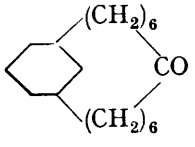
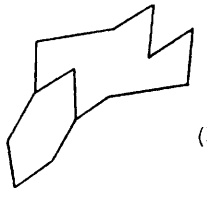
376. *Conditions for the Formation of Rings attached to the Meta-positions of the Benzene Nucleus.*

By S. G. P. PLANT.

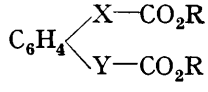
A STRIKING feature of benzene chemistry is the almost complete absence of derivatives in which a cyclic structure is attached in the meta- or the para-positions. The compound (I), prepared in very small yield by Ruzicka, Buijs, and Stoll (*Helv. Chim. Acta*, 1932, **15**, 1220) from the cerium salt of the corresponding dibasic acid, appears to be the only definitely established example of the former type. There seems to be no reason why the main factors involved in the cyclisation of compounds containing side chains in the meta-positions should differ essentially from those by which ring closure in simple aliphatic substances is governed. Thus the preparation of a compound with a highly strained ring attached in the meta-positions would be extremely difficult. Furthermore, the formation of a large strainless "meta-ring" will involve the well-known difficulties arising from the elaborate rotational changes which the long-chain substituents can undergo.

The use of models indicates that there is considerable strain in a ring attached to the meta-positions if it contains fewer than ten atoms, and that larger ring structures are not greatly strained. A saturated seven-membered chain (resulting in a ten-membered ring) between the meta-carbon atoms of the benzene nucleus can readily assume a shape, such as in (II), reminiscent of the strainless configurations of decahydronaphthalene. The benzene nucleus does not fit into such a model without a little strain, but this is small

(I.) 



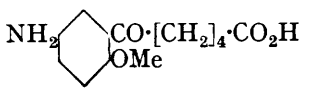
(II.)



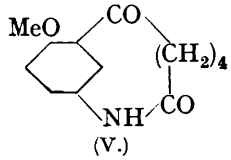
(III.)

and does not exceed that associated with many well-known compounds containing rings attached in the ortho-positions. It follows, therefore, that attempts to effect cyclisation in meta-disubstituted benzene derivatives will be more likely to succeed if the configuration of the product is of the type mentioned than if the attached ring is smaller or considerably larger, and modern theory indicates that these considerations apply to both carbocyclic and heterocyclic systems. The failure of Titley (J., 1928, 2571) to obtain definite evidence of cyclisation during the application of the Dieckmann reaction to esters of the type (III) may be explained by the fact that in all the cases investigated the side chains in the meta-positions were of insufficient length for the formation of a nearly strainless molecule. Under the most favourable conditions, however, the process is not likely to be easier than the formation of a strainless monocyclic system containing approximately ten atoms in the ring.

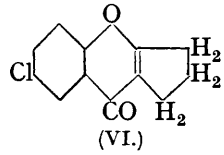
With these considerations in mind the possibility of converting δ-5-*amino*-2-*methoxybenzoylvaleric acid* (IV) into the compound (V) has been investigated. In this case the difficulties due to the rotational changes in the side chain might be expected to be overcome to some extent by the polar character of the groups concerned in the cyclisation



(IV.)



(V.)



(VI.)

process. δ-*o*-Hydroxybenzoylvaleric acid can be obtained fairly readily by the alkaline hydrolysis of 2 : 3-dihydropentachromone (Hall and Plant, this vol., p. 232), and its methyl

ether has now been nitrated to give δ-5-*nitro*-2-*methoxybenzoylvaleric acid*, which has been reduced to the compound (IV). The position of the amino-group in (IV) has been established by the action of phosphoric oxide on a mixture of *p*-chlorophenol and ethyl *cyclo*pentanone-2-carboxylate, and by the alkaline degradation of the resulting 6-*chloro*-2 : 3-*dihydropentachromone* (VI) into δ-5-*chloro*-2-*hydroxybenzoylvaleric acid*. The *methyl ether* of the latter was identical with the compound obtained from (IV) by a Sandmeyer reaction.

Although many attempts have been made to effect ring closure with (IV), its hydrochloride, and its *benzoyl* derivative, no indication has so far been obtained of the ready formation of the compound (V). It is proposed, however, to investigate the possibility of ring closure in other compounds which fulfil the conditions mentioned above.

Similar considerations regarding the possibility of effecting cyclisation in para-disubstituted benzene derivatives indicate that the product would be highly strained unless the attached ring is more than twelve-membered. It is also apparent that there is appreciable strain in a thirteen-membered ring and that there will probably be the best chance of success when the saturated chain uniting the para-positions in the product contains ten atoms (a fourteen-membered ring).

Experimental.

δ-o-*Methoxybenzoylvaleric Acid.*—This acid was made by von Braun (*Ber.*, 1922, **55**, 3761) by the prolonged action of methyl iodide on δ-*o*-hydroxybenzoylvaleric acid in alkaline solution, but the following procedure proved to be very convenient for the preparation of relatively large amounts of the substance. The hydroxy-acid (20 g., obtained by the method of Hall and Plant, *loc. cit.*) in aqueous potassium hydroxide (150 c.c. of 10%) was shaken for 10 minutes at about 20° with methyl sulphate (12 c.c.); more methyl sulphate (12 c.c.) was then added, and shaking resumed for 5 minutes. After further agitation for 10 minutes with the addition of aqueous potassium hydroxide (200 c.c. of 10%), the solution was heated for an hour on the steam-bath. The solid which was precipitated by the addition of concentrated hydrochloric acid was extracted with ether, and the residue obtained by the evaporation of the dried (sodium sulphate) extract was dissolved in methyl alcohol. After this solution had been saturated with dry hydrogen chloride and refluxed for 6 hours, most of the methyl alcohol was distilled off and the residue was shaken with water and ether. After the methyl ester of the unchanged hydroxy-acid had been removed from the ethereal solution with aqueous caustic soda, δ-*o*-methoxybenzoylvaleric acid was obtained in good yield by evaporation and hydrolysis. It gave no colour with ferric chloride, and separated from benzene in colourless prisms, m. p. 82°.

