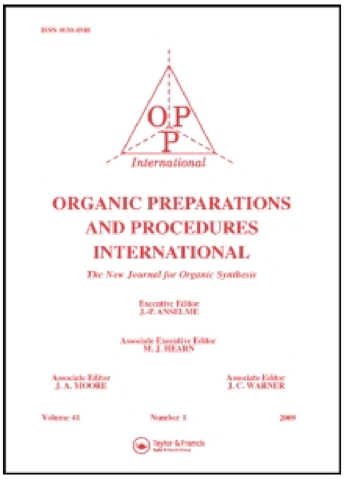

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4-(ISOPROPYLIDENE)-2-(2'-PHENYLETHYL)-5-OXAZOLONE

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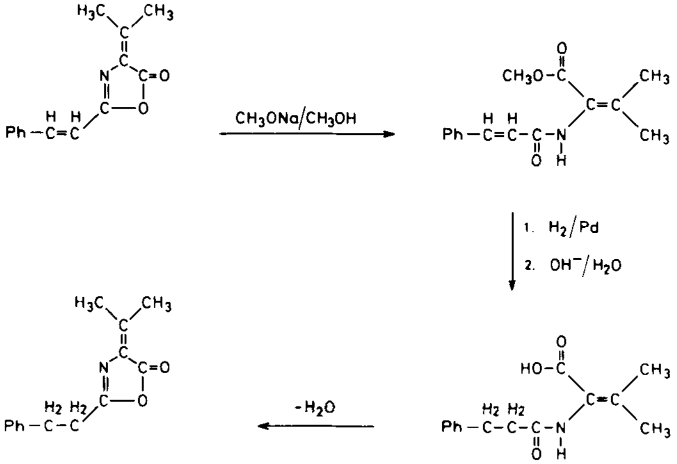
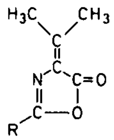
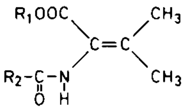


2-Substituted-4-isopropylidene-5-oxazolones are valuable as starting material for the synthesis of penicillin[1,2] and of dyes[3]. The 2-<u>aryl</u>-4-isopropylidene-5-oxazolones are simply prepared, in good yield, by Erlenmeyer condensation of N-<u>aroylg</u>lycines and acetone[4]. This reaction cannot be used, however, for the synthesis of 2-<u>alkyl</u>-4-isopropylidene-5-oxazolones, owing to the instability of the intermediate 2-<u>alkyl</u>-5-oxazolones[5]. Other routes to the 2-alkyl-4-isopropylidene-5-oxazolones are described[1,6,7], but these are laborious and give poor yields. These 2-alkyl-4-isopropylidene-5-oxazolones are of particular interest, because of the rapid hydrolysis of the oxazolone ring in a neutral medium[7]. In this paper we present a preparation of a 2-alkyl-4-isopropylidene-5-oxazolone (I; alkyl = 2'-phenylethyl) based on an Erlenmeyer condensation[5,8]. We obtained 4-isopropylidene-2-styryl-5-oxazolone (II) from a condensation of cinnamoylglycine and acetone[5,9]. This compound could not be hydrogenated specifically to the desired oxazolone I.



I, $R = C_6H_5(CH_2)_2$
II, $R = C_6H_5CH=CH$



III, $R_1 = CH_3$ and $R_2 = C_6H_5CH=CH$
IV, $R_1 = CH_3$,, $R_2 = C_6H_5(CH_2)_2$
V, $R_1 = H$,, $R_2 = C_6H_5(CH_2)_2$

Therefore the oxazolone II was converted into the α-(3-phenylacryloylamino)-β,β-dimethylacrylic acid methyl ester (III). The styryl group in this compound was hydrogenated and the α-(3-phenylpropionylamino)-β,β-dimethylacrylic acid methyl ester was subsequently hydrolyzed to the corresponding acid (V). Dehydration of α-(3-phenylpropionylamino)-β,β-dimethylacrylic acid with dicyclohexylcarbodiimide in dimethylformamide yielded the 4-isopropylidene-2(2'-phenylethyl)-5-oxazolone (I).

EXPERIMENTAL[10]

4-Isopropylidene-2-styryl-5-oxazolone (II)

In a 2 l. three-necked flask, a mixture of 41.0 g (0.2 mole) of N-cinnamoylglycine and 13.1 g (0.16 mole) of freshly fused sodium acetate, was suspended in 1.2 l of dry acetone. The suspension was stirred vigorously and 51.0 g (0.5 mole) of acetic anhydride was added over a period of 45 minutes. After heating under reflux for 19 hours, the reaction mixture was poured on ice, and water was added until the total volume was 3 l. The resulting precipitate was filtered and washed with water. After drying over phosphorus pentoxide *in vacuo*, 30.9 g (68%) practically pure oxazolone (II) was obtained, m.p. 117-118° (117-118°[4b]).

