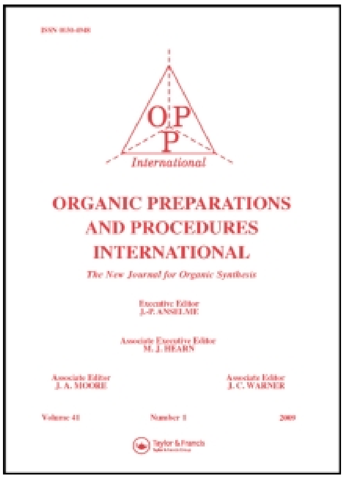


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. PART IV

S. H. Doss[a][b]
[a] Fachbereich 14, Organische Chemie, Universität Saarlandes, Saarbrücken, WEST GERMANY [b] National Research Center, Cairo, Egypt

To cite this Article Doss, S. H.(1977) 'SYNTHESIS OF SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. PART IV', Organic Preparations and Procedures International, 9: 1, 27 — 33
To link to this Article: DOI: 10.1080/00304947709355657
URL: http://dx.doi.org/10.1080/00304947709355657

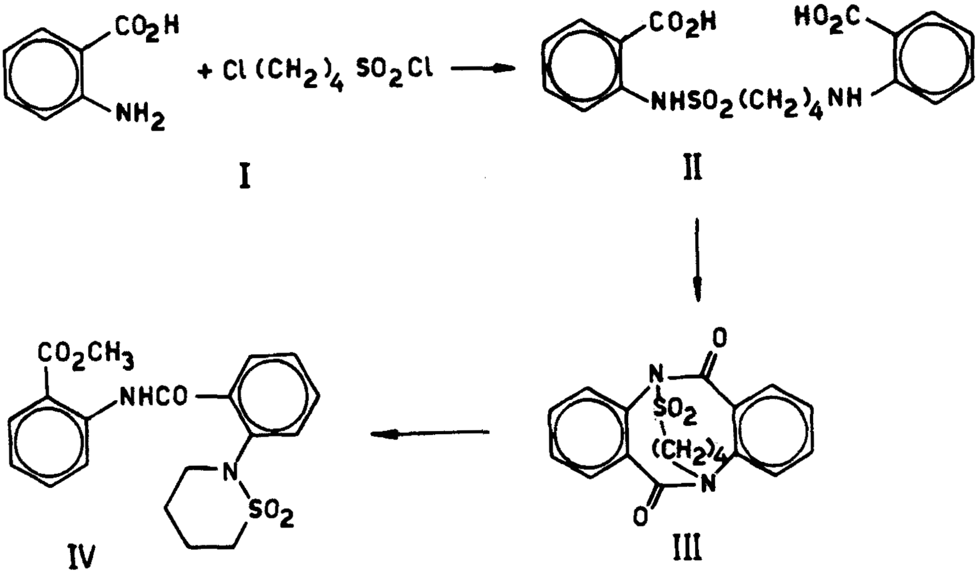
ORGANIC PREPARATIONS AND PROCEDURES INT. 9(1), 27-33 (1977)

SYNTHESIS OF SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. Part IV[†]

S. H. Doss*

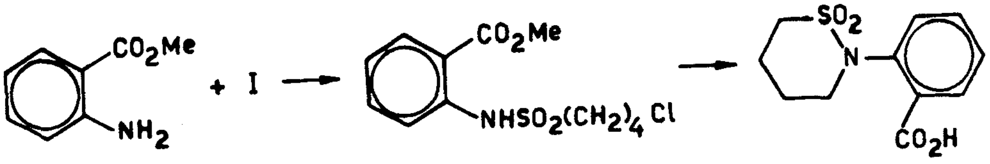
Universität Saarlandes
Fachbereich 14, Organische Chemie
6600 Saarbrücken, WEST GERMANY

Procaine solutions are reported to possess bactericidal, bacteriostatic, fungicidal and fungistatic properties and is effective in restoring the deformability of irreversibly sickled cells.[1] It has also been suggested that the sultam ring plays a pharmacological role as an anticonvulsant[2] and that N-substituted aminosulfonic acids possess pharmacological activity.[3] Helferich et al.[4] described procaine derivatives containing the sultam ring in the m- and p-positions as well as the combination of an unsaturated substituted ring with methyl p-aminobenzoate. These compounds proved to be pharmacologically inactive.



