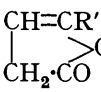
94. *Some Reactions of Δ^{β}-γ-Lactones.*

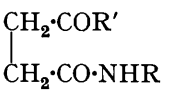
By E. Walton.

Unsaturated lactones of type (I) have been found to react with ammonia and monosubstituted amines to give pyrrolidones, the structure of which (III) has been confirmed, in several cases, by synthesis from the corresponding substituted succinimide and Grignard compound. The *N*-alkyl-substituted pyrrolidones are all amphoteric, readily decomposed by acid into the corresponding γ-keto-acid, and stable in alkaline solution.

In the course of another investigation involving β-benzoylpropionic acid, it was found necessary to re-examine the reactions of this acid in the light of certain discrepancies in the literature.

It seems well established that β-benzoylpropionic acid, when warmed with acetic anhydride, is converted into its unsaturated γ-lactone (I; R′ = C_6H_5) (Biedermann, *Ber.*, 1891, **24**, 4077; Kugel, *Annalen*, 1898, **299**, 54; Thiele and Sulzberger, *Annalen*, 1901, **319**, 196). Fittig (*Annalen*, 1898, **299**, 18), for example, by addition of bromine to the lactone, obtained what was probably the racemic mixture of dibromides, which, he found, decomposed spontaneously to give β-bromo-β-benzoylpropionic acid. There is also little doubt that lævulic acid, on slow distillation, yields angelicalactone (I; R′ = CH_3) (Wolff, *Annalen*, 1885, **229**, 256).


(I.)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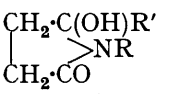
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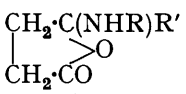
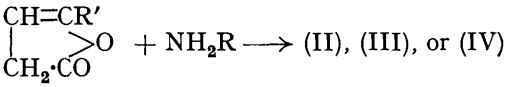
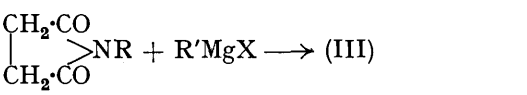

(IV.)

On the other hand, the published evidence as to how such lactones react with amines seems quite inconclusive. Wolff (*loc. cit.*) assumed that ammonia reacted with angelicalactone to give the open-chain amide (II; R = H, R′ = CH_3). Biedermann (*loc. cit.*) also thought that open-chain amides (wrongly formulated as crotonic acid derivatives) were obtained from the aromatic lactone (I; R′ = C_6H_5) when this was treated with ammonia or aniline, whereas Beilstein (" Handbuch," 4th edition, III, 676) was probably the first to indicate the possibility of isomeric structures (II, III, or IV) for such compounds. More recently, Lukeš and Prelog (*Coll. Czech. Chem. Comm.*, 1929, **1**, 119, 282, 334, 461, 617) have sought to differentiate between these structures, by comparing the products of reactions (A) and (B):

(A.) 

(B.) 

They prepared (*loc. cit.*, p. 119) 2-hydroxy-1 : 2-dimethyl-5-pyrrolidone (III; R = R′ = CH_3) by reaction (B), and, on very slender evidence, claimed that it differed from the product obtained from angelicalactone and methylamine (reaction A), which was consequently thought to have structure (II) or (IV). In a later paper (*loc. cit.*, p. 282), similar evidence is adduced for the non-identity of the products obtained from the interaction of methylmagnesium bromide and succinanil on the one hand, and from that of angelicalactone and aniline on the other. Here the distinction between the products is based solely on the fact that an anil (?) could be prepared from the product of reaction (A), but not from that of reaction (B). As both products are correctly stated to melt at about 101°, it is curious that no reference is made to any mixed melting point determination. Having ruled out formula (III) for the products of reaction (A), Lukeš and Prelog (*loc. cit.*, p. 617) eventually conclude that such products must be open-chain amides (II), rather

than amino-lactones of type (IV). The present study, however, leads to quite a different conclusion.

