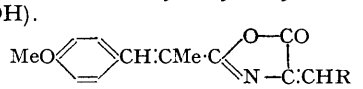
40. *Derivatives of 2-Styryl-4 : 5-dihydro-oxazol-5-one.*

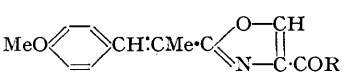
By WILSON BAKER.

p-*Methoxy-α-methylcinnamoylglycine* reacts with ethyl orthoformate and acetic anhydride to give the *ethoxymethyleneoxazolone* (I; R = OEt) some reactions of which are described.

THE interaction of p-*methoxy-α-methylcinnamoyl chloride* and glycine in alkaline solution gave p-*methoxy-α-methylcinnamoylglycine*, and this was converted by the action of ethyl orthoformate and acetic anhydride into 4-*ethoxymethylene*-2-(p-*methoxy*-β-*methylstyryl*)-4 : 5-*dihydro-oxazol*-5-*one* (I; R = OEt). Treatment of (I; R = OEt) with alkali very rapidly gave the sparingly soluble sodium salt of 4-*hydroxymethylene*-2-(p-*methoxy*-β-*methylstyryl*)-4 : 5-*dihydro-oxazol*-5-*one* (I; R = OH).



(I.)



(II.)

The ethoxymethylene compound (I; R = OEt) reacted immediately with aniline at room temperature yielding *4-anilinomethylene-2-(p-methoxy-β-methylstyryl)-4 : 5-dihydro-oxazol-5-one* (I; R = NHPh); a similar behaviour was shown by the hydroxymethylene compound (I; R = OH), but the reaction took several hours. These reactions, and especially the latter, exclude the possibility that the compounds might be the isomeric derivatives of oxazole-4-carboxylic acid (II; R = OEt, OH, or NHPh).

Reduction of the sodium salt of the hydroxymethylene compound (I; R = OH) with hydrogen in presence of Raney nickel resulted in the uptake of one molecule of hydrogen, giving the sodium salt (uncharacterised) of 4-hydroxymethylene-2-(β-*p*-methoxyphenyl*iso*propyl)-4 : 5-dihydro-oxazol-5-one. This salt gave an intensely blue ferric chloride complex soluble in benzene.

This whole series of reactions is similar to the behaviour of cinnamoylglycine which gives the related 2-styryloxazolone derivatives (Committee for Penicillin Synthesis, C.P.S. 35, 55, 66), but is remarkable for the unusual ease with which the various products are isolated in the crystalline state.

Experimental.

p-*Methoxy-α-methylcinnamoyl Chloride.*—*p*-Methoxy-α-methylcinnamic acid (48 g.; 1 mol.) and thionyl chloride (36 g.; 1·2 mols.) were heated on the water-bath for 3 hours; excess of thionyl chloride was removed in a vacuum leaving an oil which solidified on cooling. By crystallisation from light petroleum (b. p. 40—60°) at 0° the p-*methoxy-α-methylcinnamoyl chloride* was obtained in thick, hexagonal plates, m. p. 31° (Found: C, 62·4; H, 5·5. $C_{11}H_{11}O_2Cl$ requires C, 62·7; H, 5·3%).

p-*Methoxy-α-methylcinnamoylglycine.*—The crude acid chloride prepared as above from the acid (48 g.) was dissolved in dry ether (50 c.c.) and added dropwise during 1 hour to an ice-cooled, stirred solution of glycine (22·5 g.; 1·2 mols.) in 2N-sodium hydroxide (150 c.c.; 1·2 equivs.), simultaneously with 2N-sodium hydroxide (150 c.c.). After stirring for a further hour without cooling the ether was removed in a current of air and the liquid filtered (charcoal) and acidified to Congo-red with hydrochloric acid. The solid was collected, washed well with cold water, and crystallised from a mixture of boiling water (2 l.) and glacial acetic acid (200 c.c.) (charcoal 20 g.), giving p-*methoxy-α-methylcinnmoylglycine* as thin, colourless prisms (45·7 g.), m. p. 127° with some previous softening (Found: C, 62·9; H, 6·2; N, 5·5. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·0; N, 5·6%).

