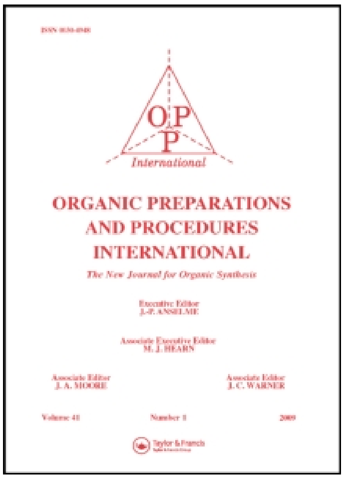


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. NAPHTHOSULTAMS Part XIV

S. H. Doss[a]; M. Hamed[a]
[a] National Research Centre, Dokki, Cairo, Egypt-ARE

To cite this Article Doss, S. H. and Hamed, M.(1981) 'SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. NAPHTHOSULTAMS Part XIV', Organic Preparations and Procedures International, 13: 2, 163 — 170

To link to this Article: DOI: 10.1080/00304948109356118

URL: http://dx.doi.org/10.1080/00304948109356118

** Present address: Chemistry Department, Brock University, St. Catherines, Ontario, Canada.

1. E. Bueding and L. Peters, J. Pharmacol. Exptl. Therap., 101, 210 (1951); E. Bueding, L. Peters and J. F. Waite, Proc. Soc. Exptl. Biol. Med., 64, 11 (1947).

2. E. F. Elslager, L. M. Werbel and D. F. Worth, J. Med. Chem., 13, 104 (1970).

3. E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel and D. F. Worth, ibid., 6, 646 (1963).

4. The nomenclature of cis/trans isomers used herein follows the IUPAC 1968 Tentative rules, Section E. Fundamental Stereochemistry, J. Org. Chem., 35, 2849 (1970).

5. F. G. Baddar, L. S. El-Assal and V. B. Baghos, J. Chem. Soc., 986 (1958). A mixture mp. with an authentic sample of IX, kindly provided by Dr. Baghos showed no depression; the infrared spectra of the two samples were superimposable.

6. A. M. El-Abbady and S. H. Doss, Can. J. Chem., 43, 2408 (1963).

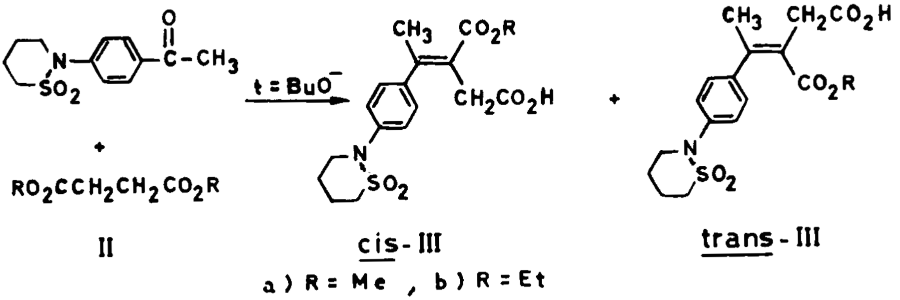
7. F. G. Baddar, L. S. El-Assal and N. A. Doss, J. Chem. Soc., 1027 (1959); see also L. S. El-Assal and A. H. Shehab, ibid., 1020 (1959).

SULTAM DERIVATIVES WITH POSSIBLE SCHISTOSOMICIDAL ACTIVITY. NAPHTHOSULTAMS Part XIV

Submitted by S. H. Doss* and M. Hamed
(5/4/79)

National Research Centre
Dokki
Cairo, Egypt - A.R.E.

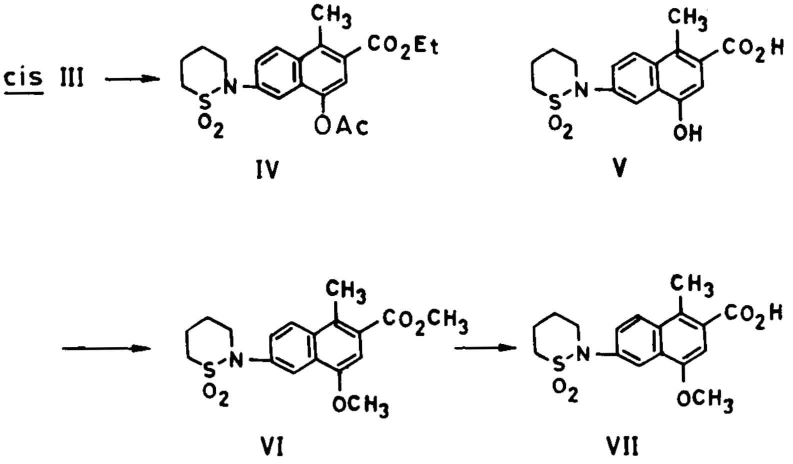
In continuation of our study of schistosomicidal agents,[1,2] we have synthesized some naphthosultams as shown in Schemes 1 and 2. The structure of *cis*-IIIb was established by its spectral data and by its cyclization to IV. Attempts to improve the yield of the Stobbe condensation, such as using sodium hydride, sodium methoxide, or changing the order of addition or increasing the molality of potassium *t*-butoxide were not en-