It has now been found that the lactone (I; R′ = C_6H_5) of β-benzoylpropionic acid reacts with aqueous methylamine, ethylamine, *n*-propylamine and *p*-bromoaniline, as well as with ammonia and aniline (Biedermann, *loc. cit.*), to give crystalline products * in all cases. The reaction with aliphatic amines is spontaneous, and presents a striking sequence of colour changes, covering the whole visible spectrum, from green, through blue, violet and red, to yellow, and indicating complex intramolecular changes. The products have also very significant properties. All, except the ammonia and aniline derivatives, are amphoteric, dissolving in about 6N-hydrochloric acid and in 2N-caustic soda, though in the latter there is decreasing solubility with increasing molecular weight and rise in temperature. The methylamine derivative readily dissolves in both cold and hot 2N-caustic soda, the *ethylamine* product only in cold alkali, and the n-*propylamine* derivative is only slightly soluble in the latter. These derivatives are also remarkably stable in alkali. A solution of the methylamine derivative in excess of 2N-caustic soda was refluxed for 5 minutes without appreciable decomposition; and the less soluble ethylamine and *n*-propylamine derivatives appeared to be equally stable. Moreover the aniline derivative was recovered unchanged after its solution in methyl-alcoholic caustic potash had been refluxed. On the other hand, with hydrochloric acid (alcoholic in the case of the aniline derivative), the products are all readily decomposed into β-benzoylpropionic acid and the corresponding amine. The ammonia derivative is exceptional, in so far as, with alkali, it is decomposed into highly coloured products and ammonia. With hydrochloric acid, however, it behaves like its homologues.

The unsaturated *γ-lactones* (I) from β-*p*-toluoyl-, β-*p*-bromobenzoyl- and β-*p*-methoxybenzoyl-propionic acids have also been found to react very easily with ammonia and methylamine to yield *derivatives* with properties very similar to those of the corresponding phenyl derivatives.

The facts described above undoubtedly point to structure (III) for the products of the reaction between Δ^{β}-γ-lactones (I) and amines. Their stability in alkali is incompatible with their formulation as amides of type (II). Amides stable to alkali are limited to those with ample protecting groups (*e.g.*, 2 : 6-dibromo- and 2 : 6-dinitro-benzamides; Claus *et al.*, *Annalen*, 1891, **265**, 377; **266**, 226), and, moreover, such amides are also resistant to acids. The solubility of the products of reaction (A) in acid and in alkali also indicates the pyrrolidone structure (III), which bears some resemblance to those of oxindole, dioxindole and indoxyl, which also are amphoteric. The exceptional behaviour of the ammonia derivatives (III; R = H) towards alkali is probably due to the enhanced activity of the free imide group, and the possibility of tautomerism.

Structure (III) is, moreover, confirmed by the identity now established between the products of reactions (A) and (B), in those cases where R = CH_3 and R′ = C_6H_5, *p*-C_6H_4Me or *p*-C_6H_4Br, and where R = C_6H_5 and R′ = CH_3 (contrary to the evidence of Lukeš and Prelog, *loc. cit.*, p. 282). It has been found impossible to extend this comparison, as all attempts to condense phenylmagnesium bromide with succinimides, other than succinomethylimide, were unsuccessful.

Various attempts to confirm the presence of the hydroxyl group in (III) failed. 2-Hydroxy-2-phenyl-1-methyl-5-pyrrolidone (III; R = CH_3, R′ = C_6H_5) was recovered unchanged after suitable treatment with methyl sulphate, acetic anhydride, and phenyl *iso*cyanate, and with acetyl chloride the same pyrrolidone gave a yellow unsaturated product, similar to that obtainable by its distillation (Lukeš and Prelog, *loc. cit.*, p. 339), indicating the elimination of water rather than acetylation. The unsaturated product was not further investigated, as, theoretically, it is also obtainable from the open-chain amide (II), and, as such, could afford no additional evidence for (III).

