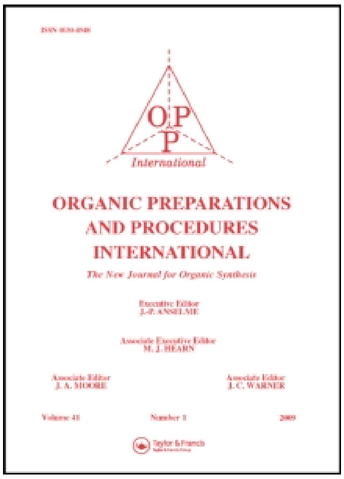

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SULTAMS WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. PART V

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over sodium sulfate. Evaporation of the solvent in vacuo gave an oil which solidified on trituration with n-hexane. The resulting crude 2-amino-3',4,4',5-tetrachlorobiphenyl was recrystallized from aqueous ethanol affording 1.2 g. (52.5%), mp. 86°, lit.[1] mp. 79-82°, of pure compound. The purity was confirmed by GC to >98%.

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REFERENCE

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SULTAMS WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. PART V[†]

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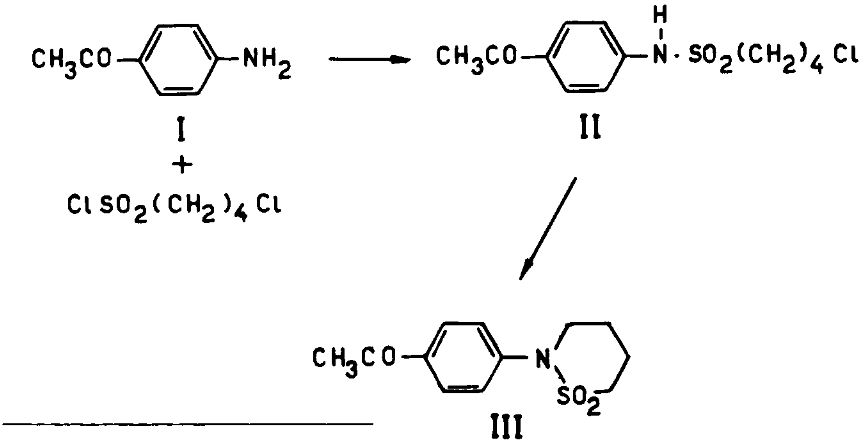
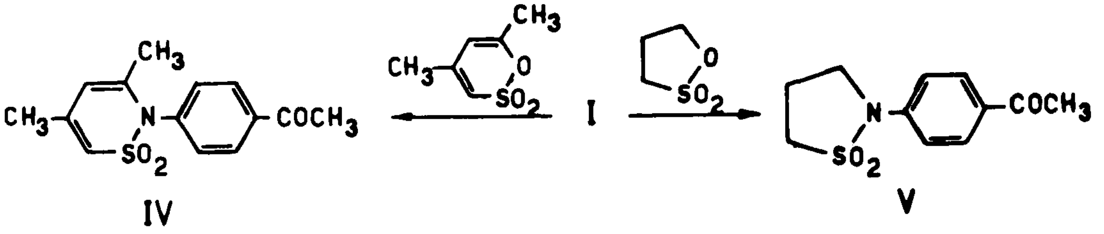
In continuation of our investigation of sultam derivatives with possible schistosomicidal activity, we have prepared compounds III-V from p-



(1)

[†] Part IV. S. H. Doss, Org. Prep. Proced., Int., 9, 27 (1977)

aminoacetophenone (I) as shown in the equations 1 and 2. Various derivatives of III-V were prepared. Attempts to reduce III or its oxime with lithium aluminum hydride or sodium amalgam in alcohol or by hydrogenation over Raney nickel failed. Addition of phenylmagnesium bromide to III gave the expected alcohol (75%), isolated as the 3,5-dinitrobenzoate ester. All the compounds prepared were characterized by their elemental analyses and spectral data (see Experimental).



(2)

EXPERIMENTAL

All melting points are uncorrected, I.R. spectra were obtained on the Perkin-Elmer Spectrophotometer Model 221 with Gitterprismen-Austauscheinheit and Beckman IR$_4$ (by Sadtler Research Laboratories). Nmr spectra were determined in CDCl$_3$ on Varian A-60 spectrometer and EM-390 90 MHZ spectrometer (by Varian AG Switzerland) with TMS as an internal reference. Mass spectra were obtained with Atlas CH$_4$ and Hitachi Double Focusing Mass Spectrometer RMV-7. Some of the microanalyses were carried out in Organisch Chemisches Institut der Universität des Saarlandes.

