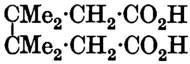
CII.—*The Effect of* gem-*Dialkyl Groups on the Formation and Stability of the Anhydrides of Dicarboxylic Acids.*

By Ernest Harold Farmer and Jacob Kracovski.

Reference has been made by various authors to the modifying effect of substituent alkyl groups on the ease of formation and the stability of the anhydrides of dicarboxylic acids. Auwers and Meyer (*Ber.*, 1890, **23**, 101), referring to the marked effect of alkyl substituents in the succinic and glutaric series and the failure of adipic acid to yield an anhydride, asked whether "durch Einführung mehrerer Methylgruppen in das Molekül der Adipinsäure eine Säure erhalten wird, welche der Anhydridbildung fähig ist," and Ingold (J., 1921, **119**, 308), dealing with the effect of *gem*-dialkyl groups on ring formation, pointed out that the same effect is equally apparent in heterocyclic ring-formation (lactones and glutaric anhydrides). It is clear from numerous incidental observations that in the succinic and glutaric series the ease of formation and the stability of anhydrides tend to increase with the number and size of substituted alkyl groups; even in the malonic series, in which the anhydrides, although capable of reacting as simple molecules, are almost certainly multimolecular, the correspondence of increased stability with increased substitution has been observed. How far this tendency extends is uncertain; many highly-substituted anhydrides of these series have not yet been obtained and at present comparisons are legitimate probably only between the members of a series. With members of different series, the hetero-structure of the ring presents difficulty; the extent to which the oxygen atom may relieve or transmit strain is unknown. Although in general an oxygen atom in a ring appears to function much as a carbon atom (leading to stability in the five- and six-membered anhydrides), yet there is a difference between homocyclic and heterocyclic rings in that the stability of the six-membered glutaric anhydrides increases with further substitution (compare Ingold, J., 1921, **119**, 952).

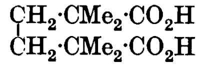
Any general attempt to compare anhydrides and homocyclic rings is confronted, when the adipic series is reached, by the problem of the close approach or the overlapping of the terminal groups. The possibility of obtaining stable, unimolecular anhydrides in this and higher series has not been explored. Consequently the nature of the factors tending chiefly towards stability, whether angular modifications as in the lower homocyclic rings, multiplanarity, re-entrant angles, or accommodative power of the oxygen atom, is quite unknown. The anhydrides of various mono-, di-, and trialkyladipic acids have been obtained by Blanc and other workers. All of these pass into the corresponding ketones on heating, but no evidence as to their complexity is offered.

We have examined the anhydrides of adipic acid and of β-methyladipic acid. Both of these substances may be obtained in the pure condition and they are definitely unimolecular. They are distillable at low pressures without decomposition, but pass readily into the corresponding acids by absorption of moisture from the atmosphere. For the purpose of testing whether any considerable degree of stability may be conferred on the anhydrides of this series by the introduction of alkyl groups, two tetramethyladipic acids have been synthesised (J., 1926, 2318). Each of these acids (I and II) yields a crystalline, unimolecular anhydride. That of the ββ′β′-acid is partly converted into the ketone (III) on prolonged heating and is readily hydrolysed by hot water. The highly crystalline anhydride of the αα′α′-acid shows no tendency to pass into the corresponding ketone; it may be prepared by prolonged heating of the acid and is not hydrolysed by boiling water or aqueous sodium carbonate. Moreover, it yields an anilic acid with much greater difficulty than its isomeride. The two substances correspond roughly in properties with glutaric and di- or tri-methylglutaric acids respectively. Therefore it is evident, not only that substitution produces a considerable change in the stability of anhydrides in this series, but also that equivalent substitution causes effects varying with the position of substitution.



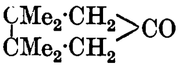
$$\begin{array}{l}CMe_2\cdot CH_2\cdot CO_2H\\ |\\ CMe_2\cdot CH_2\cdot CO_2H\end{array}$$

(I.)



$$\begin{array}{l}CH_2\cdot CMe_2\cdot CO_2H\\ |\\ CH_2\cdot CMe_2\cdot CO_2H\end{array}$$

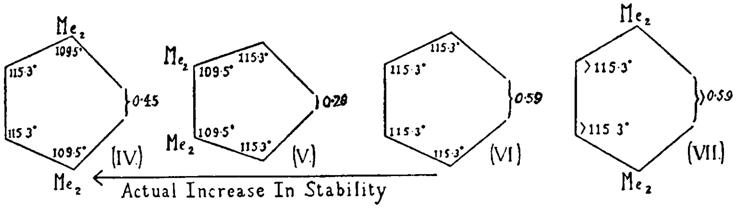
(II.)



$$\left.\begin{array}{l}CMe_2\cdot CH_2\\ |\\ CMe_2\cdot CH_2\end{array}\right>CO$$

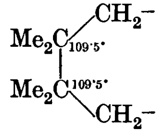
(III.)