Scheme 1

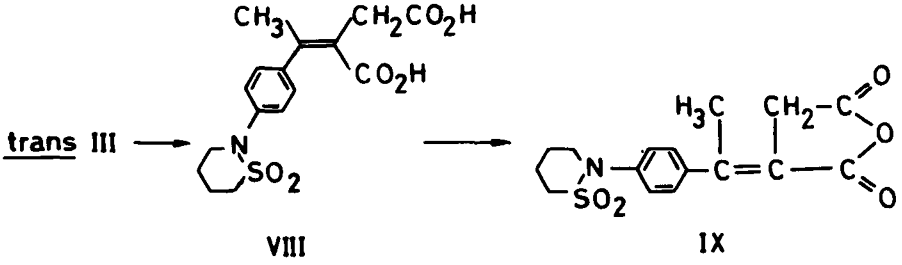
couraging. The low yield may be attributed to the cleavage of the sultam ring to the soluble sulfonic acid derivative[3] in the highly alkaline or acidic media.

Cyclization of the crude mixture of half esters with sodium acetate in acetic anhydride[4] gave a mixture of an acid and neutral fractions. The neutral fraction was a viscous oil which solidified by scratching into a solid yellowish mass (IV); the acidic fraction was the unreacted trans-IIIb



Scheme 2

The ethyl acetoxynaphthoate IV on alkaline hydrolysis afforded the hydroxynaphthoic acid V. Treatment of V with dimethyl sulfate and potassium carbonate in acetone gave the methoxy methyl ester of the naphthosultam VI, which on alkaline hydrolysis yielded the methoxy naphthoic acid (VII). Alkaline hydrolysis of the crude trans-IIIb afforded the unsaturated diacid (VIII), which on heating with acetyl chloride and acetic anhydride gave the anhydride IX; cyclization of the mixture of half ester III with conc. sulfuric acid also gave IX.



Scheme 3

The schistosomicidal activity of the compounds synthesized is still under investigation.

EXPERIMENTAL

All melting points are uncorrected. The I.R. spectra were obtained on a Perkin-Elmer Spectrophotometer Model 221 and a Beckman IR4 (by Sadtler Research Laboratories). The N.M.R. spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer with TMS as an internal reference. The UV spectra were measured on a Cary 14 recording spectrophotometer (Applied Physics Corporation, Monrovia, California). The mass spectra were determined on Hitachi Double Focusing Mass Spectrometer R -7M. Heating temperature of the samples was 120° and the ion source temperature was 170°. The ionising energy was kept at 70 eV, the target current at 65 μA and the total current at 80 μA.

cis-IIIb.- To a stirred solution of t-BuOK [from 3.12 g. potassium metal (0.08 mole) in 50 ml. dry t-butanol] was added dropwise a mixture of 5.06 g. (0.02 mole) of I and 6.96 g. (0.04 mole) of diethyl succinate dissolved in 25 ml. warm t-butanol in nitrogen atmosphere at 50-60° over a period of 10 minutes. The color changed to orange, then to brownish red. The reaction mixture was cooled to about 20° and stirred at that temperature for about 3 hrs. After standing overnight at 0°, the reaction mixture was neutralized with cold dil. acetic acid; the color changed to yellow. Evaporation of the solvent left a solid which was extracted with chloroform and washed with water, then extracted with conc. sodium bicarbonate solution. The bicarbonate extract was neutralized to pH 7 and extracted with chloroform. After drying and evaporation of the chloroform layer under vacuum, the remaining oil, 2.4 g. (42%) solidified on scratching. Crystallization from benzene gave cis-IIIb as colorless crystals, mp. 159-160°; compound cis-IIIb is soluble in methanol, ethanol, chloroform, acetone, partially soluble in benzene, insoluble in pet. ether, ether, toluene, acetic acid and water.

Anal. Calcd. for $C_{18}H_{23}NO_6S$: C, 56.69; H, 6.08; N, 3.67

Found: C, 57.0; H, 6.18; N, 3.60

The separation of trans-IIIb was carried out by stirring the crude alkylidene half ester with cold benzene; after removal of the insoluble cis-isomer, the benzene solution on dilution with pet. ether (40-60°) gave 0.5 g. (6%) of trans-IIIb, mp. 139-140°; mixed mp. for the two isomers is 130-132°.