4-Acetyl-4-chlorobutanesulfonanilide (II).- To a stirred solution of 1.3 g. (0.01 mole) *p*-aminoacetophenone in 20 ml. benzene and 3 ml. pyridine, 1.9 g. 4-chloro-1-butanesulfonyl chloride were added dropwise over 0.5 hr. at room temperature. The color of the solution changed to yellow then to orange and finally to red. The reaction mixture after standing overnight, was diluted with ether, washed several times with dil. hydrochloric acid and then with water. The ethereal layer was separated and dried over anhydrous sodium sulfate. After evaporation of the ether, the remaining solid was crystallized from benzene affording 1.74 g. (60%) of colorless crystals, mp 108-112°. Compound II is soluble in methanol, ethanol, acetone, chloroform and acetic acid and insoluble in water, petroleum ether, benzene and cyclohexane.

Anal. Calcd. for $C_{12}H_{16}ClNO_3S$: C, 49.74; H, 5.57; Cl, 12.23: N, 4.83; S, 11.06. Found: C, 49.86; H, 5.69; Cl, 12.60; N, 4.8; S, 11.00.

IR: 3150 cm^{-1} (NH), 1690 cm^{-1} (C=O), 1366 cm^{-1} (SO_2N), 1334 cm^{-1} (SO_2 asym.), 1160 cm^{-1} (SO_2 sym.), 840 cm^{-1} (two adjacent aromatic hydrogen atoms) and 745 cm^{-1} (C-Cl).

UV: $\lambda_{max.}^{CH_2Cl_2}$ 269, 258, 253 μ (log. ε 4.52, 4.03 and 3.74). The nmr spectrum exhibited an ill-defined multiplet centered at δ 2.00 (2 CH_2), singlet at δ 2.62 (CH_3CO), triplet centered at δ 3.52 (CH_2Cl), two triplets centered at δ 7.35 and δ 7.85 (4 aromatic ring protons) and singlet centered at δ 8.1 (NH). MS: m/e 289 $(M)^+$.

Semicarbazone (84%), mp. 178°, soluble in methanol, benzene while insoluble in ethanol, water, ether, petroleum ether, cyclohexane and acetic acid.

Anal. Calcd. for $C_{13}H_{19}ClN_4O_3S$: C, 45.02; H, 5.52; Cl, 10.22; N, 16.15; S, 9.24. Found: C, 45.4; H, 5.4; Cl, 10.3; N, 16.2; S, 9.2.

IR.· 3430 cm^{-1} ($CONH_2$), 1335 cm^{-1} (SO_2 asym.); 1150 cm^{-1} (SO_2 sym.).

2,4-Dinitrophenylhydrazone (74%), mp. 220-221°, soluble in acetone, insoluble in water, ether, petroleum ether and benzene while partially soluble in methanol, chloroform and acetic acid.

Anal. Calcd for $C_{18}H_{20}ClN_5O_6S$: C, 46.06; H, 4.28; Cl, 7.56; N, 14.90; S, 6.81. Found: C, 46.04; H, 4.20; Cl, 7.9; N, 14.7; S, 6.8.

4-(Tetrahydro-2H-1,2-thiazin-2-yl)acetophenone S,S-dioxide (III).- A solution of II (1.74 g., 6.0 mmoles) in 50 ml. of 20% sodium hydroxide was warmed for 1.5 hr.; the resulting oil, which solidified on cooling, was filtered and washed with water. The solid was crystallized from benzene-petroleum ether (40-60°) to give 1.03 g. (68%) of product, mp. 98-100°. The sultam is soluble in acetone, benzene, chloroform, acetic acid, partially soluble in petroleum ether, methanol, ethanol while insoluble in cyclohexane and water.

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H. 5.97; N, 5.53; S, 12.64. Found: C, 56.9; H, 5.98; N, 5.5; S, 12.84.

IR: 1690 cm^{-1} (C=O), 1565 cm^{-1} (SO_2N), 1348 cm^{-1} (SO_2 asym.), 1280 cm^{-1} (sultam band), 845 cm^{-1} (two adjacent aromatic hydrogen atoms).

