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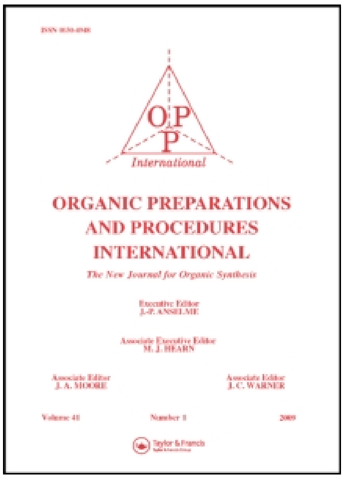

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SYNTHESIS OF SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. PART XII*. SYNTHESIS OF KETOSULTAMS

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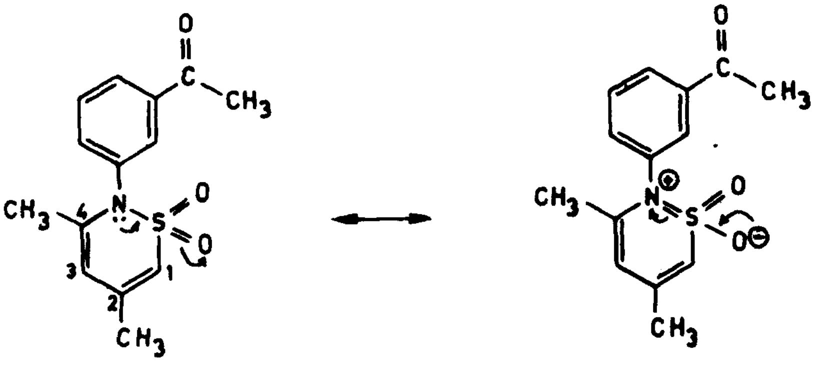
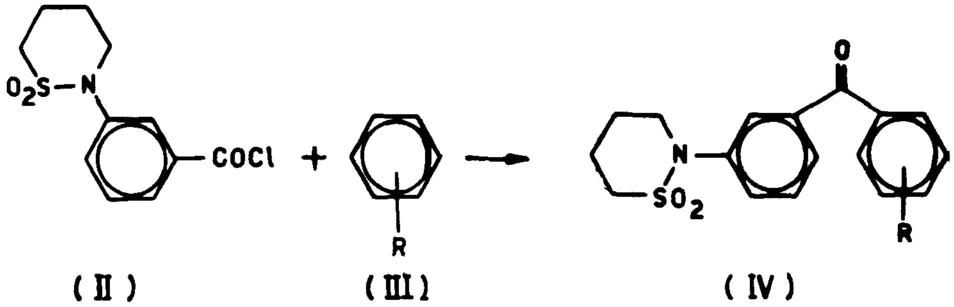
It has been shown that the unsaturated sultam ring attains considerable aromatic character,[1] with a large contribution of canonical structures, due to the substantial overlap of the nitrogen p orbital with the sulfur d orbital. It has also been reported that thioxanthenones which contain tertiary aromatic amines exhibit good schistosomicidal activity.[2,3] On this basis, we have synthesized compound I which can achieve aromaticity via canonical structures Ia and Ib. We also report the synthesis of IVa-f.



(I a) (I b)

Compounds IVa-f (Table 1) were prepared by the Friedel-Crafts acylation of the appropriate benzene derivatives with II,[4] albeit in low yields because of the known sensitivity[5] of the sultam ring to acidic medium (ring opening to the soluble sulfonic acid).