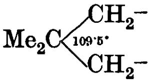
The abnormal effect of an α-substituent was observed by Ingold in studying ring-formation from bromo-α-methylglutaric acid (J., 1925, **127**, 387); here the introduction of an α-methyl group greatly hinders the formation of a *cyclo*propane ring. The abnormality was attributed to a " branched-chain " (volume) effect tending to open the valencies of the chain at the β-carbon atom. Short (*Chem. News*, 1926, **133**, 145), however, in criticising the suitability for comparing ring-forming tendencies of the method employed in this and other similar cases—that of hydrogen bromide removal from α-brominated esters—states that the inferior yield of the cyclic acid is probably to be attributed, in part, to the polar factors which control the ease with which the components of hydrogen bromide are removed. If the ready formation and superior stability of αα′α′-tetramethyladipic anhydride are attributable to the " opening " effect caused by branching of the chain at the α-carbon atoms, it would appear that the properties of αα$\alpha'\alpha'$-tetramethyladipic acid in relation to adipic acid are in keeping with the " terminal approach" explanation of the inferior ring-forming capacity and anhydride stability of the latter. Further, the approach in stability of ββ$\beta'\beta'$-tetramethyladipic anhydride towards that of ββ-dimethylglutaric acid would seem to have a rough correspondence with the almost identical distances (using Ingold's angular value for $CMe_2<$) between the terminal carbon atoms of the tetramethylbutane- (VIII) and dimethylpropane- (IX) chains. It would seem, however, that if a " branched-chain " effect is imagined to result from α-substitution, a similar effect might quite well be caused by the proximity of the *gem*-groups at the β-carbon atoms of ββ$\beta'\beta'$-tetramethyladipic acid. If the carbon atoms of the adipic chain are regarded as uniplanar, then on the basis of Ingold's angular values for $CH_2<$ and $CMe_2<$, the approach of the carboxyl carbon atoms may be indicated as in figures IV, V, and VI. The relative magnitude of the " approach " figures does not correspond with the observed ease of formation and stability of the anhydrides and no better agreement is to be obtained by regarding a " branched-chain " effect (Fig. VII) as operative in the α-substituted acid. It is clear from such representations of members of the same and of different series of dicarboxylic acids that the powerful effect of *gem*-groups in promoting anhydride formation is not to be accounted for purely on the basis of tetrahedral angular modifications in a uniplanar carbon chain.



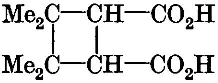
The above-mentioned approximation of the distances separating the terminal carbon atoms of the systems (VIII) and (IX) would suggest comparable tendencies towards *cyclo*butane ring-formation.

(VIII.)





(IX.)



$$\begin{array}{l} Me_2C—CH—CO_2H \\ \quad | \qquad\ \ | \\ Me_2C—CH—CO_2H \end{array}$$

(X.)

By the action of alcoholic potash on α-bromo-ββ$\beta'\beta'$-tetramethyladipic ester, 25% of the latter suffered replacement of bromine by hydrogen. The remaining material appeared to undergo severe degradation, the products of which escaped identification; no trace of the *cyclo*butane acid (X) could be isolated. Attempts to prepare this cyclic acid from di*iso*propylidenesuccinic acid have likewise been unsuccessful. In view of the wide difference between the extents of cyclisation achieved with αα′-dicarboxyadipic ester (100%; Perkin, J., 1887, **51**, 18) and α-bromoadipic ester (1·5%; Ingold, J., 1921, **119**, 954) these results are possibly of little significance as an index to ring-forming capacity.

Other alkylated dicarboxylic acids are at present being examined.

EXPERIMENTAL.

Tetramethyladipic Acids.—These were obtained by electrolysis (Farmer and Kracovski, J., 1926, 2318). Since only about 12 g. of the ββ β′β′-acid could be accumulated, the experiments with this substance were of necessity carried out with small amounts of material.

Anhydride of ββ β′β′-*Tetramethyladipic Acid.*—Tetramethyladipic acid was heated for about 2 hours with three times the quantity of acetic anhydride theoretically required. The product was evaporated in a vacuum over caustic potash; a solid was then obtained which crystallised from petroleum (b. p. 60—80°) in long, colourless, flat needles, m. p. 189° (Found: C, 65·2; H, 8·55. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%). The anhydride, which was very soluble in benzene, and moderately easily soluble in ether or petroleum, passed into the original acid (m. p. 207—208°) on warming with water. The molecular weight, determined cryoscopically in benzene, showed it to be of simple constitution (Found: *M*, 188. Calc.: *M*, 184).

The *anilic acid*, formed by treating a benzene solution of the anhydride with the calculated quantity of aniline dissolved in the same solvent, separated from hot chloroform as a crystalline powder (Found: C, 68·8; H, 8·1; *M*, monobasic, 281. $C_{16}H_{23}O_3N$ requires C, 69·3; H, 8·3%; *M*, 277).

