SYNTHESIS OF SOME NEW HETEROCYCLIC COMPOUNDS WITH EXPECTED POTENTIAL BIOLOGICAL ACTIVITY

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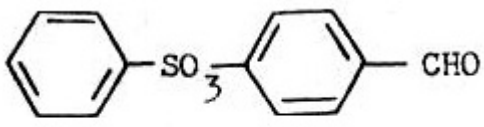
SUMMARY: Benzenesulphonate of p-hydroxybenzaldehyde reacts with hippuric acid in the presence of acetic anhydride and sodium acetate to give 4-(benzylidene-4'-benzenesulphonate)-2- phenyl -2- oxazolin -5- one II. Reaction of II with chloroaniline or o-phenylenediamine in ethyl alcohol afforded the corresponding arylcarboxamides of α-arylcarb-oxamido-cinnamic acids III a, b. When the reaction was carried out in acetic acid containing sodium acetate the products were the imidazolone IV and benzimidazole V derivatives. Under the same conditions II reacts with p-phenylenediamine to give the bis-imidazolone VI derivative. Also II undergoes addition reactions with piperidine and thiophenol to yield the addition products VII a, b. Michael reaction of ethyl cyanoacetate with II affords compound VIII.

Key Word: Heterocyclic compounds.

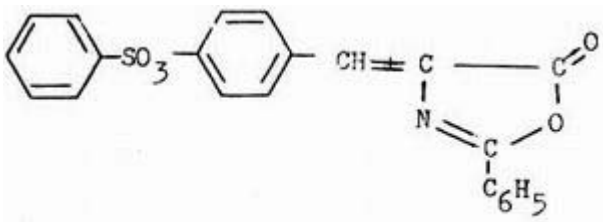
The promising usefulness of the oxazole derivatives as biologically active products has been previously reported (1-3). On the other hand, the aromatic esters of arylsulphonic acids are known to exhibit marked acaricidal (4), insecticidal (5) and bactericidal activity (6). These observations have encouraged us to synthesize some new products containing the oxazole and arylsulphonate moiety hoping to obtain new compounds with potential biological activity.

In continuation of our previous work in this area (7,8), we have synthesized 4-(benzylidene-4'- benzenesulphonate)-2- phenyl -2-oxazolin-5- one and studied some of its reactions. Thus, benzenesulphonyl chloride reacts with p-hydroxybenzaldehyde to give the benzene sulphonate of p-hydroxybenzaldehyde I. This product was characterised by correct analytical data and by i.r. measurements. The ^{1}HNMR spectrum of I gave signals at δ 9.6 ppm (s, 1H, CHO) and 6.8 - 7.4 ppm (m, 9H, aromatic).



I

Treatment of I with hippuric acid in the presence of acetic anhydride and freshly fused sodium acetate afforded 4.(benzylidene-4-benzenesulphoate) -2-phenyl -2-oxazolin -5- one II. This product was identified by elemental analysis and i.r. spectra revealing bands at 1800, 1640 and 1310 cm^{-1} characteristics for the C=0 of the lactone, C=N and $SO_3C_6H_5$ groups, respectively.



II

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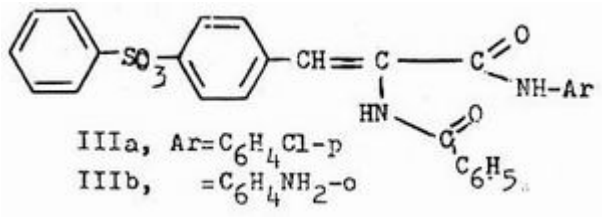
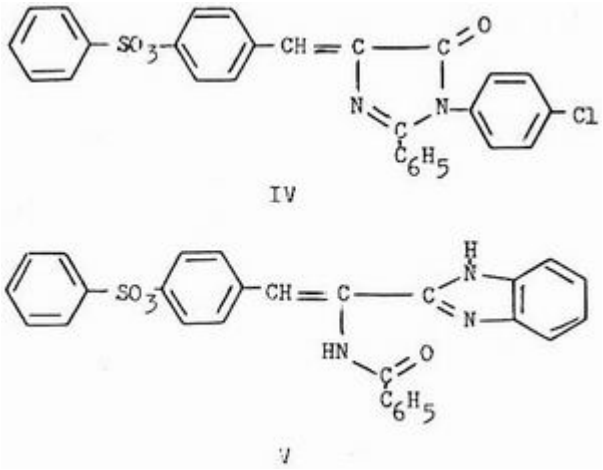


