CXX.—*The Influence of Groups and Associated Rings on the Stability of Certain Heterocyclic Systems. Part IV. The Substituted Butyro- and Valero-lactones.*

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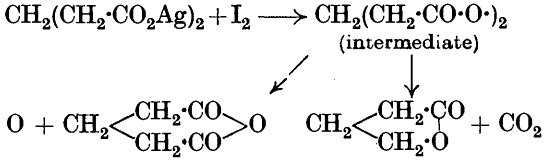
In continuation of the work on substituted paraconic acids (J., 1927, 1257) systems of a still simpler nature have been studied. Although the literature on lactones is fairly extensive, many of the methods described therein are unsuitable for the preparation of the β-mono- and ββ-di-substituted lactones that are necessary to bring the present work into line with the author's previous work on the substituted succin- and glutar-imides (J., 1927, 600, 1252). For instance, reduction of the chlorides or anhydrides of dibasic acids with sodium or aluminium amalgam (Saytzeff, Fichter) generally gives unsatisfactory yields (5—20%). The methods employing γ- and δ-halogenated butyric and valeric acids (Funk, Henry, Cloves) are inapplicable to the higher members of the series owing to the difficulty of preparing suitable halogen compounds. The βγ- and γδ-unsaturated acids (Fittig, Hjelt) corresponding to β-*spiro*-substituted lactones are again obviously unrealisable. The use of acetoacetic or malonic ester (Traube, Wolff, Marburg) is also inexpedient. Reduction of the readily accessible anhydrides of succinic and glutaric acids has its limitations, for the unsymmetrically substituted succinic acids give a difficultly separable mixture of the α- and β-substituted lactones produced by reduction of one or other of the two carbonyl groups (Blanc, *Compt. rend.*, 1904, **139**, 1213).

A general method for the preparation of β-substituted butyrolactones consists in heating the dry silver salt of a glutaric acid with iodine, a mixture of the acid anhydride and the lactone with one carbon atom less than the original acid being formed (Windaus, *Ber.*, 1921, **54**, 581):



$$CH_2(CH_2\cdot CO_2Ag)_2 + I_2 \longrightarrow \underset{\text{(intermediate)}}{CH_2(CH_2\cdot CO\cdot O\cdot)_2}$$

$$O + CH_2{<}{\begin{matrix}CH_2\cdot CO\\ CH_2\cdot CO\end{matrix}}{>}O \qquad CH_2{<}{\begin{matrix}CH_2\cdot CO\\ CH_2\cdot O\end{matrix}} + CO_2$$

The yield of lactone is 30—40%, and since a good part of the anhydride can be recovered as the acid and used again, this method has been utilised in the present instance to prepare simple and mono- and di-substituted butyrolactones.

The substituted valerolactones are best prepared by reduction of the corresponding glutaric anhydrides with sodium and absolute alcohol; sodium amalgam, aluminium amalgam, and zinc dust and acetic or hydrochloric acid give less satisfactory results.

The substituents present in the series of lactones thus prepared are: H, H; Me, H; Et, H; Me, Me; Me, Et; Et, Et; *cyclo*pentane; *cyclo*hexane. The application of the valerolactones in preparing β-substituted adipic acids and the corresponding *cyclo*pentanones is reserved for a future communication.

One method of comparing the stabilities of the two series of lactones would be the determination of their velocity of formation from the hydroxy-acids by means of hydrochloric acid (compare Hjelt, *Ber.*, 1896, **29**, 1855). This method, however, is inapplicable on account of the extreme ease of lactone formation from the higher hydroxy-acids. Henry's method (*Z. physikal. Chem.*, 1892, **10**, 96), therefore, was used, the velocity of hydrolysis of the lactones in *N*/200-solution in 25% ethyl alcohol by the equivalent quantity of alkali hydroxide being determined on the assumption that the reactions are bimolecular.

The results (see table) show that, although the tendency is towards greater stability as each series of lactones is ascended, there are one or two important deviations. For instance, the greatest stability is shown by diethylbutyrolactone in the first series and by *cyclo*-pentane*spiro*valerolactone in the second series.

	Butyrolactones.		Valerolactones.	
Substituents.	Limits of $k \times 10^5$.	Mean $k \times 10^5$.	Limits of $k \times 10^5$.	Mean $k \times 10^5$.
H, H	2660—2870	2790	1470—1570	1520
Me, H	1550—1660	1600	1610—1710	1660
Et, H	1760—1920	1820	1000—1770	1330
Me, Me	460— 524	483	428— 562	494
Me, Et	400— 444	422	350— 399	378
Et, Et	380— 426	415	190— 250	220
*cyclo*Pentane	500— 568	504	126— 133	129
*cyclo*Hexane	476— 541	506	322— 359	340

The number of determinations was 5—7 in each case.

