Fused Heterocycles. IV.[1] Synthesis of 7-(*o*-Hydroxyphenyl)-3,5-dimethyl-7,8-dihydro-6*H*-isoxazolo[4,5-*b*]azepines

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Synopsis. Michael addition of acetylacetone to 3-methyl-4-nitro-5-(*o*-hydroxystyryl)isoxazoles gives 4-(*o*-acetoxyphenyl)-5-(3-methyl-4-nitro-5-isoxazolyl)-2-pentanones (**4**). Reductive cyclization of **4** with tin(II) chloride and concentrated hydrochloric acid leads to 7-(*o*-hydroxyphenyl)-3,5-dimethyl-7,8-dihydro-6*H*-isoxazolo[4,5-*b*]azepines. The formation of **4** has been rationalized through ortho effect. NMR and mass spectra of products have been discussed.

Though the formation of isoxazoles fused to a variety of heterocycles[2] has been extensively investigated, the isoxazoloazepines[3] have received very little attention. Furthermore, there is no general method of synthesis of isoxazoloazepines to date. Hence we recently reported the formation of hitherto unknown 3-methyl-5,7-diarylisoxazolo[4,5-*b*]azepines[4] by a facile reductive cyclization of ε-nitro ketones. In continuation of our interest, the report describes the preparation of title compounds.

Condensation of 3,5-dimethyl-4-nitroisoxazole (**1**) with various salicylaldehydes in boiling ethanol in the presence of piperidine gave the regioselective products namely, 3-methyl-4-nitro-5-(*o*-hydroxystyryl)isoxazoles (**2**).[5,6] Michael addition of acetylacetone to **2** has been carried out in boiling triethylamine for 4 h. The products which were insoluble in aq dil. sodium hydroxide and gave no colouration with iron(III) chloride have been identified as 4-(*o*-acetoxyphenyl)-5-(3-methyl-4-nitro-5-isoxazolyl)-2-pentanones (**4**) on the basis of IR (transparent in the hydroxyl region, 1775 cm^{-1} for ester >CO and 1725 cm^{-1} for ketonic >C=O) and NMR spectra (δ 2.35, s, 3H-OCOCH$_3$ and two doublets one each for 2H at 3.50 and 2.85 from two CH_2 groups). The 2-pentanone (**4**) might come through the intermediacy of **3** *via* **3A** and **3B** *i.e.*, due to ortho effect. The mechanism put forth is amply supported by the fact that 3-methyl-4-nitro-5-styrylisoxazoles (with no *o*-hydroxyl in the styryl moiety) and acetylacetone under identical conditions gave the β-diketones (**5**).[7]

The Michael products (**4**) on heating with tin(II) chloride and concd hydrochloric acid for 1.5—3.5 h underwent reductive cyclisation to 7-(*o*-hydroxyphenyl)-3,5-dimethyl-7,8-dihydro-6*H*-isoxazolo[4,5-*b*]azepines (**6**) through the intermediacy of the transient amino ketone. Five isoxazoloazepines thus prepared have been included in the table along with the characterization data. Chemical as well as spectroscopic evidence has been adduced for the occurrence of deacetylation during reduction. The cyclized product is not only soluble in dil. sodium hydroxide but also gives fairly intense colouration with iron(III) chloride. The IR spectrum shows no carbonyl absorption but a hydroxyl function (3300 cm^{-1}). Mass spectrum supports the same as it shows molecular ion at *m/e* 256. NMR spectrum shows only two methyls (δ 2.2, s, 3-CH_3; 1.8, s, 5-CH_3) and a hydroxylic proton at δ 3.8 which was neatly exchanged with D_2O. The four protons of the two methylenes and one methine proton of the azepine ring are not displayed distinctly and show complex splitting pattern in the region δ 2.4—3.5. Probably the chemical shift differences of these three types of protons are very little. The NMR