It has been reported that treatment of 4-arylmethylene-2-aryl-2-oxazolin-5- one with aromatic amines generally leads to ring opening at C_5 to give the corresponding aryl-carboxamides of α-arylcarboxamido-cinnamic acids (9-11). These producst may be recyclised to the corresponding imidazolone derivatives under the effect of acetic acid and sodium acetate. Thus, treatment of II with p-chloroaniline and o-phenylenediamine in ethanol afforded the corresponding cinnamic acid derivatives III a, b.

The i.r. spectra of compounds III a, b showed absorption bands at 3300, 1680, 1620 and 1300 cm^{-1} attributable to the NH, CONH, C=N and $SO_3C_6H_5$ groups, respectively.

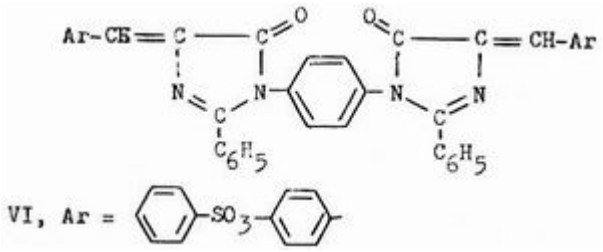


On the other hand, treatment of II with p-chloroaniline and o-phenylenediamine in acetic acid containing freshly fused sodium acetate gave the corresponding imidazolone IV and benzimidazole V derivatives, respectively.

The i.r. spectrum of compound IV revealed stretching frequencies at 1720, 1635, and 1320 cm^{-1} characteristic for the CONR, -C=N and $SO_3C_6H_5$ groups, respectively; those of product V showed bands at 3400, 3300, 1640 and 1330 cm^{-1} attributable to the NH, enolised OH, -C=N and $SO_3C_6H_5$ groups, respectively.

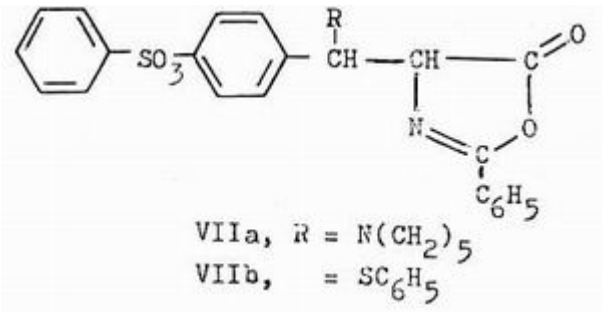
It seems that the above interactions lead to opening of the oxazolone ring at C_5 to give compounds IIIa, b which cyclised to the imidazolone and benzimidazole derivatives IV and V, respectively. In order to verify this mechanism, the open structures IIIa, b were treated with acetic acid and fused sodium acetate and the products were the imidazolone IV and benzimidazole V derivatives.

Treatment of compound II with p-pehenylenediamine in acetic acid containing catalytic amounts of freshly fused sodium acetate gave the corresponding bis-imidazolone derivative VI. This product was caharacterised by analysis

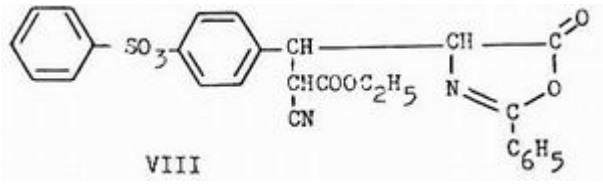


and by i.r. spectra which showed bands at 1725, 1640 and 1330 cm^{-1} attributable to the -CONR, -C=N and $SO_3C_6H_5$ groups, respectively.