From the results described here and in previous papers, it seems reasonable to conclude that, though the influence of substituents is generally exerted in the direction of increasing stabilisation of the molecule towards hydrolysing agents, it is not easy to predict at what point of any one series the maximum stability will be reached. There seems to exist in each particular class of compounds an optimum condition of stability which is reached by a certain member, the other members falling away from this ideal state according to the extent to which the substituents present in them fail to relieve the strain in the molecular framework. If, as in the present series, the first or the unsubstituted member is in a condition of maximum strain, the tendency of more and more bulky substituents would naturally be to relieve the strain with better and better effect, till the optimum stability is reached. After this, the introduction of still bulkier substituents, or the further forcing together of the extracyclic bonds by the influence of a ring attached to the other bonds of the central carbon atom, can diminish the stability only by straining the bonds of the oxygen atom from the position of greatest stereochemical "ease." A similar case of the reversal of the anticipated effect of substituents was noticed by Dickens, Kon, and Thorpe (J., 1922, **121**, 1496) in the formation of the *cyclo*pentanedione ring by the condensation of oxalic ester with substituted glutaric esters. It was there found that, as the glutaric series was ascended, the difficulty of ring formation was increased owing to the overlapping of the ends of the intermediate open chain (of the oxalyl derivative) brought about by the substituents.

EXPERIMENTAL.

Preparation of the Butyrolactones.—The silver salts of the glutaric acids (precipitated in 80—90% yield by the usual method) crystallised from much boiling water in needles, without appreciable decomposition. They were dried in the steam-oven for 12 hours, finely powdered, and mixed thoroughly with fine sand (3 parts) and then with iodine (1·1 equivs.). The mixtures were each heated at

100—150° for 1—1½ hours and the cooled product was exhaustively extracted with ether. The extract was concentrated somewhat, shaken with a saturated solution of potassium carbonate containing a little sodium sulphite, to remove the anhydride and most of the iodine (in the case of the higher members dilute alkali can be used with advantage, as the anhydrides are somewhat stable; removal of iodine is also thus facilitated), dried with potassium carbonate, and distilled. A small quantity of iodine in the distillate can be removed by means of mercury, but if the amount is considerable the distillate is diluted with ether and the washing is repeated, before distillation of the lactone under reduced pressure.

In each case the structure of the lactone was proved by oxidising 0·5—1·0 g. of it with a mixture of 2 g. of potassium dichromate and 40 c.c. of 10% sulphuric acid on the steam-bath for 3—5 hours. The succinic acid corresponding to the lactone was obtained in very good yield and it was directly compared (mixed melting point) with a genuine specimen.

The lactones are colourless, mobile, pleasant-smelling liquids (except the dimethyl compound, m. p. 57—58°). The lower members are completely miscible with water, but the solubility gradually diminishes and the boiling point increases as the series is ascended.

Butyrolactone was obtained in 30% yield from glutaric acid; b. p. 206°, or 89°/12 mm. (Windaus, *loc. cit.*, gives b. p. 203°) (Found: C, 55·6; H, 7·1; Ag, in silver salt, 51·2. Calc.: C, 55·8; H, 7·0; Ag, 51·2%).

β-*Methylbutyrolactone* was obtained in 35% yield from β-methylglutaric acid; b. p. 88°/12 mm. (Found: C, 59·35; H, 7·85. $C_5H_8O_2$ requires C, 60·0; H, 8·0%. Found for the *silver* salt: Ag, 47·8. $C_5H_9O_3Ag$ requires Ag, 48·0%).

β-*Ethylbutyrolactone* (40% yield) has b. p. 99°/12 mm. (Found: C, 63·05; H, 8·65. $C_6H_{10}O_2$ requires C, 63·15; H, 8·8%. Found for the *silver* salt: Ag, 45·05. $C_6H_{11}O_3Ag$ requires Ag, 45·2%).

ββ-Dimethylbutyrolactone (30% yield) has b. p. 206°, or 89°/12 mm. It solidifies in the receiver and then has m. p. 55—56°. Windaus records b. p. 207—208° and m. p. 55—57° (Found: C, 63·1; H, 9·0; Ag, in silver salt, 44·9. Calc.: C, 63·15; H, 8·8; Ag, 45·2%).

β-*Methyl*-β-*ethylbutyrolactone* (40% yield) has b. p. 98°/10 mm. (Found: C, 65·3; H, 8·95. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%. Found for the *silver* salt: Ag, 42·6. $C_7H_{13}O_3Ag$ requires Ag, 42·7%).

ββ-*Diethylbutyrolactone* (50% yield) has b. p. 117°/12 mm. (Found: C, 67·35; H, 9·6. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%. Found for the *silver* salt: Ag, 40·4. $C_8H_{15}O_3Ag$ requires Ag, 40·75%).

β-cyclo*Pentane*spiro*butyrolactone* was obtained in 20% yield from *cyclo*pentanediacetic acid; b. p. 120—121°/11 mm. (Found: C, 67·5; H, 8·6. $C_8H_{12}O_2$ requires C, 67·6; H, 8·6%. Found for the *silver* salt: Ag, 40·7. $C_8H_{13}O_3Ag$ requires Ag, 40·75%). On oxidation it gave *cyclo*pentane-1-carboxy-1-acetic acid, m. p. 158—159°.

