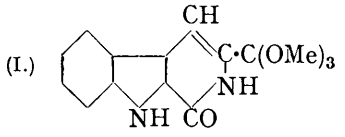
104. *The Hydrolysis of Azlactones with Alcoholic Potassium Hydroxide.*

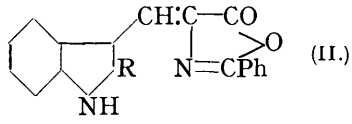
By Eric T. Stiller.

In view of the isolation of methyl 2-keto-2 : 3-dihydro-β-carboline-4-orthoformate (I) from the hydrolytic products of the azlactone, 2-phenyl-4-(2′-carbomethoxyindolylidene)-oxazolone (II, R = CO_2Me), with alcoholic potassium hydroxide (King and Stiller, preceding paper), it was desirable to examine other azlactones when subjected to similar hydrolytic conditions.

When 2-phenyl-4-(*o*-carbomethoxybenzylidene)oxazolone (III, R = CO_2Me), prepared from methyl phthalaldehydate by condensation with hippuric acid in the presence of acetic anhydride (Bain, Perkin and Robinson, J., 1914, **105**, 2397), was hydrolysed by 10% methyl-alcoholic potassium hydroxide, the principal product was *methyl* 1-*keto*-1 : 2-*dihydro*-iso*quinoline*-3-*orthoformate* (IV; R = Me, R′ = H). The properties of this substance were in all respects analogous to those of the corresponding methyl ketocarbolineorthoformate

(I). It was hydrolysed by dilute acids slowly in the cold and rapidly when warmed to give *methyl* iso*carbostyril*-3-*carboxylate* (V; R = Me, R′ = H). On warming with dilute aqueous


(I.)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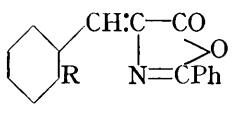
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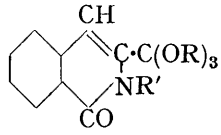
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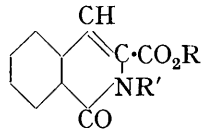
(V.)

potassium hydroxide, it formed a crystalline *potassium* derivative, but prolonged heating converted it into *iso*carbostyril-3-carboxylic acid. By the action of diazomethane *methyl* 1-*keto*-2-*methyl*-1 : 2-*dihydro*isoquinoline-3-*orthoformate* (IV; R = R′ = Me) was produced, which on hydrolysis with dilute acid readily gave *methyl* 1-*keto*-2-*methyl*-1 : 2-*dihydro*isoquinoline-3-*carboxylate* (V; R = R′ = Me).

The corresponding *ethyl* 1-*keto*-1 : 2-*dihydro*isoquinoline-3-*orthoformate* (IV; R = Et, R′ = H) was formed when ethyl alcohol was substituted for methyl alcohol in the hydrolysis of 2-phenyl-4-(*o*-carbomethoxybenzylidene)oxazolone (III, R = CO_2Me). Its properties were completely analogous to those described above for the methyl orthoformate.

The mechanism of the formation of these orthoformates appears to require a carbalkoxy-group R (II or III) on the adjacent nuclear carbon atom, since 2-phenyl-4-benzylideneoxazolone (III, R = H) and 2-phenyl-4-indolylideneoxazolone (II, R = H) gave normal products, namely, α-benzamidocinnamic acid and indole-3-(α-benzamido)acrylic acid respectively.

Beattie (*Amer. Chem. J.*, 1908, **40**, 424) has reported the isolation of an inseparable mixture of methyl and ethyl *iso*carbostyril-3-carboxylates as abnormal constituents of a fasciated variety of *Anemone thalictroides* L. (Rue anemone). *iso*Carbostyrilcarboxylic acid was not esterified when treated with alcohol containing normal concentrations of sulphuric acid (5—10%), but when methyl or ethyl alcohol containing 35—40% of sulphuric acid was used, esterification proceeded smoothly and gave quantitative yields of the methyl or the *ethyl* ester of *iso*carbostyrilcarboxylic acid.

Experimental.