Of all the pyrrolidones examined, only the *N*-phenyl derivatives (III; R = C_6H_5, R′ = CH_3 or C_6H_5) decolourise bromine water instantaneously. This is due, not to unsaturation, but to the formation of N-p-*bromophenyl* derivatives, the structures of which were confirmed by synthesis from *p*-bromoaniline and the appropriate lactone.

* It is significant that no such product could be obtained with dimethylamine.

Experimental.

2-Hydroxy-1-phenyl-2-methyl-5-pyrrolidone (III; R = C_6H_5, R′ = CH_3).—γ-Methyl-Δ^{β}-crotonolactone (I; R′ = CH_3) (Wolff, *loc. cit.*) was heated with a slight excess of aniline for 3 minutes at 180°, and the product carefully acidified with dilute hydrochloric acid. The solid obtained crystallised from benzene–petrol in silky needles, m. p. 101°. It dissolved readily in cold 2N-caustic soda, but reappeared as an oil on warming. After the same solution had been boiled for 3 minutes, no free aniline could be detected by diazotisation tests. The pyrrolidone also dissolved in 6N-hydrochloric acid, the solution liberating aniline on warming. The addition of the theoretical quantity of bromine water to a solution of the pyrrolidone in glacial acetic acid led to immediate decolorisation with formation of *2-hydroxy-1-p-bromophenyl-2-methyl-5-pyrrolidone* (III; R = *p*-C_6H_4·Br, R′ = CH_3), which crystallised from benzene in flat prisms, m. p. 159—161° (some decomp.) (Found: Br, 29·5. $C_{11}H_{12}O_2NBr$ requires Br, 29·6%). The structure of the latter was confirmed by its production from angelicalactone (I; R′ = CH_3) and *p*-bromoaniline, which were condensed as described above.

2-Hydroxy-1-phenyl-2-methyl-5-pyrrolidone was also prepared by the following modification of Lukeš and Prelog's Grignard method (*loc. cit.*, p. 285). A solution of succinanil (4·5 g.) in dry benzene (200 c.c.) at 80° was rapidly added to a solution of methylmagnesium iodide prepared from methyl iodide (7·1 g.) and magnesium turnings (1·2 g.) in ether (30 c.c.). There was an immediate precipitate. The mixture was refluxed for 4—5 hours and decomposed with a little water, and the benzene layer dried and evaporated under reduced pressure. The residue crystallised from benzene–petrol in needles (1 g.), m. p. 99—100°, identical in all respects with the product obtained from angelicalactone and aniline. There was, of course, no mixed melting point depression.

γ-Phenyl-Δ^{β}-crotonolactone (I; R′ = C_6H_5) was prepared from β-benzoylpropionic acid and acetic anhydride as described by Kugel (*loc. cit.*). It was found to crystallise best from methyl alcohol, forming pearly leaflets, m. p. 91—92°, which, after some weeks, decomposed into an orange-coloured syrup.

2-Hydroxy-2-phenyl-5-pyrrolidone (III; R = H, R′ = C_6H_5) was obtained in theoretical yield by warming a mixture of the preceding lactone (2 g.) and concentrated aqueous ammonia (10 c.c.) for ½ minute. The resulting solution was cooled and diluted with water; the solid obtained crystallised from water in large tablets, m. p. 123—125° (decomp.) (Found: N, 8·0. Calc. for $C_{10}H_{11}O_2N$: N, 7·9%). 2-Hydroxy-2-phenyl-5-pyrrolidone yielded (*a*) a purple solid on warming with dilute sodium carbonate solution, (*b*) a green tar and ammonia on boiling with 2N-caustic soda, (*c*) β-benzoylpropionic acid and ammonium chloride on warming with concentrated hydrochloric acid for 3 minutes. It dissolved in cold 6N-hydrochloric acid but not in alkali, and was recovered unchanged after treatment with acetic anhydride, methyl sulphate in alkali, and sodium nitrite in glacial acetic acid.