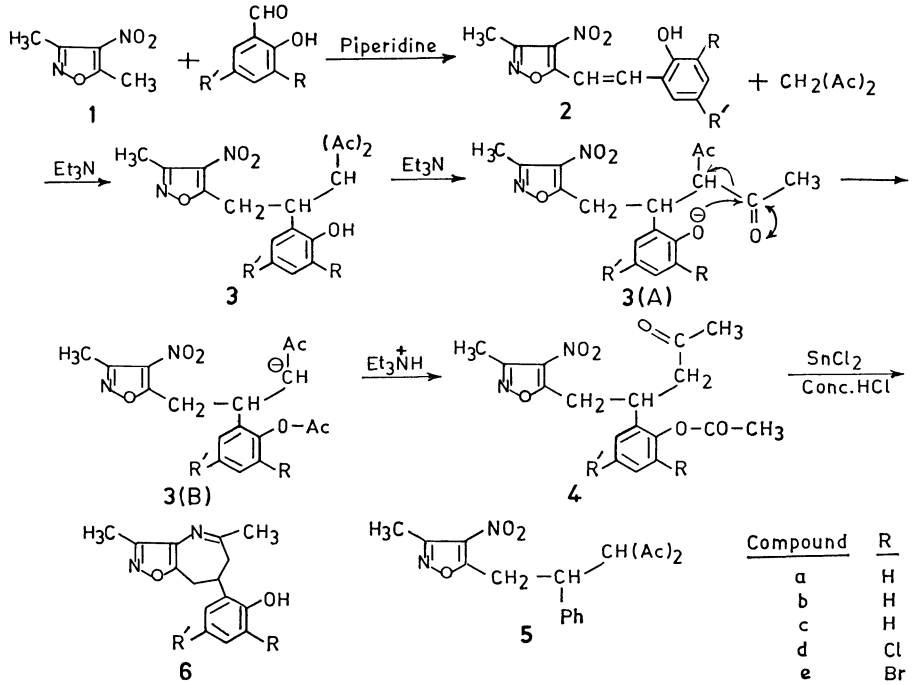

Fig. 1.

Table 1. The physical properties and elemental analysis of the products

Compound	Mp °C	Reaction time h	Yield %	Formula	Found (%) C	Found (%) H	Found (%) N	Calcd (%) C	Calcd (%) H	Calcd (%) N
2a	230	1.5	85	$C_{12}H_{10}N_2O_4$	58.40	3.99	11.10	58.53	4.06	11.30
2b	195	2.0	85	$C_{12}H_9N_2O_4Cl$	51.15	3.10	9.85	51.42	3.21	10.00
2c	250	2.0	80	$C_{12}H_9N_2O_4Br$	44.00	2.58	8.56	44.30	2.76	8.61
2d	203	2.5	82	$C_{12}H_8N_2O_4Cl_2$	45.52	2.37	8.78	45.71	2.53	8.88
2e	200	2.5	80	$C_{12}H_8N_2O_4Br_2$	35.27	1.75	6.80	35.64	1.98	6.93
4a	80	3.0	60	$C_{17}H_{18}N_2O_6$	58.65	5.10	8.00	58.95	5.20	8.09
4b	152	4.0	55	$C_{17}H_{17}N_2O_6Cl$	53.90	4.27	7.25	53.68	4.47	7.36
4c	95	4.5	50	$C_{17}H_{17}N_2O_6Br$	48.50	3.95	6.38	48.00	4.00	6.58
4d	155	4.5	40	$C_{17}H_{16}N_2O_6Cl_2$	49.10	4.00	6.59	49.15	3.85	6.74
4e	140	5.0	35	$C_{17}H_{16}N_2O_6Br_2$	40.25	3.25	5.43	40.47	3.17	5.55
6a	180	2.0	45	$C_{15}H_{16}N_2O_2$	70.25	6.00	10.82	70.31	6.25	10.93
6b	176	2.0	40	$C_{15}H_{15}N_2O_2Cl$	61.90	5.25	9.54	62.06	5.17	9.65
6c	166	2.0	45	$C_{15}H_{15}N_2O_2Br$	53.50	4.15	8.27	53.73	4.47	8.35
6d	178	2.5	30	$C_{15}H_{14}N_2O_2Cl_2$	55.17	4.52	8.50	55.38	4.30	8.61
6e	175	2.5	25	$C_{15}H_{14}N_2O_2Br_2$	43.60	3.28	6.67	43.47	3.38	6.76