Anal. Calcd. for $C_{18}H_{23}NO_6S$: C, 56.69; H, 6.08; N, 3.67 ; S, 8.39

Found: C, 56.6; H, 6.1; N, 3.4; S, 8.6

cis-IIIa was prepared similarly in 39% yield, mp. 167°. MS: m/e = 367 $(M)^+$.

Compound IV.- A solution of 1 g. of cis-IIIb (0.0262 mole) in 20 ml. acetic anhydride containing 1 g. fused sodium acetate was refluxed for 0.5 hr. on a sand bath. The reaction mixture was evaporated under reduced pressure to eliminate excess acetic anhydride, then left to cool, and poured into 500 ml. cold saturated sodium bicarbonate solution. The alkaline solution was extracted with benzene, dried and evaporated; the resulting solid was crystallized from benzene-pet. ether (40°-60°) to yield 0.6 g. (56%) of nearly colorless crystals, mp. 135°. The remaining alkaline solution was acidified with acetic acid; extraction gave 0.2 g. of an oil which is probably the unreacted half ester conformer <u>cis</u>-IIIb; its structure is still under investigation.

Compound IV is soluble in benzene, chloroform, acetone, acetic acid; insoluble in methanol, ethanol and pet. ether. Its IR showed absorption at 1760, 1720, 1220 and 1205 cm^{-1} with a broad band between 1250 to 1140 cm^{-1} and another at 830 cm^{-1} (out of plane bending) which is characteristic for the presence of carbonyl groups of saturated esters and conjugated esters, C-O-group of aromatic ethers, C-O group of phenolic acetates and two adjacent aromatic hydrogens; the characteristic SO_2 bands appear at 1355 and 1140 cm^{-1} and the sultam band[5] appears at 1282 cm^{-1}. The nmr spectrum displayed a triplet at δ 1.42 (J = 7Hz)($\underline{CH_3}CH_2$), singlets at δ 2.48 ($\underline{CH_3}Ar$)[6] and δ 2.92 (CH_3COO), a quartet δ 4.43 (CH_3CH_2), multiplets at δ 3.30 (CH_2-SO_2) and δ 3.90 (CH_2N). The aromatic hydrogens appeared between δ 7.2-8.4 and the remaining four hydrogens of the sultam ring exhibited a broad peak between δ 1.7-2.4.

UV: $\lambda_{max.}^{CH_2Cl_2}$ 285 nm, 240 (log ε 3.87, 4.58 respectively). MS: m/e = 4.05 $(M)^+$.

<u>Anal</u>. Calcd. for $C_{20}H_{23}NO_6S$: C, 59.25; H, 4.72; N, 3.45; S, 7.89

Found: C, 59.3; H, 5.7; N, 3.3; S, 7.9

<u>Compound V</u>.- A mixture of 1 g. (0.246 mole) of IV and 50 ml. 10% potassium hydroxide was warmed on a water bath for 2 hrs. until complete dissolution of the solid; the color of the solution changed to yellowish brown. The solution was allowed to cool and kept at room temperature overnight, then neutralized with dil. cold sulfuric acid. The resulting precipitate was filtered and washed with water. The solid was crystallized

from dilute methanol to give 0.7 g. (84%) of brownish crystals, mp. 255-257°. Compound V is soluble in chloroform, acetone, partially soluble in methanol, ethanol and water, while insoluble in benzene and pet. ether.

N.M.R. revealed two groups of ill-defined multiplets centered at δ 1.87 and δ 2.17 (the two center methylene groups of the sultam ring), a singlet at δ 2.73 (methyl group on naphthalene ring), an ill-defined triplet centered at δ 3.33 (CH_2 neighboring to SO_2) and triplet centered at δ 3.74 (CH_2 neighboring to N). The aromatic protons of the naphthalene ring showed signals at δ 7.15, 7.45, 7.56 and 8.16 and singlets at δ 10.24 (phenolic OH) and δ 12.57 (COOH) which disappeared upon D_2O exchange.

Anal. Calcd. for $C_{16}H_{17}NO_5S$: C, 57.31; H, 5.11; N, 4.18; S, 9.54
Found: C, 57.1; H, 4.8; N, 4.1; S, 9.6

Compound VI.- To a solution of 0.6 g. (0.179 mole) of V in 30 ml. dry acetone was added 2 g. anhydrous potassium carbonate and 1 ml. dimethyl sulfate; the reaction mixture was refluxed for 19 hrs., filtered, evaporated under reduced pressure. The crude yellow substance (0.5 g., 77%) was crystallized from benzene-pet. ether, mp. 185-187°. Tlc on silica gel G plate activated at 120° for 30 minutes gave R_f 0.7 [Methanol:chloroform (2/7), detection was carried out with iodine vapor]. Compound VI is soluble in benzene, acetone, alcohol and partially in chloroform, insoluble in pet. ether, acetic acid and water.