2-Hydroxy-2-phenyl-1-methyl-5-pyrrolidone (III; R = CH_3, R′ = C_6H_5).—When γ-phenyl-Δ^{β}-crotonolactone (1 g.) was stirred with 33% aqueous methylamine (8 c.c.), there was a vigorous reaction. The mixture, after passing through green and violet stages, became crimson, and, on warming for 20 seconds, gave a yellow solution, which deposited crystals of the pyrrolidone on cooling. This crystallised from water, on rapid cooling, in tablets, which slowly changed to hexagonal needles (0·5 g.), m. p. 130—135° (decomp.) (Found: N, 7·1. Calc. for $C_{11}H_{13}O_2N$: N, 7·3%). The pyrrolidone dissolved readily in 2N-caustic soda, from which it was recovered unchanged. It was also soluble in 6N-hydrochloric acid, but the solution decomposed, on warming, with production of β-benzoylpropionic acid. On evaporation of its solution in alcoholic caustic soda (molecular proportions), the pyrrolidone gave an unstable sodio-derivative, which, with water, was hydrolysed back to the original compound. With methyl sulphate, the sodio-derivative gave a yellow unsaturated product, probably similar to that obtained by Lukeš and Prelog (*loc. cit.*, p. 339) by distillation. Neither a methyl nor an acetyl derivative could be made by standard methods.

2-Hydroxy-2-phenyl-1-methyl-5-pyrrolidone, prepared by the interaction of phenylmagnesium bromide and succinomethylimide, as described by Lukeš and Prelog (*loc. cit.*, p. 337), was identical with the preceding compound.

2-Hydroxy-2-phenyl-1-ethyl-5-pyrrolidone (III; R = C_2H_5, R′ = C_6H_5).—The lactone (I; R′ = C_6H_5) and a slight excess of 33% aqueous ethylamine were stirred together, whereupon the mixture showed colour changes, ranging from green, through violet, to pink. On dilution with water, an oil separated, which, after solidification, crystallised from water in octagonal plates, m. p. 85—87° (yield, nearly theoretical) (Found: N, 7·0. $C_{12}H_{15}O_2N$ requires N, 6·8%).

The behaviour of the *pyrrolidone* towards caustic soda and hydrochloric acid was very similar to that of its methyl homologue, except that, on warming, it separated from 2N-caustic soda as an oil. It dissolved slightly in carbonate solution in the cold, separated at about 60°, and redissolved at 100°.

2-Hydroxy-2-phenyl-1-n-propyl-5-pyrrolidone was obtained by stirring the lactone (I; R′ = C_6H_5) with a slight excess of 33% aqueous *n*-propylamine. On dilution with water, it separated as an oil, which, after solidification, crystallised from water in large prisms, and from benzene–petrol in leaflets, m. p. of both forms 85—86° (Found: N, 6·4. $C_{13}H_{17}O_2N$ requires N, 6·4%). It was only slightly soluble in caustic soda solution, but dissolved readily in 10N-hydrochloric acid, which decomposed it on warming.

2-Hydroxy-1 : 2-diphenyl-5-pyrrolidone (III; R = R′ = C_6H_5).—The preceding lactone (2 g.) was boiled with an excess of aniline for 2 minutes, and the mixture acidified. The solid obtained (2·5 g.) crystallised from alcohol in needles, m. p. 148—149° (compare Biedermann, *loc. cit.*). The pyrrolidone was insoluble and quite stable in hydrochloric acid and in caustic soda solution, but was slowly decomposed by hot aqueous-alcoholic hydrochloric acid, in which it was more soluble. Its solution in glacial acetic acid rapidly decolorised bromine water with formation of *2-hydroxy-1-p-bromophenyl-2-phenyl-5-pyrrolidone*. After addition of bromine water until this was no longer decolorised, the solution was diluted with water; the bromo-derivative crystallised from alcohol in needles, m. p. 166° (Found: N, 4·1; Br, 24·15. $C_{16}H_{14}O_2NBr$ requires N, 4·2; Br, 24·1%). The structure of the bromo-derivative was confirmed by its preparation from the lactone (I; R′ = C_6H_5) and a slight excess of *p*-bromoaniline, which were heated together. The melt was acidified, and the resulting solid crystallised from alcohol. With hot aqueous-alcoholic hydrochloric acid, the bromo-compound gave β-benzoylpropionic acid and *p*-bromoaniline.