UV: $\lambda_{max.}^{CH_2Cl_2}$ 267 μ (log ε 4.39). MS: m/e 253 $(M)^+$.

Semicarbazone (84%), mp. 242°, soluble in acetone, chloroform, acetic acid, while insoluble in methanol, benzene, petroleum ether and cyclohexane.

Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.32; H, 5.85; N, 18.05; S, 10.21 Found: C, 49.7; H, 5.85; N, 17.6; S, 10.10.

2,4-Dinitrophenylhydrazone (76%), mp. 247°, soluble in acetone, benzene, chloroform, acetic acid, partially soluble in ethanol, ether, petroleum ether and cyclohexane.

Anal. Calcd. for $C_{18}H_{19}N_5O_6S$: N, 16.16; S, 7.39. Found: N, 15.16; S, 7.3.

Oxime (95%), mp. 165°, soluble in methanol, ethanol, acetone, benzene, ether, chloroform, acetic acid while insoluble in petroleum ether, cyclohexane and water.

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 53.73; H, 6.01; N, 10.44; S, 11.93. Found: C, 53.60; H, 5.92; N, 10.00; S, 12.30.

IR: 3230 cm^{-1} (OH), 1375 cm^{-1} (SO_2N), 1330 (SO_2 asym.), 1270 cm^{-1} (sultam band), 1140 cm^{-1} (SO_2 sym.), 835 cm^{-1} (two adjacent aromatic hydrogens).

UV: $\lambda_{max.}^{CH_2Cl_2}$ 258 μ (log. ε 4.18).

Hydrazone (91%), mp. 135-137°, solvent of crystallization ethanol, soluble in methanol, acetone, chloroform; partially soluble in benzene and insoluble in ethanol, water, ether, petroleum ether, acetic acid and cyclohexane.

Anal. Calcd. for $C_{12}H_{17}N_3O_S$: C, 53.92; H, 4.61; N, 15.72; S, 11.99. Found: C, 54.10; H, 6.36; N, 15.7; S, 11.5.

IR: 3370 cm^{-1} (two adjacent aromatic protons).

NMR: multiplet centered at δ 1.91 (CH_2 of sultam ring), singlet at δ 2.2 (CH_3), multiplet at δ 2.29 (CH_2 sultam ring), triplet at δ 3.22 (CH_2-SO_2), triplet at δ 3.8 (CH_2-N), singlet at δ 4.5 (NH_2), two doublets centered at δ 7.37 and δ 7.7 (4 aromatic protons).

Reaction of Hydrazone of III with Isocyanates.

a) *n-Propyl Isocyanate*.- To 1 g. hydrazone (0.374 mole) in 20 ml. pyridine, 2 ml. *n*-propyl isocyanate was added dropwise with stirring in an ice bath for 0.5 hr. The reaction mixture was left overnight at room temperature, then heated on a water bath for 0.5 hr. and left to cool. Upon addition of ice-cold water a precipitate was formed; it was filtered, washed with water and crystallized from benzene-petroleum ether, to yield 0.9 g. (68%), mp. 165°. The compound is soluble in acetone, chloroform, acetic acid and benzene while insoluble in methanol, ethanol, water, petroleum ether, ether and cyclohexane.

Anal. Calcd. for $C_{16}H_{24}N_4O_3S$: C, 54.54; H, 6.86; N, 15.90; S, 9.08. Found: C, 54.40; H, 6.81; N, 15.90; S, 9.00.

IR: 3500 cm^{-1} (NH), 1550 cm^{-1} (CONH), 1318 cm^{-1} (SO_2 asym.), 1290 cm^{-1} sultam band), 1140 cm^{-1} (SO_2 sym.), 830 cm^{-1} (two adjacent aromatic hydrogen atoms).