β-cyclo*Hexane*spiro*butyrolactone*, obtained in 45% yield from the corresponding diacetic acid, has b. p. 138°/11 mm. (Found: C, 70.0; H, 9·2. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1. Found for the *silver* salt: Ag, 38·6. $C_9H_{15}O_3Ag$ requires Ag, 38·7%). On oxidation it gave *cyclo*hexane-1-carboxy-1-acetic acid, m. p. 132°.

Preparation of the Valerolactones.—The requisite glutaric anhydrides were obtained in 80—90% yield by boiling the acid (1 mol.) with acetic anhydride (2·5 mols.) and distilling the product under reduced pressure; they collected in the receiver as colourless liquids which rapidly solidified. Care is necessary in distilling dimethylglutaric anhydride, which melts at 124° and tends to block the outlet tube during distillation. Rapid boiling and the use of not very low pressure, or distillation from a retort at ordinary pressure, avoids this difficulty.

The anhydride (1 mol.) is reduced in boiling absolute alcohol (10 mols). by the gradual addition of sodium (4 mols.; twice the theoretical quantity). The cooled mixture is decomposed with water, the alcohol distilled in steam, and the residue acidified with hydrochloric acid and refluxed for 10 minutes to complete the lactone formation; it is then cooled and repeatedly extracted with pure ether. The ethereal solution is washed free from acid (a good proportion of the unchanged glutaric acid may be recovered from the washings), dried over potassium carbonate, and distilled. The residue after removal of ether gave the lactone as the main product in 25—45% yield, together with a small lower-boiling fraction containing the glycol (compare Blanc, *loc. cit.*).

On oxidation with chromic acid each lactone gave the corresponding glutaric acid.

Valerolactone was obtained from glutaric anhydride in 25% yield; b. p. 114°/17 mm. After several weeks the b. p. rises, owing no doubt to partial polymerisation (Found: C, 59·95; H, 8·3; Ag, in silver salt, 47·9. Calc.: C, 60·0; H, 8·0; Ag, 48·0%).

β-*Methylvalerolactone* was obtained from β-methylglutaric anhydride in 25% yield; b. p. 90°/12 mm. (Found: C, 62·85; H, 8·65. $C_6H_{10}O_2$ requires C, 63·15; H, 8·8%. Found for the *silver* salt: Ag, 44·9. $C_6H_{11}O_3Ag$ requires Ag, 45·2%).

β-*Ethylvalerolactone* (28% yield) has b. p. 104°/13 mm. (Found:

C, 65·5; H, 9·5. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%. Found for the *silver* salt: Ag, 42·45. $C_7H_{13}O_3Ag$ requires Ag, 42·7%).

ββ-Dimethylvalerolactone (30% yield) has b. p. 108°/12 mm. and m. p. 30°. Blanc (*loc. cit.*) gives b. p. 232—233° and m. p. 30° (Found: C, 65·4; H, 9·4; Ag, in silver salt, 42·85. Calc.: C, 65·6; H, 9·4; Ag, 42·7%).

β-*Methyl*-β-*ethylvalerolactone* (30% yield) has b. p. 122°/10 mm. (Found: C, 67·5; H, 9·6. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%. Found for the *silver* salt: Ag, 40·25. $C_8H_{15}O_3Ag$ requires Ag, 40·45%).

ββ-*Diethylvalerolactone* (50% yield) has b. p. 143—144°/15 mm. (Found: C, 69·05; H, 10·05. $C_9H_{16}O_2$ requires C, 69·2; H, 10·25%. Found for the *silver* salt: Ag, 38·55. $C_9H_{17}O_3Ag$ requires Ag, 38·4%).

β-cyclo*Pentane*spiro*valerolactone* was obtained in 30% yield from the anhydride (b. p. 176—178°/12 mm., m. p. 68°); b. p. 146°/12 mm. (Found: C, 69·8; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%. Found for the *silver* salt: Ag, 38·8. $C_9H_{15}O_3Ag$ requires Ag, 38·7%).

β-cyclo*Hexane*spiro*valerolactone* was obtained in 35% yield from the anhydride (b. p. 186°/15 mm., m. p. 73°); b. p. 158—159°/10 mm. (Found: C, 71·4; H, 9·25. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%. Found for the *silver* salt: Ag, 36·8. $C_{10}H_{15}O_3Ag$ requires Ag, 36·9%).

Hydrolysis.—The hydrolysis constants of the lactones in *N*/200-solution at 25° in the presence of an equivalent quantity of sodium hydroxide were determined as described in Parts I and II (*loc. cit.*), the only difference being the employment of 25% alcohol (by volume) for making up the solutions, as the higher members were found to be sparingly soluble in water at the dilution employed. In the presence of alcohol the velocity coefficients are higher than when water alone is used, the value for butyrolactone, for example, being 0·0279 instead of 0·0253 as obtained by Henry.

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