a) R = H b) R = p-CH_3 c) R = p-CH_3O d) R = o-Br e) R = p-Br

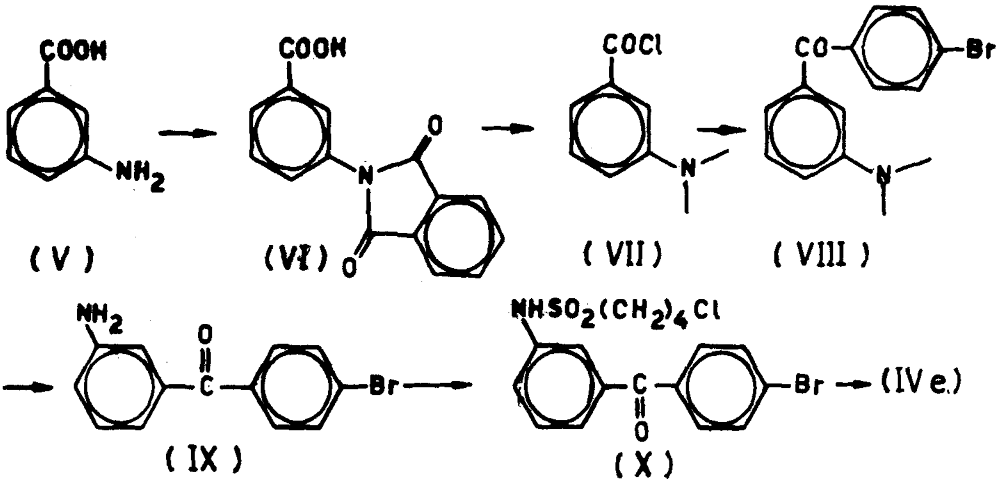
f) R = p-Cl

Table 1. Physical Constants for Sultams IV

	Yield (%)	mp. (°C)	Elemental Analyses Calcd (Found) C	H	N	S	UV (mμ)
IVb	33	93-94[a]	65.54	5.82	4.25	9.71	260,230
			(65.90)	(5.87)	(4.20)	(9.40)	(log ε 6.23, 6.23)
IVc	35	104-106[b]	62.60	5.55	4.06	0.26	
			(62.40)	(5.33)	(3.90)	(9.60)	
IVd	6	brownish oil			3.55	8.12	255,240
					(3.30)	(8.70)	(log ε 4.84, 4.78)
IVe	46	124-125[c]	51.77	4.06	3.55	8.12	262
			(51.40)	(4.15)	(3.20)	(8.30)	(log ε 6.32)
IVf	40	102-103[d]	58.36	4.57	4.00	9.15	260
			(58.70)	(4.66)	(3.90)	(8.90)	(log ε 6.32)

a) White needles from pet ether-chloroform or dil. acetone. b) White needles from pet ether-chloroform or dil. ethanol. c) Brown needles from methanol. d) White needles from benzene-pet ether.

In order to overcome this obstacle, it seemed preferable to synthesize the original aminoketone followed by conversion to the sultam ring as exemplified below for IVe, which was obtained in 66% overall yield.



The infrared spectra of IV, VII-X exhibited the characteristic carbonyl band at 1645, 1660, 1625, 1620, 1610, 1620 cm^{-1} (diaryl ketones). The sultam band[6] for IV appeared between 1277-1290 cm^{-1}. The nmr spectrum of Ia revealed a characteristic peak[7] for the sultam ring at δ 6.22 (proton at C^1) and additional peaks at δ 1.89 (methyl at C_2), δ 5.70 (proton at C_3), δ 2.15 (methyl at C_4). The methylene hydrogens adjacent to the nitrogen atom and the other methylene hydrogens of the saturated six-membered ring sultam ketone (IV) exhibited a downfield shift of 0.3 ppm and 0.09-0.2 ppm respectively with respect to previously reported sultams.[8] Such deshielding may be ascribed to the substituent effect of the C=O.[9,10]

The ^{13}C.M.R.[11] of the unsaturated sultam I showed the following values: $C_1 = \delta$ 107.83 (d); $C_2 = \delta$ 143.44 (s); $C_3 = \delta$ 112.44 (d); $C_4 = \delta$ 145.52 (s); $C_5 = \delta$ 21.45 (q); $C_6 = \delta$ 21.90 (q).

The sultam ring possesses no molluscicidal effect;[12] the schistosomicidal and bactericidal activity for these ketones are currently under investigation.

EXPERIMENTAL

All mps. are uncorrected. The IR spectra were obtained on the Perkin-Elmer Spectrophotometer Model 221 with Gitter-prismen-Austanscheinheit and Beckman IR_4 (by Sadtler Research Laboratories); the NMR spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer and EM-390-90 MHZ spectrometer (Varian AG Switzerland) with TMS as an internal reference. ^{13}C.M.R. were measured on Brucker WH-90 spectrometer at 22.628 MHZ in PFT-anode.