A small quantity (4 g.) of the original hydroxy-acid, which was again submitted to the methylation process, was recovered by acidification of the above alkaline extract of its methyl ester. The rapid hydrolysis of this ester by cold aqueous alkali was confirmed by the examination of an authentic specimen.

δ-5-*Amino*-2-*methoxybenzoylvaleric Acid.*—When δ-*o*-methoxybenzoylvaleric acid (1 g.) was dissolved gradually in nitric acid (7 c.c., *d* 1·5) at between − 5° and 0°, and the solution poured on ice, δ-5-*nitro*-2-*methoxybenzoylvaleric acid*, pale yellow needles, m. p. 112°, from benzene, was precipitated (Found : C, 55·6; H, 5·7; N, 5·1. $C_{13}H_{15}O_6N$ requires C, 55·5; H, 5·3; N, 5·0%). Attempts to nitrate the methoxy-acid on a larger scale were less satisfactory.

The nitro-acid (1·5 g.) in hot aqueous ammonia was poured into a boiling solution of ferrous sulphate (13·5 g.) to which an excess of concentrated aqueous ammonia had been added. After the mixture had been boiled and shaken for 10 minutes, the aqueous solution was filtered, and evaporated to dryness on a steam-bath. When the residue was washed with water, and the remaining solid crystallised from hot water (charcoal), δ-5-*amino*-2-*methoxybenzoylvaleric acid*, small colourless prisms, m. p. 118°, from alcohol, separated in a practically pure condition (Found : C, 62·0, 62·1; H, 6·7, 7·1. $C_{13}H_{17}O_4N$ requires C, 62·2; H, 6·8%). It was readily soluble in aqueous sodium carbonate, and gave a hydrochloride, m. p. 168° (decomp.), from dilute hydrochloric acid. When diazotised and coupled with alkaline β-naphthol, it gave a red dye.

δ-5-*Benzamido*-2-*methoxybenzoylvaleric acid*, colourless plates, m. p. 146°, from alcohol, separated when a solution of the amino-acid (1 g.) in aqueous sodium hydroxide (50 c.c. of 2%) was shaken with benzoyl chloride (1 c.c.) for 10 minutes and then acidified with hydrochloric acid (Found : C, 68·0; H, 6·0. $C_{20}H_{21}O_5N$ requires C, 67·6; C, 5·9%). δ-5-*Acetamido*-2-*methoxybenzoylvaleric acid*, which separated as its monohydrate in clusters of small prisms,

m. p. 112° (efferv.), from dilute alcohol, was obtained when a solution of the amino-acid in an excess of acetic anhydride was heated for ½ hour on the steam-bath and then diluted with much water (Found: C, 57·9; H, 7·1. $C_{15}H_{19}O_5N,H_2O$ requires C, 57·9; H, 6·8%).

δ-5-*Chloro*-2-*methoxybenzoylvaleric Acid*.—A mixture of ethyl *cyclo*pentanone-2-carboxylate (36 g.) and *p*-chlorophenol (54 g.) was treated with phosphoric oxide (60 g.); frothing quickly set in and much heat was evolved. When cold, the mixture was stirred with ether and an aqueous solution of sodium hydroxide (60 g.) until two clear layers resulted. When the ethereal solution had been well shaken with aqueous sodium hydroxide, dried (calcium chloride), and evaporated, and the residue distilled, 6-*chloro*-2 : 3-*dihydropentachromone*, pale yellow plates, m. p. 129—130°, from alcohol, was collected at approximately 233—235°/23 mm. in small yield (Found: Cl, 16·0. $C_{12}H_9O_2Cl$ requires Cl, 16·1%).

Hydrolysis of this chloro-compound and an investigation of the products by the process described by Hall and Plant (*loc. cit.*) for several analogous 1 : 2 : 3 : 4-tetrahydroxanthone derivatives led to the isolation of δ-5-*chloro*-2-*hydroxybenzoylvaleric acid*, colourless plates, m. p. 136°, from alcohol (Found: Cl, 13·7. $C_{12}H_{13}O_4Cl$ requires Cl, 13·8%); no appreciable quantity of *cyclo*pentanone or 5-chlorosalicylic acid was formed in the reaction.

When this hydroxy-acid, which gave an intense violet-purple colour with ferric chloride, was methylated, and the product purified by a process analogous to that described above for δ-*o*-hydroxybenzoylvaleric acid, δ-5-*chloro*-2-*methoxybenzoylvaleric acid*, colourless plates, m. p. 94°, from dilute alcohol, was obtained (Found: Cl, 13·1. $C_{13}H_{15}O_4Cl$ requires Cl, 13·1%). The acid gave no colour with ferric chloride.

δ-5-Amino-2-methoxybenzoylvaleric acid (0·4 g.) was diazotised in dilute hydrochloric acid and added to a solution of cuprous chloride (0·8 g.) in concentrated hydrochloric acid. On being warmed to 50°, the mixture evolved nitrogen freely and δ-5-chloro-2-methoxybenzoylvaleric acid separated; after crystallisation from dilute alcohol, it melted, alone or mixed with the synthetical product described above, at 94°.

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