Repetition of the reaction of 4-chloro-1-butanesulfonyl chloride (I) with o-aminobenzoic acid gave a low yield of compound whose analysis did not correspond to those of similar intermediates prepared in the p- and m-series. The condensation of o-aminobenzoic acid with I in a 2:1 ratio yielded II. It was confirmed that II was unchanged upon reflux in 1 N NaOH.[4] With thionyl chloride, II was converted to III which upon reflux with methanol gave a solid, mp. 168°, assigned structure IV on the basis of its analytical and spectral data.

The reaction of I with methyl o-aminobenzoate gave V which upon being heated to reflux with 10% sodium hydroxide gave the o-(carboxyphenyl) sultam derivative VI. Attempts to convert VI to its acid chloride or to attach the p-diethylaminoethyl ester side chain were unsuccessful. These failures are probably the result of the steric hindrance of the bulky sultam ring ortho to the carboxy group; since the N and S atoms of the sultam ring are rigid, any substituents on the hydrogen of the secondary amine will lie in the plane of the molecule.[8] Alternatively activation of the p-position of the benzene ring giving rise of self-condensation of the resulting acid chloride, may explain the formation of the resins observed.



V

VI

EXPERIMENTAL

All melting points are uncorrected, IR spectra were obtained on the Perkin-Elmer Spectrophotometer Model 221 with Gitter-Prismen-Austaucheinheit; NMR spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer, with TMS as an internal reference. MS were obtained with Atlas CH_4. Microanalyses was carried out by Dr. Pascher, Bonn, West Germany.

1-[N-(2-Carboxyphenyl)sulfamoyl]-4-[2-carboxyanilino]butane (II).- To a stirred solution of 6.89 g. (0.05 mole) of o-aminobenzoic acid in 25 ml of 2 N NaOH was added during 30 min., 12.4 g (0.065 mole) 4-chloro-1-butanesulfonyl chloride. After standing overnight at room temp., the precipitated solid (3.1 g, 16%) was filtered, washed thoroughly with water and dried under vacuum. The solid was crystallized from methanol giving nearly colorless crystals mp. 183-184°. Compound I is readily soluble in acetone and insoluble in petroleum ether, benzene and chloroform. Its IR showed a group of small bands near 2850 cm^{-1} (OH), a considerably stronger band at 1770 cm^{-1} and additional bands at 1335, 1155 cm^{-1} (SO_2N group)[5] and at 1225 and 1250 cm^{-1} (ArNHR). It was impossible to obtain an nmr spectrum as the compound was insoluble in all solvents suitable for this measurement. M.S.: m/e = 392 (M^+).[6]

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.10; H, 5.14; N, 7.14; S, 8.15;
Found: C, 55.28; H, 4.81; N, 7.17; S, 8.38.

1.5-(Tetramethylenesulfonyl)-2,6-dioxo-1,2,5,6-tetrahydro-1.5-diazadibenzo[c,g]cyclooctatetraene (III).- A mixture of 3.9 g. of I (0.01 mole) and 25 ml $SOCl_2$ was heated to reflux for 1 hr. Excess $SOCl_2$ was removed under reduced pressure and the resulting solid residue washed twice with 20 ml portions of dry benzene. The solid was crystallized from benzene or benzene-pet ether (also from acetic acid without being affected) yielding pale brown crystals (2 g, 56%) of mp. 162.5-163°. Compound III is soluble in chloroform, acetone and carbon tetrachloride and insoluble in alcohol, petroleum ether and benzene. Its IR showed bands at 1740 cm^{-1} characteristic of CON since H-bonding with NH is absent, so that its position will be higher than in the free state (similar to other C=O groups[5]) at 1140 and 1335 cm^{-1} for SO_2 (sym) and SO_2 (asym) respectively.[7]