1 : 1 : 2 : 2-*Tetramethyl*cyclo*pentan*-4-*one.*—The anhydride of the ββ β′β′-acid (2 g.) was refluxed for some time and then allowed to distil slowly. A small quantity of an oil (b. p. 186—189°) of strong camphoraceous odour was obtained. This substance readily yielded a semicarbazone, which crystallised from hot aqueous alcohol in shining plates, m. p. 223°. Comparison of the latter with a specimen (m. p. 223°) prepared by Francis and Willson's method (J., 1913, **103**, 2245) proved the identity of the two.

The anhydride of αα α′α′-*tetramethyladipic acid* was obtained in similar fashion to the ββ β′β′-anhydride. The crude, solid anhydride, which was moderately easily soluble in benzene or ether but only very sparingly soluble in petroleum, crystallised from benzene–petroleum in long, colourless prisms, m. p. 166° (Found : C, 64·9; H, 8·5; *M*, cryoscopic in benzene, 180. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%; *M*, 184). The *anilic acid* separated when a benzene solution of the calculated quantities of anhydride and aniline was heated and then kept. It was insoluble in water, but crystallised from hot chloroform in needle clusters, m. p. 218° (Found : C, 68·6; H, 8·4; *M*, monobasic, 282. $C_{16}H_{23}O_3N$ requires C, 69·3; H, 8·3%; *M*, 277). The anhydride was unaffected by boiling with water or even sodium carbonate solution. It dissolved, however, on boiling with strong caustic potash solution; acidification of the product precipitated the corresponding αα′α′-acid (m. p. 191°). Slow distillation of the anhydride failed to yield the corresponding cyclic ketone, the substance distilling unchanged. Prolonged heating of the acid, however, prior to distillation caused partial conversion into the anhydride.

Anhydride of β-*Methyladipic Acid.*—β-Methyladipic acid, obtained by the oxidation of 1-methyl*cyclo*hexan-4-ol, was treated with acetic anhydride as above. The acetic acid and excess of acetic anhydride were removed at 15 mm. pressure; the syrupy liquid so obtained distilled at 165°/1 mm. without decomposition. The pure anhydride is a colourless syrup which readily hydrolyses in moist air (Found : C, 59·0; H, 7·15; *M*, cryoscopic in benzene, 140. Calc. : C, 59·15; H, 7·0%; *M*, 142).

The anhydride of adipic acid, obtained as above, was a solid, m. p. 97°. It distilled without decomposition at 1 mm. (Found : *M*, cryoscopic in benzene, 130. Calc. : *M*, 128).

Ethyl α-*Bromo*-ββ′β′-*tetramethyladipate.*—The βββ′β′-acid (3 g.) was converted into the acid chloride by warming with the requisite amount of phosphorus pentachloride. Bromine (1 mol.) was gradually added to the product. When the absorption, which took place readily, was complete, the mixture was poured into well-cooled alcohol. After 12 hours, the bromo-ester was precipitated by means of water and obtained as a yellow oil. It was not distilled, owing to the small quantity available, but was kept for several days in an evacuated desiccator before being analysed (Found : Br, 22·8. $C_{14}H_{25}O_4Br$ requires Br, 23·7%).

Action of Concentrated Caustic Alkali Solution on Ethyl Bromotetramethyladipate.—The bromo-ester (5 g.) was warmed and then poured into boiling 6*N*-methyl-alcoholic potassium hydroxide (20 c.c.). Potassium bromide separated at once. Heating was continued for a short time; the product was then cooled, diluted with absolute alcohol (40 c.c.), and filtered. The solid material was washed with alcohol until only inorganic salts remained, the washings being added to the filtrate. Free caustic alkali was removed from the filtrate by saturating it with carbon dioxide and filtering. The alcoholic filtrate was evaporated to dryness and the residue was treated several times with water and evaporated to dryness. A solution of the final residue in a small amount of water was filtered through a wet filter-paper to remove a small amount of neutral oil and then acidified with dilute hydrochloric acid, ββ′β′-tetramethyladipic acid being precipitated; a further small quantity separated when the acid solution was concentrated, the total yield (allowance being made for the slight deficit of bromine in the bromo-ester employed) being 25% of the material taken. The filtrate was finally evaporated to dryness in a vacuum, and the residue extracted with acetone. By this means a yellow syrup was obtained which, absence of severe degradation being assumed, represented about 50% of the material taken. After standing for nearly a year, the syrup deposited an acid which was readily soluble in water and separated from acetone–petroleum in colourless prisms, m. p. 212°. Owing to the very small quantity obtained, the acid could not be identified. Its low equivalent showed, however, that it was not the *cyclo*butane acid (X).

The residual syrup could not be solidified. It was distilled to free it from traces of inorganic matter, the distillate being collected in three portions. None of these reduced alkaline permanganate solution, and each had an equivalent weight and a carbon content much lower than those of the *cyclo*butane acid or hydroxytetramethyladipic acid. The syrup was almost certainly a mixture of acids, probably produced by severe degradation of tetramethyladipic acid.

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