The reactivity of the exocyclic C=C in the four position of the oxazolone ring is due to conjugation with the adjacent carbonyl group. Thus addition of piperidine and thiophenol to the olefinic double bond in the four position of compound II gives the corresponding addition products VIII a, b.



The i.r. spectra of compounds VIIa, b showed bands at 1780, 1620, 3300 and 1310 cm^{-1} characteristic for the CO of the lactone, -C=N, enolised OH and $SO_3C_6H_5$ groups, respectively. In addition VIIb gave a band at 1710 cm^{-1} attributable to the -C-S-C- group.



The present investigation deals also with the Michael addition on the exocyclic double bond in compound II. Thus, addition of ethyl cyanoacetate to II gave the compound VIII. The i.r. spectrum of VIII showed bands at 1785, 1725, 3450, 1640, 1310 and 2240 cm^{-1} characteristic for the CO of the lactone, CO of the ester, enolised OH, -C=N-,$SO_3C_6H_5$ and -C=N groups, respectively.

EXPERIMENTAL

Melting points are uncorrected. Analytical data were determined by the Microanalytical Unit, Faculty of Science, Mansoura University. The infra-red spectra were recorded on a Unicam spectrophotometer Model SP 1200 using KBr Wafer technique. ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard with 60 MHz spectrometer

Benzenesulphonate of p-hydroxybenzaldehyde I.

A mixture of sodium hydroxide (0.5 mol) in water (80 ml), p-hydroxy-benzaldehyde (0.5 mol) and benzenesulphonyl chloride (0.5 mol) and benzenesulphonyl chloride (0.5 mol) was stirred at room temperature for 15 minutes then heated at 60-70°C with stirring for further one hour. The reaction mixture was left to cool at room temperature and the precipitated solid product was filtered and crystallised from ethanol to give compound I as white crystals, m.p. 78°C in 85% yield.

Analysis: Calcd. For $C_{13}H_{10}O_4S$: C, 59.54; H, 3.82. Found: C,59.20; H, 3.55.

4-(Benzylidene-4'- benzenesulphonate) -2- phenyl-2-oxazolin -5- one II.

A mixture of I (0.1 mol) and hippuric acid (0.1 mol) in acetic acid anhydride (100 ml) containing freshly fused sodium acetate (1.0 g) was heated at 100°C for three hours. The reaction mixture was cooled to room temperature and ethyl alcohol (50 ml) was added cautiously, then was heated under reflux for one hour and cooled. The formed solid product was filtered washed with ethyl alcohol and crystallised from ethanol to give orange crystals of II, m.p. 140°C in 72% yield.

Analysis: Calc. For $C_{22}H_{15}NO_5S$: C, 65.19; H, 3.70. Found : C, 65.28; H, 3.92.

4-(Benzenesulphonato - α - benzamido) -cinnamic acid -4- chloroanilide IIIa.

A mixture of II (0.03 mol) and p-chloroaniline (0.03 mol) in ethanol (25 ml) was refluxed for three hours. The reaction mixture was cooled and the formed solid product was filtered and crystallised from solid product was filtered and crystallised from ethanol to give grey crystals of IIIa, m.p. 180°C in 43% yield.

Analysis: Calcd. For $C_{28}H_{21}C1N_2O_5S$: C, 63.10; H, 3.94. Found: C, 63.13; H, 4.20.

4. (Benzenesulphonato - α - benzamido) -cinnamic acid 2 - aminoanilide IIIb.

A mixture of II (0.05 mol) and o-phenylenediamine (0.05 mol) in ethanol (50 ml) was refluxed for four hours. The reaction mixture was left to stand at room temperature overnight and the precipitated solid product was filtered and crystallised from ethanol to give compound IIIb, m.p. 115-116°C in a 49% yield.