Anal. Calcd. for $C_{18}H_{21}NO_5S$: C, 59.50; H, 5.78; N, 3.85; S, 8.81
Found: C, 59.3; H, 5.6; N, 3.6; S, 9.0

Compound VII.- A solution of 0.5 g. (0.137 mole) of VI in 30 ml. of 10% sodium hydroxide was refluxed for 3 hrs. then allowed to cool and acidified with dil. cold HCl. The reaction mixture was extracted with chloroform; after drying over anhydrous Na_2SO_4, the solvent was evaporated under vacuum and the residue was crystallized from dilute methanol into brownish yellow crystals, (0.3 g., 63%), mp. 235-238° (shrinking at 230°). Compound VII is soluble in acetone, chloroform,ether, insoluble in pet. ether, acetic acid and water, partially soluble in benzene and methanol.

Anal. Calcd. for $C_{17}H_{19}NO_5S$: C, 58.45; H, 5.48; N, 4.01

Found: C, 58.5; H, 5.2; N, 4.3

Compound VIII.- A solution of 1 g. (0.262 mole) of trans-IIIb in 30 ml. 10% potassium hydroxide was left at 10° overnight, then kept at 60-80° for 1 hr. with shaking, allowed to cool and neutralized with ice-cold dil. HCl. The precipitated solid was extracted with ether, dried and evaporated. The resulting solid was crystallized from benzene-pet. ether to give 0.8 g. (87%) white crystals, mp. 163°. The mp. was depressed upon admixture with an authentic sample of the half ester IIIb (130-142°). Compound VIII is soluble in methanol, ethanol, chloroform, ether, acetone; insoluble in pet. ether, acetic acid and water.

Anal. Calcd. for $C_{16}H_{19}NO_6S$: C, 54.39; H, 5.42; N, 3.96; S, 9.06

Found: C, 54.2; H, 5.3; N, 4.1; S, 8.8

Compound IX.- A solution of 0.9 g. (0.25 mole) of VIII was refluxed with 7 ml. acetic anhydride and 5 ml. acetyl chloride on a sand bath for 30 min. Evaporation of the anhydride under vacuum left a residue which was crystallized from benzene-pet. ether to give 0.5 g. (58%) of colorless crystals, mp. 180-182°.

Anal. Calcd. for $C_{16}H_{17}NO_5S$: C, 57.31; H, 5.11; N, 4.18

Found: C, 57.2; H, 5.1; N, 4.2

Action of Concentrated Sulfuric Acid on IIIb.- Treatment of 0.5 g. of IIIb (0.131 mole) at 0° with 3 ml. conc. sulfuric acid with cooling and stirring for 0.5 hr., followed by decomposition with ice cold water (50 ml) gave a precipitate which was filtered with water, dried and crystallized from benzene-pet. ether to yield 0.3 g. (63%) of colorless crystals, mp. 180°.

There was no depression of the mp. upon admixture with an authentic sample of the anhydride.

Acknowledgement.- The authors thank Prof. Dr. A. Sakla of Cairo University for his interest, Prof. Dr. H. Dürr of Universität des Saarlandes and Prof. J. Streith of Ecole Supérieure de Chimie de Mulhouse for facilities provided.

REFERENCES

1. S. H. Doss and S. S. A. Dimitry, Org. Prep. Proced. Int., 12, 246 (1980).

2. A. M. El-Abbady, S. H. Doss and M. S. Ahmed, J. Drug Res. Egypt, 4, 123 (1972); S. H. Doss and S. S. A. Dimitry, Org. Prep. Proced. Int., 9, 299 (1977).

3. B. Helferich and K. G. Kleb, Ann., 635, 91 (1960); B. Helferich and K. H. Hermann, ibid., 651, 33 (1962).

4. W. Broche, S. Kettner, M. Cillies, H. Kuhn and R. Manteufell, ibid., 526, 1 (1936); A. M. El-Abbady and S. H. Doss, Can. J. Chem., 43, 2408 (1965); 47, 1483 (1969).

5. S. H. Doss, Acta Chim. Sci. Hung., 72, 361 (1972); Chem. Ind., 961 (1971); Applied Spectroscopy, 32, 110 (1978).

6. S. H. Doss, Rev. Roumaine Chim., 17, 905 (1972).

EFFECT OF METAL IONS IN ORGANIC SYNTHESIS. PART VIII

CONVERSION OF ACYLHYDRAZINES AND N-ACYL-N'-TOSYLHYDRAZINES TO AMIDES IN THE PRESENCE OF CUPRIC CHLORIDE

Submitted by Orazio Attanasi* and Franco Serra-Zanetti
(6/9/80)
Cattedra di Chimica Organica della Facolta di Scienze
Universita di Urbino
Piazza Rinascimento 6, 61029 Urbino, ITALY

In the general context of the increasing interest in the role of the transition and non-transition metals in organic and biological chemistry,[1]