α-(3-Phenylacryloylamino)-β,β-dimethylacrylic acid methyl ester (III)

To a solution of sodium methoxide (from 1.04 g of sodium) in 300 ml of methanol, 47.4 g (0.21 mole) of 4-isopropylidene-2-styryl-5-oxazolone dissolved in 360 ml of benzene was added at 0°. After stirring for 4 hours, 5 ml of concentrated hydrochloric acid was added, and the reaction mixture was evaporated to dryness. The residue was crystallized from benzene to give 48.7 g (90%) of the ester (III), m.p. 152-153°.[11]

Anal. Calcd. for $C_{15}H_{17}NO_3$: C 69.48; H 6.61; N 5.40
Found : C 69.6 ; H 6.6 ; N 5.5
IR ($CHCl_3$):3230 (NH), 1723 (C=O), 1675 and 1652 (C=C) cm^{-1}.
NMR ($CDCl_3$): NH at δ 7.92 (1), CH=CH at δ 7.72 and 6.72 (2,J_{AB}= 16 Hz), C_6H_5 at δ 7.40 (5), CH_3COO at δ 3.75 (3), $(CH_3)_2$ C=C at δ 2.13 (3) and δ 1.88 (3).

α-(3-Phenylpropionylamino)-β,β-dimethylacrylic acid methyl ester (IV)

A solution of 29.5 g (0.11 mole) of α-(3-phenylacryloylamino)-β,β-dimethylacrylic acid methyl ester (III) in 1.5 l of ethyl acetate was hydrogenated at atmospheric pressure over 0.6 g of palladium (10% on carbon). Hydrogen uptake ceased after absorption of 3.1 l (0.13 mole). Removal of the catalyst by filtration and evaporation of the solvent gave a solid residue, which was crystallized from benzene to give 27.5 g (93%) of the ester (IV), m.p. 114-115°.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C 68.94; H 7.33; N 5.36
Found : C 69.0 ; H 7.3 ; N 5.4
IR ($CHCl_3$): 3300 (NH), 1721 (C=O), 1643 (C=C) cm^{-1}.
NMR $(CDCl)_3$: C_6H_5 at δ 7.30 (5), NH at δ 6.93 (1), CH_3COO at δ 3.70, $(CH_2)_2$ at δ 2.83 (4, A_2B_2), $(CH_3)_2$ at δ 2.13 (3) and δ 1.72 (3).

α-(3-Phenylpropionylamino)-β,β-dimethylacrylic acid (V)

A mixture of 15.7 g (0.06 mole) of α-(3-phenylpropionylamino)-β,β-dimethylacrylic acid methyl ester (IV), 37.2 g (0.13 mole) of sodium carbonate 10 aq., and 300 ml of water was heated under reflux for 2 hours. The mixture was then cooled to room temperature and acidified by adding concentrated hydrochloric acid. The resulting precipitate was filtered off and washed with water. After drying and crystallization from benzene/ethyl acetate (1:1), 13.5 g (91%) of the acid (V) was obtained, m.p. 175-176° (dec.).
IR (KBr): 3310 (N-H), 1689 (C=O), 1622 (C=C) cm^{-1}.
NMR (DMSO-d_6); COOH at δ 8.97, C_6H_5 at δ 7.25 (5), $(CH_2)_2$ at δ 2.70 (4, A_2B_2), $(CH_3)_2$-C=C at δ 2.01 and δ 1.66.
Structure proof of this compound was furnished by conversion with diazomethane into the methyl ester (IV).

4-Isopropylidene-2-(2'-phenylethyl)-5-oxazolone (I)

A mixture of 8.2 g (0.033 mole) of α-(3-phenylpropionylamino)-β,β-dimethylacrylic acid (V), 6.9 g (0.033 mole) of dicyclohexylcarbodiimide, and 60 ml of dry dimethylformamide was stored at 4° for 4 hours. The resulting precipitate (3.0 g) was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was partly dissolved in ether and the insoluble material (4.4 g) was filtered off. The filtrate was concentrated and the residue distilled to give 4.7 g (62%) of the oxazolone (I), b.p. 145-146°/1.5 mm.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C 73.34; H 6.59; N 6.11

Found : C 73.2 ; H 6.6 ; N 6.0

IR (neat): 1782 (C=O), 1672 (C=C), 1616 (C=N) cm^{-1}.

NMR ($CDCl_3$): C_6H_5 at δ 7.25 (5), $(CH_2)_2$ at δ 2.90 (4, A_2B_2), $(CH_3)_2$ C=C at δ 2.28 (3) and δ 2.20 (3).

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