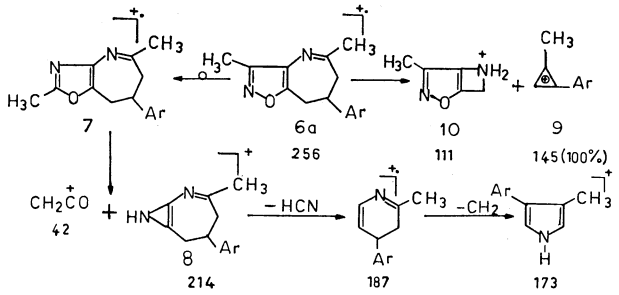

Fig. 2. Mass fragmentation of **6a**. Ar=*o*-OH-C_6H_4-

behaviour of these protons is in keeping with our eariler observation.[4]

In the mass spectrum of **6a**, the signal at *m/e* 214 is due to the ion **8** formed along with ketene by the fragmentation of **7** which comes from the molecular ion. This decomposition of the molecular ion is initiated by the cleavage of the N–O bond, the weakest linkage,[8] followed by ring transformation.[9] The base peak at *m/e* 145 is due to the resonance stabilised cation (**9**) formed together with **10** from the molecular ion.

Experimental

All the melting points are uncorrected. The purity of the compounds was checked by TLC. The IR spectra were recorded on Perkin-Elmer 283 model as KBr discs. ^{1}H NMR spectra were run on 90 MHz Varian EM-390 and 100 MHz JEOL spectrometers using TMS as internal reference and the mass spectra on Varian MAT CH-7 instrument at 70 eV. All the compounds prepared have been included in the table along with the characterization data.

*3-Methyl-4-nitro-5-(o-hydroxystyryl)isoxazoles (**2**).* 3,5-Dimethyl-4-nitroisoxazole (2.8 g, 0.02 mol) and salicylaldehydes (2 ml, 0.02 mol) were refluxed in ethanol (30 ml) in presence of traces of piperidine for 1.5 h. The reaction mixture was cooled and the products crystallized from ethanol–acetone.

*4-(o-Acetoxyphenyl)-5-(3-methyl-4-nitro-5-isoxazolyl)-2-pentanones (**4**).* 3-Methyl-4-nitro-5-(*o*-hydroxystyryl)isoxazoles (2.4 g, 0.01 mol), acetylacetone (3 ml, 0.03 mol), and triethylamine (35 ml) were refluxed for 3 h. Triethylamine was allowed to evaporate at room temperature. The residue was triturated with pet.ether and finally decomposed in methanol and filtered; colourless crystals from methanol. ^{1}H NMR ($CDCl_3$) of **4a**: δ 7.0—7.4 (m, 4H, Ar–H); 4.05 (m, 1H, >C–H); 3.5 (d, 2H, isoxazole-CH_2); 2.85 (d, 2H, -$COCH_2$-); 2.5 (s, 3H, isoxazole-CH_3); 2.35 (s, 3H, -$OCOCH_3$) and 2.05 (s, 3H, -$COCH_3$).

*7-(o-Hydroxyphenyl)-3,5-dimethyl-7,8-dihydro-6H-isoxazolo[4,5-b]azepines (**6**).* Compound **4** (1.7 g, 0.005 mol), tin(II) chloride (12 g), and concd hydrochloric acid (15 ml) were heated together on water bath. Within a few minutes the reaction mixture became clear solution. After 0.5 h yellow crystalline compound began to separate. The heating is continued for further 2 h, cooled, filtered and washed with water. Recrystallization was effected from methanol. ^{1}H-NMR ($CDCl_3$) of **6a**: δ 6.9—7.2 (m, 4H, Ar–H); 3.8 (s, 1H, Ar–OH); 2.4—3.5 (5H, 6-CH_2-, 8-CH_2-, and >CH); 2.2 (s, 3H, 3-CH_3) and 1.8 (s, 3H, 5-CH_3).

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