Synthesis of I.- A mixture of 3.2 g (0.02 mole) of 2,4-dimethyl-1,3-butadiene sultone(1-4) and 2.7 g (0.02 mole) of m-aminoacetophenone was heated slowly under vacuum in an oil bath; at 90° the reaction began with the evolution of water vapor, which was removed by the suction of the vacuum. The reaction mixture was then heated at 125-130° at normal pressure for 30 minutes until the evolution of water vapors ceased. After cooling, the solid mass was treated with dilute hydrochloric acid in order to remove the unreacted amine, filtered, washed with water and dried. The yield of product crystallized from methanol as pale brownish crystals was 3.8 g (68.5%), mp. 150-151°. Its IR spectrum showed bands at 1675 cm^{-1} (C=O), 1340, 1150 (SO_2), 1290 (sultam band), 825, 790 and 680 cm^{-1} (three adjacent aromatic protons plus one proton). The nmr revealed two singlets at δ 1.87 and δ 2.15 (showing long range coupling with the proton at C_1, J = 1.6 cps,[1] a singlet at δ 2.65 ($CO-CH_3$), two singlets at δ 5.75 and δ 6.30 (protons at C_1 and C_3), two multiplets centered at δ 7.65 and δ 8.0 (aromatic protons).

Anal. Calcd. for $C_{14}H_{15}NO_3S$ (277): C, 60.64; H, 5.45; N, 5.05; S, 11.55.
Found: C, 60.9; H, 5.50; N, 5.0; S, 11.4.

N-[m-Butansultamyl(1-4)]-benzophenone(IVa). General Procedure.- To a solution 2.74 g (0.01 mole) of m-(N-butansultamyl(1-4) benzoyl chloride in 50 ml dry benzene, was added 1.5 g (ca. 0.01 mole) of $AlCl_3$. The reaction mixture was refluxed for 45 min. on a water bath, then cooled in ice for 30 min. and decomposed with cold dilute hydrochloric acid. After steam distillation for the remaining benzene layer; the resulting brownish solid 1.2 (38%) was crystallized from benzene-petroleum ether to give white needles of mp. 111°. Compound III is readily soluble in chloroform, benzene, ether, insoluble in water-petroleum ether. UV: λ_{max}^{MeOH} 254, 235 nm (log ε 6.21, 6.20).

IR revealed the characteristic bands for (C=O) 1645 cm^{-1}, (SO_2), 1350, 1140 cm^{-1}, (sultam band) 1290 cm^{-1}. Nmr showed multiplets at δ 1.9 and δ 2.35 (2 CH_2), a triplet at δ 3.25 (CH_2-SO_2), a triplet at δ 3.82 (CH_2N) and a multiplet centered at δ 7.6 (9 aromatic protons) (Fig. 2).

Anal. Calcd. for $C_{17}H_{17}NO_3S$ (315): C, 64.75; H, 5.43; N, 4.44; S, 10.15.

Found: C, 64.9; H, 5.39; N, 4.4; S, 10.2.

Compound IVb-f were prepared in an analogous fashion. Table 1 describes their properties. Compound IVd was obtained in very low yield after evaporation of the mother liquor of compound IVe; its IR proved the presence of O-substitution in the benzene ring.

N-Phthalimidyl-m-benzoic acid(VI).- A mixture of 2.8 g (0.02 mole) of the m-aminobenzoic acid and 3 g (0.02 mole) of phthalic anhydride in 40 ml glacial acetic acid was refluxed for 30 min. On cooling, VI separated as a brownish solid; crystallization from acetic acid gave 4.3 g (80%) of browhish white crystals, mp. 280°.

N-Phthalimidyl-m-benzoyl chloride(VII).- A solution of 2.7 g (0.01 mole) of VI in 50 ml dry benzene and 30 ml redistilled thionyl chloride was refluxed on a water bath for 1 hr.; after cooling, thionyl chloride was evaporated under vacuum, then the reaction mixture was washed three times with dry benzene, the semi-solid brownish residue was left under dry benzene at 0° for 3 hrs. The resulting solid was crystallized from benzene to give colorless crystals, mp. 219°. IR: 1800 cm^{-1} (COCl).