NMR: triplet centered at δ 0.98 (CH_3 of the propyl group), pentet centered at δ 1.5 (CH_2 adjacent to CH_3), ill defined multiplet centered at δ 1.9 (CH_2 of C_3 of the sultam ring), ill defined multiplet centered at δ 2.2 (CH_3CO) and CH_2 of the sultam ring, triplet centered at δ 3.2 (CH_2-SO_2), doublet centered at δ 3.35 (CH_2 adjacent to NH), triplet centered at δ 3.8 (CH_2 adjacent to N of the sultam ring), triplet centered at δ 6.39 (NH), two doublets centered at δ 7.3 and δ 7.7 (4 aromatic protons), singlet centered at δ9 (NH). MS: m/e = 352 $(M)^+$.

b) Phenyl Isocyanate.- Product obtained in 90% yield, mp. 198°, from benzene-petroleum ether, soluble in methanol, ethanol, acetone, chloroform and acetic acid, while insoluble in water petroleum ether and cyclohexane.

Anal. Calcd. for $C_{26}H_{27}N_5O_4S$: N, 13.95; S, 6.33.
Found: N, 14.3; S, 6.0

IR: 3333 cm^{-1} (NH), 1700 cm^{-1} (C=N), 1660 cm^{-1} (C=O), 1550 cm^{-1} (CONH), 1310 cm^{-1} (SO_2 asym.), 1282 cm^{-1} (sultam band), 1136 cm^{-1} (SO_2 sym.), 830 cm^{-1} (two adjacent aromatic hydrogens). MS: m/e = 252 (fragment $C_{12}H_{15}N_2O_2S^+$).

Reaction of III with Phenylmagnesium Bromide.- To a suspension of 0.2 g. magnesium metal in 30 ml. dry ether was added 0.78 g. of bromobenzene. After 1 hr., 0.5 g. of III (0.197 mole) in dry ether was added with stirring. The complex was decomposed with ice-cold water and the ether layer was separated, dried and evaporated. The resulting brown yellowish oil (0.5 g., 75%) was converted to a solid derivative with 3,5-dinitrobenzoyl chloride which was washed with bicarbonate, dried and crystallized from benzene-petroleum ether, mp. 180° (72%).

Anal. Calcd. for $C_{25}H_{23}N_3O_8S$: N, 8.00
Found: N, 7.5
IR: 1750 cm^{-1} (C=O), 1560 cm^{-1} (NO_2), 1389 cm^{-1} (SO_2 asym.), 1289 cm^{-1} (sultam band), 1100 cm^{-1} (SO_2 sym.).

Compound IV.- p-Aminoacetophenone (1.35 g., 0.01 mole) was fused with 1.6 g. (0.01 mole) of sultone at 110° for 0.5 hr. The reaction mixture changed to red oil which solidified upon pouring into ice-cold water. The solid was washed with dil. hydrochloric acid, then water and crystallized from methanol to yield 0.49 g. (17%), mp. 155°.

Anal. Calcd. for $C_{14}H_{15}NO_3S + H_2O$: C, 56.94; H, 5.76; N, 4.74, S, 10.80.

Found: C, 56.4; H, 5.8; N, 4.5; S, 10.4.

IR: 3680, 2920 cm^{-1} (water of crystallization), 1675 cm^{-1} (C=O), 1140, 1350 cm^{-1} (SO_2 bands), 1280 cm^{-1} (sultam band).

A solution of 0.5 g. of IV (0.18 mole) in methanol and 1 g. Raney nickel was hydrogenated for 8 hrs. The solution was filtered, then concentrated and kept in the refrigerator whereupon white crystals separated, mp. 128°; yield after crystallization 0.35 g. (70%).

Anal. Calcd. for $C_{14}H_{19}NO_3S + H_2O$: C, 56.18; H, 7.01; N, 4.68.

Found: C, 56.65; H, 6.5; N, 4.7.

IR showed the presence of water of crystallization at 3670 cm^{-1} and at 2920 cm^{-1}.

Compound V.- p-Aminoacetophenone (1.35 g., 0.01 mole) was fused with 1.22 g. (0.01 mole) of sultone at 90° in an oil bath for 0.5 hr. The reaction mixture changed to a yellow then red brownish oil with evolution of water vapor. It was left to solidify and then crystallized from methanol/ether to yield 1.8 g. (75%) of fine yellow crystals, mp. 226° (dec.).

Anal. Calcd. for $C_{11}H_{13}NO_3S$: S, 13.38

Found: S, 13.8.

2,4-Dinitrophenylhydrazone (74%). mp. 188° from acetic acid.

Anal. Calcd. for $C_{17}H_{17}N_5O_6S$: N, 16.70; S, 7.63.

Found: N, 17.0; S, 7.9.

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