Analysis: Calcd. For $C_{28}H_{23}N_3O_5S$: C, 65.49; H, 4.48. Found: C, 65.52; H, 4.60.

1-(4"-Chlorophenyl) -2- phenyl-4 (benzylidene- 4' benzenesulphonate) -2- imidazolin -5- one IV.

A mixture of II (0.03 mol) and p-chlororoaniline (0.03 mol) in acetic acid (25 ml) and freshly fused sodium acetat (0.5) g was heated under reflux for four hours. The reaction mixture was cooled and the obtained solid product was filtered and crystallised from ethanol to give the imidazolone derivative IV, m.p. 202°C in 64% yield.

Analysis: Calcd. For $C_{28}H_{19}C1N_2O_4S$: C, 65.31; H, 3.69. Found: 65.71; H, 4.00.

2-(α - Benzamido - β - phenyl benzenesulphonate) - vinyl- benzimidazole V.

A mixture of II (0.03mol) and o-phenylenediamine (0.03 mol) in acetic acid (50 ml) containing freshly fused sodium acetate (0.5 g) was heated under reflux for four hours. The reaction mixture was left to stand overnight at room temperature and the precipatate was filtered and crystallised from ethanol to give the benzimidazole derivative V, m.p. 250°C in 56% yield.

Analysis: Calcd. For $C_{28}H_{21}N_3O_4S$: C, - &.88; h, 4.24. Found: C, 67.56; H, 4.48.

Cyclisation of Compounds IIIa, b, into IV and V.

Compounds IIIa, b (1.0 g in each case) were refluxed in acetic acid (30 ml) containing freshyl fused sodium acetate 0.5 g for three hours. The reaction mixture was cooled and the precipitated solid was filtered and crystallised from ethanol to give the imidazolone IV and benzimidazole V derivatives, respectively. These products were characterised by analysis, m.p. and mixed melting points.

1-(1", 4" -phenylene) -bis (2-phenyl-4 (benzylidene-4'-benzenesulphonate) -2-imidazolin-5- one VI.

A mixture of II (0.05 mol) and p-phenylenediamine (0.025 mol) in acetic acid (40 ml) containing freshyl fused sodium acetate (0.5 g) was heated under reflux for three hours. The reaction mixture was cooled and the formed solid product was filtered and crystallised from acetic acid to give the bis-imidazolone derivative VI, m.p. 278°C, in 74 % yield.

Analysis: Calcd. For $C_{50}H_{34}N_4O_8S_2$: C, 68.03; H, 3.85. Found: C, 68.18; H, 3.92

Reaction of II with piperidine and thiophenol. Formation of the addition products VII a, b.

A mixture of II (0.05 mol) and of the appropriate reagent (0.05 mol) in dry benzene (30 ml) was heated at 60°C with stirring for one hour. The reaction mixture was left to stand overnight at room temperature. Petroleum ether (40-60°C) was added and the precipitated solid products were filtered and crystallised from ethanol to give VIIa, m.p. 210°C in 72°C in 72% yield.

Analysis : Calcd. For $C_{27}H_{26}N_2O_5S$: C, 66.12; H, 5.31. Found: C, 66.43; H, 4.21.

Reaction of II with ethyl Cyanoacetate. Formation of compound VIII.

A mixture of II of (0.03 mol), ethyl cyanoacetate (0.06 mol) and few drops of piperidine in dry chloroform (50 ml) was heated under reflux for five hours. The solvent was distilled under reduced pressure and the obtained solid product was filtered, washed with cold water and crystallised from ethanol to give compound VIII, m.p. 160° in 62% yield.

Analysis: Calcd. For $C_{27}H_{22}N_2O_7S$: C, 62.54; H, 4.25. Found: C,62.44; H, 4.20.

The biological activity of all prepared compounds are now under consideration.

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