Anal. Calcd. for $C_{15}H_8Cl\ NO_3$ (285.5): N, 4.90.

Found: N, 5.5.

4-Bromo-3'-N-(phthalimidyl)benzophenone(VIII).- To a solution of 2.9 g (0.01 mole) of compound VII in 60 ml dry benzene was added bromobenzene 1.6 g (0.01 mole). Then with cooling and stirring, 2 g anhydrous aluminum chloride was added portionwise. The reaction mixture was refluxed for 1 hr. on water bath with stirring. After cooling, it was decomposed with cold dilute hydrochloric acid. Benzene was removed by steam distillation and the remaining solid (2.8 g, 69%) was crystallized from benzene: petroleum ether to give brownish crystals, mp. 156-157°. The IR revealed the characteristic carbonyl band at 1650 cm^{-1}. The nmr displayed five distinct peaks in the aromatic region: (a) a triplet centered at δ 7.95 (6 aromatic protons deshielded by C=O) which is in agreement with previously published[14a] (b) a singlet at δ 7.77 (2 aromatic protons adjacent to aromatic protons)[14b] (c) a doublet centered at δ 7.65 (two aromatic protons adjacent to the bromine atom)[14c] (d) an ill-defined doublet centered at δ 7.55 (one aromatic proton between two aromatic protons)[14d] (e) a singlet at δ 7.31 (aromatic proton adjacent to nitrogen).[14e]

Anal. Calcd. for $C_{21}H_{12}BrNO_3$: C, 62.21; H, 2.95; N, 3.44.

Found: C, 62.0; H, 2.84; N, 3.3.

4-Bromo-3-aminobenzophenone(IX).- To a solution of 4 g (0.01 mole) of VIII in 50 ml ethanol was added 10 ml of a 93% solution of hydrazine hydrate.[15] The reaction mixture was refluxed for 2 hrs. The resulting solid was filtered 2.1 g (77%) and crystallized from ethanol to give brownish white needles, mp. 134-136°. Its IR revealed bands at 3360 and 3190 cm^{-1} (NH_2), 1650 cm^{-1} (C=O), 860 cm^{-1} (two adjacent hydrogen atoms). The nmr spectrum displayed a singlet at δ 4.25 (NH_2), doublets at δ 6.65 and δ 6.78 (two aromatic protons thanking the NH_2 group),[14f] an ill-defined multiplet centered at δ 7.85 (aromatic protons adjacent to the CO) and a multiplet at δ 7.45 (remaining aromatic protons). Evaporation of the mother liquor gave a solid, mp. 66-68°, whose structure is currently under investigation.

4-Bromo-3'-N-(4-chloro-n-butane-1-sulfonyl)-3'-aminoacetophenone(X).- To a stirred solution of 2.8 g (0.01 mole) of IX in 30 ml dry benzene and 3 ml pyridine, was added over a period of 30 min. 2.3 g (ca. 0.01 mole) 4-chloro-n-butane-1-sulfonyl chloride. After standing overnight at room temp., the reaction mixture was diluted with ether, then washed with cold dil. HCl several times and finally with water. The organic layer was dried over anhydrous sodium sulfate and upon removal of benzene and ether, a viscous brown oily mass was obtained which solidifies upon standing (2.8 g 70%). This solid was crystallized from benzene to give brownish crystals of mp. 93-95°; its IR displayed bands at 1640 cm^{-1} (CO), 1340, 1150 cm^{-1} (SO_2).

Anal. Calcd. for $C_{17}H_{17}BrClNO_3S$ (430.5): N, 3.25.

Found: N, 3.5.

N-3-Butansultamyl(1-4)-4'-bromobenzophenone(IVe).- A solution of 4 g (0.01 mole) of X in 60 ml 10% NaOH was warmed on a water bath for 5 hrs. After cooling, a solid was formed, which was crystallized to give brownish crystals 3.1 g (78%) of mp. 124-125° which showed no depression on admixture with an authentic sample of IVe. Its IR was identical to that of a sample prepared by the method previously described.

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