Backer and Mulder (*Proc. K. Akad. Wetensch. Amsterdam*, 1928, **31**, 301), in an investigation of the racemisation of the compounds $AsO_3H_2{\cdot}CHR{\cdot}CO_2H$ under the influence of acid catalysts, found the sequence Pr^{α}>Et>Me, and this inversion is to be anticipated as a consequence of the change of catalytic mechanism. An example illustrating the effect of the introduction of an alkyl group at a point relatively distant from an asymmetric centre is furnished by a comparison of *l*-mandelamide with its *N*-ethyl derivative, for the racemisations of which the half-change periods are 4 and 25 days, respectively, under identical conditions of alkaline catalysis (McKenzie and Smith, J., 1922, **121**, 1348).

In view of the special activating influence of aryl groups in three-carbon prototropy, it would be anticipated that a corresponding effect should be traceable in racemisation. The appreciation of this has led McKenzie to assert on several occasions that for facile racemisation the system Aryl·CH·CO must be present (J., 1920, **117**, 680; *Chem. and Ind.*, 1931, **50**, 928; *Ber.*, 1925, **58**, 894); *e.g.*, active lactates and tartrates are much more stable than active mandelates. Moreover, *l*-phenylsulphoacetic acid, $CHPh(SO_3H){\cdot}CO_2H$, is easily racemised at the ordinary temperature (Brust, *Rec. trav. chim.*, 1928, **47**, 153), whereas α-sulphopropionic acid, $CHMe(SO_3H){\cdot}CO_2H$, is stable (Franchimont and Backer, *ibid.*, 1920, **39**, 751). Active phenyl-*p*-tolylacetic acid is extremely labile (McKenzie and Widdows, J., 1919, **115**, 602), and the high activating power of phenyl is further exemplified by the work of Levene and Steigler (*J. Biol. Chem.*, 1931, **86**, 703), who quote data, readily intelligible on the basis already indicated, for the degree of racemisation of monosubstituted diketopiperazines in the presence of alkalis.

C-Substituent	Ph	CH_2Ph	$CO{\cdot}NH_2$	p-$O^{\ominus}{\cdot}C_6H_4{\cdot}CH_2$
Racemisation, %	100	92	82	10

These authors have, in addition, provided evidence that the phenyl group also facilitates racemisation occurring by the acid mechanism. Fitger (*op. cit.*) has recorded data for the racemisation of acids of the type $HO_2C{\cdot}CHR^1{\cdot}SR^2$ in the presence of acid and basic catalysts. From these it is possible to derive a sequence representing the influence of groups in facilitating racemisation by the basic mechanism :

$$Ph>CH_2{\cdot}CO_2H>Me>CH_2{\cdot}CO_2^{\ominus}>Et$$

It is also clear from Fitger's results that phenyl again heads the series which obtains when acids are used as catalysts.

In conclusion, reference is made to an observation of McCombs, Packer, and Thorpe (J., 1931, 547; cf. Fitzgerald and Packer, J., 1933, 595), who measured the velocity of racemisation of *l-trans*-αγ-dimethylglutaconic acid under various catalytic conditions; they suggested that the observed rate was also that of prototropic change, an hypothesis which derives support both from Part II and from this paper. The glutaconic acid exhibits asymmetric rearrangement with strychnine, and the authors suggest that in resolutions of this type the separated material possesses the same sign in rotatory power as that of the alkaloid used; several instances are available, however, to show that this rule is by no means invariable (cf. Backer and Mook, *Rec. trav. chim.*, 1928, **47**, 464; Leuchs and Wutke, *Ber.*, 1913, **46**, 2425).

UNIVERSITY COLLEGE, LONDON. [*Received, November 11th*, 1933.]