Its nmr spectrum (Fig. 1) exhibited two quartets centered at δ 8.18 and δ 7.57, characteristic for the 8 aromatic protons of the two separate benzene rings and two poorly resolved triplets centered at δ 6.2 and δ 6.8, characteristic for the two methylene groups adjacent to nitrogen and SO_2. The difference between these values and those published previously[8] is about 0.2-0.4 ppm. which may be attributed to the absence of the sultam ring. The spectra also showed a poorly resolved multiplet representing 4 hydrogens centered at δ 2.22 characteristic for the other two methylene groups which is in good agreement with previously published results.[8] M.S.: m/e = 356 (M^+).[6]

Anal. Calcd. for $C_{18}H_{16}N_2O_4S$: C, 60.67; H, 4.53; N, 7.86; S, 8.98;
Found: C, 60.61; H, 4.43; N, 7.86; S, 8.88.

N-[2-(N-Carbomethoxyphenyl)carbamoylphenyl]-1.4-butanesultam (IV).- A solution of 3.6 g. (0.01 mole) of III in 30 ml methanol was heated to reflux for 2 hrs on the water-bath. After cooling, excess methanol was evaporated under vacuum. The solid formed was crystallized from benzene-petroleum ether yielding 3 g. (77 %) of colorless needles, mp. 168°. Compound IV is soluble in chloroform, acetone, carbon tetrachloride, sparingly soluble in benzene and insoluble in petroleum ether.

Its infrared spectrum revealed strong bands at 3250 and 1530 cm^{-1} (CONH),[5] at 1435, 1380 and 760 cm^{-1} (C-COOME),[9] at 1315 and 1340 cm^{-1} (SO_2) and at 1272 cm^{-1} characteristic for the sultam ring.[7,10] Its nmr spectrum displayed two triplets centered at δ 2.2, another singlet at δ 1.85 characteristic for $COCH_3$, and a singlet at δ 7.88 (NH). The 8 aromatic protons appeared at δ 8.17 and δ7.57 M.S. m/e = 388 (M^+).[6]

Anal. Calcd. for $C_{19}H_{20}N_2O_5S$: C, 58.76; H, 5.19; N, 7.21; S, 8.24;
Found: C, 58.60; H, 5.07; N, 7.28; S, 8.12.