Action of Methyl-alcoholic Potassium Hydroxide on 2-Phenyl-4-(o-carbomethoxybenzylidene)-oxazolone.—The oxazolone (7·4 g.) (Bain, Perkin, and Robinson, *loc. cit.*) was dissolved in methyl alcohol (140 c.c.) containing potassium hydroxide (7 g.), and the yellowish-green solution refluxed for 3 hours. A third of the methyl alcohol was removed by distillation, and water (3 vols.) added to the clear cooled solution, which was then neutralised to litmus by the addition of dilute hydrochloric acid, local acidity being prevented by vigorous stirring. The crystalline *methyl* 1-*keto*-1 : 2-*dihydro*isoquinoline-3-*orthoformate* (IV; R = Me, R′ = H) was collected after standing overnight (yield 4·1 g.), and a further quantity (0·6 g.) obtained by extracting the filtrate with ether. The two crops were combined and dissolved in methyl alcohol and warm water was added until crystallisation commenced; thin hexagonal plates, m. p. 134—135°, were then obtained (Found : C, 62·8; H, 6·2; OMe, 36·5. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·1; OMe, 37·4%), readily soluble in ethyl and methyl alcohol, acetone, and benzene, less readily in ether and light petroleum, and insoluble in water, sodium bicarbonate and cold 2*N*-potassium hydroxide solutions. In alcoholic solution the yellow colour of ferric chloride is intensified. When the orthoformate is boiled with 2*N*-potassium hydroxide for a prolonged period (2 hours), *iso*carbostyril-3-carboxylic acid is produced, m. p. and mixed m. p. 325—326° (decomp.) (Bamberger and Kitschelt, *Ber.*, 1892, **25**, 1143, give m. p. 320°). Cold dilute hydrochloric acid gradually converts the orthoformate into methyl *iso*carbostyril-3-carboxylate, m. p. and mixed m. p. 161—162°. The hydrolysis is complete and quantitative when a suspension of the orthoformate in dilute hydrochloric acid is warmed on the water-bath for a few minutes.

The alcohol from the original neutral aqueous alcoholic filtrate after the separation of the methyl orthoformate was removed by distillation under reduced pressure, and the solution acidified with dilute hydrochloric acid. The colourless crystalline precipitate was collected, dried, and extracted with boiling petrol, which removed benzoic acid. The residual *iso*carbostyril-3-carboxylic acid (0·26 g.) was recrystallised from acetone and had m. p. 325—326° (decomp.) (Found : C, 63·6; H, 4·1. Calc. : 63·4; H, 3·7%). The *methyl* ester was prepared by refluxing *iso*carbostyril-3-carboxylic acid (0·2 g.) with methyl alcohol (8 c.c.) and concentrated sulphuric acid (2 c.c.) for 2 hours; the cooled solution was diluted with water and the needles obtained were recrystallised from alcohol, giving long, fine, colourless needles, m. p. 161—162° (Found : C, 65·1; H, 4·5; OMe, 15·0. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5; OMe, 15·3%). The *ethyl* ester, obtained in quantitative yield in a similar manner, crystallised from alcohol in aggregates of colourless tablets, m. p. 147—148° (Found : C, 66·3; H, 5·0. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%). The *amide* was prepared by treating the methyl ester (1·8 g.) with concentrated aqueous ammonia (30 c.c., *d* 0·880) for 2 hours in a sealed bottle at room temperature, the long needles changing to small rectangular plates; these (1·5 g.) were recrystallised twice from glacial acetic acid and then had m. p. 289° (decomp.) (Found : C, 63·6; H, 4·3. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3%).

Potassium Derivative of Methyl 1-*Keto*-1 : 2-*dihydro*isoquinoline-3-*orthoformate* (IV; R = Me, R′ = K). The orthoformate (0·5 g.) was dissolved in 2*N*-potassium hydroxide (5 c.c.) at 65—70°; on cooling, the *potassium* derivative (0·65 g.) crystallised in colourless prismatic needles, which were dried on porous tile. The derivative is decomposed by water, giving the methyl orthoformate, and the potassium can be estimated by titration with *N*/10-hydrochloric acid (Found : loss at 110°, 17·7. $C_{13}H_{14}O_4NK,3\frac{1}{2}H_2O$ requires H_2O, 18·0%. Found for material dried at 110° : K, 13·5, 13·7 ; OMe, 31·2. $C_{13}H_{14}O_4NK$ requires K, 13·6; OMe, 32·4%).