γ-p-Tolyl-Δ^{β}-crotonolactone (I; R′ = *p*-C_6H_4Me).—β-*p*-Toluoylpropionic acid (Burcker, *Bull. Soc. chim.*, 1888, **49**, 449) (6·4 g.) and acetic anhydride (4·2 g.) were warmed together at 100° for ½ hour. When cold, the mass was washed with methyl alcohol, and the solid (4 g.) collected; it crystallised from methyl alcohol in salmon-pink rhombic leaflets, m. p. 111°, smelling somewhat of coconut oil (Found: C, 75·8; H, 6·0. $C_{11}H_{10}O_2$ requires C, 75·9; N, 5·75%).

2-Hydroxy-2-p-tolyl-5-pyrrolidone (III; R = H, R′ = *p*-C_6H_4Me) (Limpricht and Doll, *Annalen*, 1900, **312**, 111, formulated this compound as an open-chain amide).—The preceding lactone and an excess of concentrated aqueous ammonia were heated at 100° in a sealed tube for 20 minutes. At no stage of the reaction was solution complete. The product crystallised from water in cream-coloured, twinned, rectangular prisms, m. p. 165—167° (decomp. to a purple liquid) (Found: N, 7·0. $C_{11}H_{13}O_2N$ requires N, 7·3%). During the crystallisation, the solution darkened, with production of a small amount of purple solid. The pyrrolidone was decomposed by hydrochloric acid into *p*-toluoylpropionic acid, and by caustic soda solution into a red tar and ammonia.

2-Hydroxy-2-p-tolyl-1-methyl-5-pyrrolidone (III; R = CH_3, R′ = *p*-C_6H_4Me) was prepared by two methods:

(A) The lactone (I; R′ = *p*-C_6H_4Me) was stirred with an excess of 33% aqueous methylamine, and then warmed for ¼ minute. On dilution with water, the solution yielded an oil, which rapidly solidified and then crystallised from water in two forms: (i) hexagonal leaflets, partly melting at 92—93°, obtained by rapid cooling of a concentrated solution, the resulting emulsion being allowed to crystallise undisturbed. It probably contained water of crystallisation (Found: N, 6·6. $C_{12}H_{15}O_2N,\frac{1}{2}H_2O$ requires N, 6·54%). (ii) Twinned rectangular prisms, m. p. 132—140° (decomp. to a green-blue liquid) were readily obtained by slow cooling (Found: N, 6·75. $C_{12}H_{15}O_2N$ requires N, 6·83%). The *pyrrolidone* was stable in 2N-caustic soda, dissolving in the cold, but reappearing as an oil at 100°. With hydrochloric acid it gave β-*p*-toluoylpropionic acid.

(B) A solution of succinomethylimide (3·5 g.) in dry benzene (100 c.c.) was added with shaking to *p*-tolylmagnesium bromide, prepared from *p*-bromotoluene (8·5 g.) and magnesium (1·2 g.) in ether (25 c.c.). There was an immediate reaction. After being heated for 1 hour on the steam-bath, the mixture was poured on ice and concentrated sulphuric acid (1·5 c.c.). After the tarry matter had dissolved, the solution (two layers) was left at 0° for 24 hours. The solid that slowly separated was found, after crystallisation from water, to be identical in all respects with the pyrrolidone prepared by method (A).