4-Ethoxymethylene-2-(p-methoxy-β-methylstyryl)-4 : 5-dihydro-oxazol-5-one (I; R = OEt).—The condensation of the preceding acid with ethyl orthoformate and acetic anhydride has been studied in some detail. The best yields are obtained with not less than 5 molecules of acetic anhydride; with 4 molecules of the anhydride smaller yields of very dark products result even when the reaction is carried out at 100°, and the yields are even less satisfactory with 3 molecules. The optimum conditions are described below. *p*-Methoxy-α-methylcinnamoylglycine (5 g.), orthoformic ester (3·6 g.; 1·2 mols.), and acetic anhydride (10 g.; 5 mols.) were heated (oil-bath at 120—130°) for ½ hour. On cooling the oxazolone derivative separated in pinkish crystals which were collected and washed with cold alcohol (yield, 2·0 g.); a further quantity (0·1 g.) separated from the combined mother-liquors and washings. *4-Ethoxymethylene-2-(p-methoxy-β-methylstyryl)-4 : 5-dihydro-oxazol-5-one* crystallised from alcohol (charcoal) in very pale pinkish needles, m. p. 145° (Found: C, 66·8; H, 5·6; N, 5·1. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9; N, 4·9%).

4-Hydroxymethylene-2-(p-methoxy-β-methylstyryl)-4 : 5-dihydro-oxazol-5-one (I; R = OH).—The preceding compound (2·5 g.) was warmed to 50° with alcohol (20 c.c.) and a solution of sodium hydroxide (0·6 g.; *ca.* 1·5 mols.) in water (20 c.c.), whereupon solution occurred followed by separation of the very sparingly soluble sodium salt of the hydroxymethylene derivative. After cooling, the sodium salt was collected, washed with cold water, and dried (1·8 g.). The filtrate and washings were acidified whereupon the remainder of the substance separated as the free hydroxymethylene compound as a bright yellow precipitate which was collected, washed, and dried (0·5 g.). By rapid crystallisation from a small volume of warm acetic acid, the *4-hydroxymethylene-2-(p-methoxy-β-methylstyryl)-4 : 5-dihydro-oxazol-5-one* (I; R = OH) separated in small, golden-yellow, highly refracting triangular plates, m. p. (rapid heating) *ca.* 167—168° (decomp.). These crystals probably contain solvent of crystallisation, and become opaque after drying in a vacuum over sodium hydroxide (Found in material dried in a vacuum at 100° over sodium hydroxide: C, 64·6; H, 5·1; N, 5·9. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0; N, 5·4%). The compound is not stable in hot acetic acid solution which rapidly becomes red; the solution also stains organic matter, including the skin, a dark purple-red colour. Addition of ferric chloride to its alcoholic solution gives a dull blue-green colour, becoming violet on the addition of water, and then slowly red. Treatment with ethereal diazomethane gives a yellow oil, insoluble in aqueous sodium hydroxide, and which gives no colour with alcoholic ferric chloride, but does not appear to react with aniline.

4-Anilinomethylene-2-(p-methoxy-β-methylstyryl)-4 : 5-dihydro-oxazol-5-one (I; R = NHPh).—(*a*) The ethoxymethylene derivative (I; R = OEt) (0·25 g.) was dissolved in a mixture of alcohol (2 c.c.) and chloroform (2 c.c.) and aniline (0·25 c.c.) added. In about 1 minute yellow crystals began to deposit which were later collected and washed with cold alcohol (yield, 0·24 g.; m. p. 201°). The *anilinomethylene* derivative separated from a mixture of ethyl alcohol and ethyl acetate in bunches of bright yellow prisms, m. p. 201—202° (Found: C, 71·7; H, 5·5; N, 8·8. $C_{20}H_{18}O_3N_2$ requires C, 71·8; H, 5·4; N, 8·4%).

(*b*) A similar experiment using the hydroxymethylene compound (I; R = OH) in place of the ethoxymethylene compound (I; R = OEt) gave the anilino-derivative (I; R = NHPh) (0·20 g.),

m. p. without recrystallisation 202° (mixed m. p. with the previous specimen, 201—202°). In this case the reaction is slow, the derivative being deposited only after several hours.

Reduction of 4-*Hydroxymethylene*-2-(p-*methoxy*-β-*methylstyryl*)-4 : 5-*dihydro-oxazol*-5-*one*.—The sodium salt of the hydroxymethylene derivative (0·6 g.) in alcohol (15 c.c.) and water (15 c.c.) was shaken in hydrogen in presence of Raney nickel. Absorption of hydrogen ceased after 1 molecule had been taken up, and the filtered solution was evaporated to dryness under reduced pressure at 50°, leaving the sodium salt of 4-hydroxymethylene-2-(β-*p*-methoxyphenyl*iso*propyl)-4 : 5-dihydro-oxazol-5-one as a colourless, non-crystalline solid residue. An aqueous solution of this salt gave an intense blue colouration with ferric chloride, the coloured complex being soluble in benzene, a property rapidly destroyed by previously treating the solution with acid which doubtless causes opening of the oxazolone ring. Dilute aqueous or aqueous-alcoholic solutions of the salt show a marked blue fluorescence.

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