Methyl 1-*Keto*-2-*methyl*-1 : 2-*dihydro*isoquinoline-3-*orthoformate* (IV; R = R′ = Me).—(a) The methyl orthoformate (0·6 g.), dissolved in methyl alcohol (30 c.c.), was treated with diazomethane (5 mols.) in dry ether (100 c.c.) and after 24 hours the solvents were distilled. The residue was very soluble in all organic solvents and crystallised from 50% aqueous methyl alcohol in colourless, laminated, rectangular plates of *methyl* 1-*keto*-2-*methyl*-1 : 2-*dihydro*isoquinoline-3-*orthoformate*, m. p. 87—88° (Found : C, 63·7; H, 6·4; OMe, 35·4; NMe, 8·2. $C_{14}H_{17}O_4N$ requires C, 63·8; H, 6·5; OMe, 35·4; NMe, 11·0%), which gave no coloration with alcoholic ferric chloride. This *N*-methyl derivative, gently warmed in dilute hydrochloric acid, was quantitatively converted into *methyl* 1-*keto*-2-*methyl*-1 : 2-*dihydro*isoquinoline-3-*carboxylate* (V; R = R′ = Me), which crystallised from alcohol in aggregates of colourless slender prisms, m. p. 132—133° (Found : C, 66·8; H, 5·2; OMe, 14·1; NMe, 9·3. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1; OMe, 14·3; NMe, 13·4%), and gave no colour with alcoholic ferric chloride.

(b) The dried potassium derivative of methyl 1-keto-1 : 2-dihydro*iso*quinoline-3-orthoformate (1·65 g.) was refluxed with methyl iodide (20 c.c.) for 4 hours, the methyl iodide distilled, and water added to the syrupy product. The aqueous suspension was extracted three times with ether. From the dried extract a viscous syrup was obtained which became partly crystalline after several days. It was treated with dilute hydrochloric acid for a few minutes on the water-bath, and the crystalline solid collected. Fractional crystallisation from alcohol gave methyl *iso*carbostyril-3-carboxylate, m. p. 161—162°, and methyl 2-methyl*iso*carbostyril-3-carboxylate, m. p. and mixed m. p. 132—133°. Hence the syrupy methylation product was a mixture of methyl *iso*carbostyril-3-orthoformate and methyl 2-methyl*iso*carbostyril-3-orthoformate.

Action of Ethyl-alcoholic Potassium Hydroxide on 2-*Phenyl*-4-(o-*carbomethoxybenzylidene*)-*oxazolone*.—The oxazolone (5 g.) was refluxed in ethyl alcohol (100 c.c.) containing potassium hydroxide (5 g.) for 3 hours. The potassium benzoate (1·9 g.) that crystallised during the refluxing and also after cooling was removed, and the alcoholic filtrate diluted with water (3 vols.), cooled, and neutralised to litmus with dilute hydrochloric acid with vigorous stirring. The precipitate of *ethyl* 1-*keto*-1 : 2-*dihydro*isoquinoline-3-*orthoformate* (IV; R = Et, R′ = H) (2·6 g.), recrystallised from ethyl alcohol, formed colourless elongated prisms, m. p. 183—185° (Found : C, 66·0; H, 7·1; OEt, 44·1. $C_{16}H_{21}O_4N$ requires C, 65·9; H, 7·2; OEt 46·4%), readily soluble in organic solvents and insoluble in water. When warmed with dilute hydrochloric acid for a few minutes, it was quantitatively converted into ethyl *iso*carbostyril-3-carboxylate, m. p. and mixed m. p. 147—148°. The aqueous alcoholic filtrate after removal of the ethyl orthoformate was freed from alcohol by distillation and acidified with dilute hydrochloric acid, giving *iso*carbostyrilcarboxylic acid (1·7 g.).

Action of Methyl-alcoholic Potassium Hydroxide on 2-*Phenyl*-4-*benzylideneoxazolone* (III; R = H).—The oxazolone (Bain, Perkin, and Robinson, *loc. cit.*) (5 g.) was treated exactly as its

o-carbomethoxy-derivative (p. 474) (methyl alcohol, 100 c.c.; potassium hydroxide, 10 g.). The neutral (litmus) aqueous solution yielded nothing to ether, but when acidified (Congo-red) with dilute hydrochloric acid gave α-benzamidocinnamic acid in fine colourless needles (3·7 g.), m. p. 233—234° (decomp.). This acid (0·5 g.) was heated on the water-bath with acetic anhydride (1 c.c.) for 30 minutes, the cooled solution diluted with water, and the yellow precipitate crystallised from glacial acetic acid; 2-phenyl-4-benzylideneoxazolone was obtained.

Action of Methyl-alcoholic Potassium Hydroxide on 2-Phenyl-4-indolylideneoxazolone.—The azlactone (II; R = H) (1 g.) (Ellinger and Flamand, *Ber.*, 1907, **40**, 3031) was treated with methyl alcohol (20 c.c.) containing potassium hydroxide (2 g.) as in the preceding case. The only product isolated was indole-3-(α-benzamido)acrylic acid (0·87 g.), m. p. 236—237° (decomp.).

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