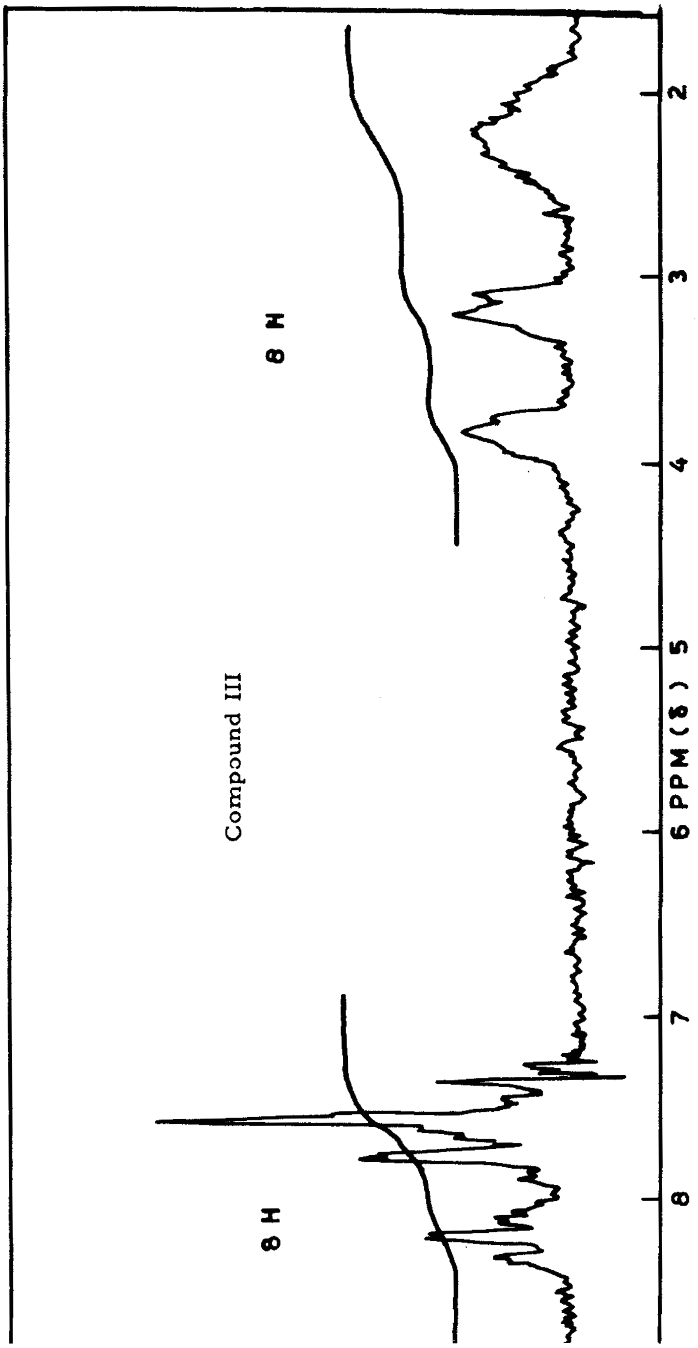


Fig. 1

Methyl N-(4-chloro-n-butane-1-sulfonyl-2-aminobenzoate (V).- To a stirred solution of 6.8 g. (0.045 mole) of methyl *o*-aminobenzoate in 25 ml dry benzene and 2 ml pyridine, was added during 30 min. 12.4 g (0.064 mole) 4-chloro-*n*-butane-1-sulfonyl chloride. After standing overnight at room temperature, the reaction mixture was diluted with ether, then washed with cold dil. HCl several times and finally with water. The ethereal layer was dried over anhydrous sodium sulfate. Upon removal of the benzene and ether, a viscous brown oily mass was obtained which solidified on standing (6.4 g., 45.6%). This solid was crystallized from methanol to give pale yellowish brown crystals, mp. 70-71° (5.3 g, 38.5%). Compound V is soluble in chloroform, carbon tetrachloride, benzene and acetone, sparingly soluble in ethanol and insoluble in petroleum ether. Its IR displayed bands at 1678 cm^{-1} (aryl COOH), 1138 cm^{-1}[SO$_2$ (sym)], 1330 cm^{-1}[SO$_2$ (asym)] and 1285 cm^{-1} (characteristic sultam band).[10]

Anal. Calcd. for $C_{12}H_{16}NO_4SCl$: C, 47.13; H, 5.27; H, 4.58; S, 10.47;
Found: C, 47.36; H, 5.24; N, 4.46; S, 10.06.

N-(o-Carboxyphenyl)-1,4-butanesultam (VI).- A solution of 3.1 g of compound V (0.01 mole) in 30 ml 10% NaOH was heated to reflux for 3 hrs. After cooling, the solution was extracted with ether and acidified with cold dil. hydrochloric acid yielding brownish white crystals. The solid was filtered, dried and crystallized from methanol giving 2 g. (81%) of nearly colorless crystals, mp. 154-155°. Its IR revealed the characteristic sultam band at 1290 cm^{-1}. Compound VI is soluble in chloroform, carbon tetrachloride, alkali, sparingly soluble in alcohol and insoluble in chloroform, benzene petroleum ether and water.

Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.76; H, 5.09; N, 5.49; S, 12.54;
Found: C, 51.72; H, 4.95; N, 5.49; S, 12.56.

Acknowledgement.- The author thanks Professor Dr. Ashworth for helpful discussions and revising the manuscript and D.F.G. for financial support.

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* Present address: National Research Center, Dokki, Cairo, Egypt.

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(Received Nov. 9, 1976; in revised form Feb. 28, 1977)