γ-p-Bromophenyl-Δ^{β}-crotonolactone (I; R′ = *p*-C_6H_4·Br).—After several experiments, the following method of preparation was found to give the best results: β-*p*-Bromobenzoylpropionic

acid (Fieser and Seligman, *J. Amer. Chem. Soc.*, 1938, **60**, 173) (1 mol.) was warmed with acetic anhydride (2 mols.) at 100° for 1 hour. The red liquid, which solidified on cooling, was treated with cold sodium carbonate solution, and the insoluble red-brown residue collected and washed with water (yield, 60%). A small portion crystallised from methyl alcohol in granular prisms, m. p. 115—130° (decomp.), but, being of doubtful purity, it was not analysed.

2-Hydroxy-2-p-bromophenyl-5-pyrrolidone (III; R = H, R′ = *p*-C_6H_4·Br).—The preceding lactone was warmed with an excess of aqueous ammonia for 2 minutes. At no stage of the reaction was solution complete. The mixture was diluted with water. The solid obtained crystallised from water in yellowish plates, m. p. 169—171° (decomp. to a violet liquid) (Found : N, 5·7. $C_{10}H_{10}O_2NBr$ requires N, 5·5%). With alkalis the *pyrrolidone* decomposed into coloured products; with concentrated hydrochloric acid it gave β-*p*-bromobenzoylpropionic acid.

2-Hydroxy-2-p-bromophenyl-1-methyl-5-pyrrolidone (III; R = CH_3, R′ = *p*-C_6H_4·Br).—The preceding lactone and an excess of 33% aqueous methylamine were warmed together for ½ minute (transient crimson coloration). On addition of water, the crude pyrrolidone separated; it crystallised from water in rectangular prisms, m. p. 145—148° (decomp.), soluble and stable in 2N-caustic soda, but readily decomposed by concentrated hydrochloric acid. It was, moreover, identical in all respects with the pyrrolidone prepared from *p*-bromophenylmagnesium bromide and succinomethylimide as described by Lukes and Prelog (*loc. cit.*, p. 343).

γ-p-Methoxyphenyl-Δ$^{\beta}$-crotonolactone (I; R′ = *p*-C_6H_4·OMe).—β-*p*-Methoxybenzoylpropionic acid (7·6 g.) and acetic anhydride (5 g.) were warmed at 100° for 10 minutes. The resulting *lactone*, after being washed with methyl alcohol, crystallised from the same solvent in pink hexagonal prisms (5·2 g.), m. p. 110—111° (Found : C, 69·3; H, 5·4. $C_{11}H_{10}O_3$ requires C, 69·5; 5·3%).

2-Hydroxy-2-p-methoxyphenyl-5-pyrrolidone (III; R = H, R′ = *p*-C_6H_4·OMe).—The preceding lactone (0·7 g.) was warmed with concentrated aqueous ammonia (5 c.c.) in a sealed tube at 100° until completely dissolved (about 3 minutes). The solution became dark brown and contained traces of green solid; on cooling, it yielded the *pyrrolidone* (0·6 g.), which crystallised from water in yellow hexagonal leaflets, m. p. 133—135° (some decomp.) (Found : N, 6·9. $C_{11}H_{13}O_3N$ requires N, 6·75%). With alkali it gave coloured products and ammonia, and with acid, β-*p*-methoxybenzoylpropionic acid.

2-Hydroxy-2-p-methoxyphenyl-1-methyl-5-pyrrolidone (III; R = CH_3, R′ = *p*-C_6H_4·OMe) was formed spontaneously on treatment of the preceding lactone with an excess of 33% aqueous methylamine. On dilution with water, it separated as an oil, which, after solidification, crystallised from water in large flat needles, m. p. 88—92° (Found : N, 6·4. $C_{12}H_{15}O_3N$ requires N, 6·3%). It had amphoteric properties, similar to those of the other *N*-methylpyrrolidones already described. Attempts to prepare this pyrrolidone by condensing succinomethylimide with *p*-methoxyphenylmagnesium bromide were unsuccessful, probably owing partly to the impurity of the Grignard compound.

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CHEMICAL RESEARCH LABORATORY, TEDDINGTON, MIDDLESEX. [*Received, February 1st*, 1940.]