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# Synthesis of Sultam Derivatives with Expected Biological Activity. $\mathbf{1 5}^{\dagger}$ 

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#### Abstract

Trihydro-2H-1,2-thiazole-1,1-dioxide-2-yl)benzophenone (1), 4-(3,5-dimethyl-1`,2`-thiazine-1`,1`-dioxide-2-yl)benzophenone (2), and 4-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenone (6) were obtained from 4-aminobenzophenone and the appropriate reagents. Isomeric ( $E$-) and (Z-) 2-Ethoxycarbonyl-4-phenyl-4-(4-tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)phenyl-3-butenoic acids ( $\mathbf{1 1}$ and 12) and 2-carboxy-4(N-phenyl-thiocarbamoyl)-1-phenyl-6-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)naphthalene were also synthesized.


Keywords: Sultam derivatives.

## Introduction

Many sultam derivatives were found to possess valuable therapeutic properties such as; e.g., antitumor activity [1a] and anticonvulsive activity [1b,c]. In conjunction with our current research on sultam [2a] and on the Stobbe condensation [2b], we attempted to synthesize compounds expected to possess biological activity.

## Results and Discussion

4-Aminobenzophenone [3] was condensed with oxathiolan-2,2-dioxide, 4,6-dimethyl-1,2-oxathiin-2,2-dioxide, cyanoacetohydrazide and phenyl isothiocyanate to give the corresponding derivatives $\mathbf{1 - 4}$, respectively. 4-(tetrahydro-2H-1,2-thiazin-1,1-dioxide-2-yl) benzophenone (6) was also prepared (cf. Scheme 1). The UV spectra of the sultamyl derivatives exhibited maximum absorption band at $\lambda_{\text {max }}$ $235-254 \mathrm{~nm}(\mathrm{EtOH})$ assigned to the vibrational structure of the sultamyl group $\left(\mathrm{n}-\pi^{*}\right)$ transition [4]. Additional bands at $\lambda_{\max } 305-335 \mathrm{~nm}(\mathrm{EtOH})$ were present, also characteristic of the sultamyl group, but which were absent from the spectrum of the thiourea derivative.



Scheme 1.

Compound 6 reacted with cyanoacetohydrazide to give 4 -(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenonecyanoacetohydrazone (7). The structure of the latter product was elucidated on the basis of its elemental analysis and spectral data ( $c f$. Experimental). Sultam derivatives $\mathbf{8 - 1 0}$ were obtained by the reaction of compound 7 with benzenediazonium chloride, benzaldehyde and salicylaldehyde, respectively ( $c f$. Scheme 2). Structures 8-10 were confirmed on the basis of elemental analyses and spectral data ( $c f$. Experimental).

Ketone 6 was condensed with diethyl succinate to give an oily half-ester ( $82 \%$ ). The ( $E-$ ) and (Z-) 3-ethoxycarbonyl-4-phenyl-4-(4-tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)-3-butenoic acids were separated by fractional crystallization; the ( $E-$ ) isomer was predominant. The relative ratio was estimated by the application of the spectrophotometric method [5], the ratio was almost the same as the ratio obtained by fractional crystallization (6:1).


Scheme 2.

The relative proportion of the two hemiesters obtained is determined by polar non-bonded interactions existing between the groups attached the carbonyl of the ketone and the carbanion. The predominance of the ( $E$-) isomer is most likely probably due to the polar factor since repulsion between Ph and -COOR is expected to be less significant than that between Ar and -COOR. The polar factor i.e., repulsion between Ph and COOEt and between Ar and COOEt probably plays the more important role (See Figure 1).

(A)

(B)


Figure 1.

The conjugation of the lone pair of N in the sultam ring will increase electron density in the Ar group. Thus the ( $E-$ ) Ar/-COOR configuration is expected to be predominant, as found experimentally. Evidence for the ( $E-$ ) configuration of the hemiester was provided by its cyclization to the corresponding 1-phenylnaphthalene derivative $\mathbf{1 3}$ with the sultam ring in position 6 . The structure of $\mathbf{1 3}$ was
proven by:
(a) analytical data;
(b) IR, ${ }^{1} \mathrm{H}-\mathrm{NMR}$ and mass spectra ( $c f$. Experimental and Table 1);
(c) No fragment of $\mathrm{m} / \mathrm{e} 210$ was obtained ( that the sultam ring is in position 6 of the 1-phenylnaphthalene and not in position 4'. Furthermore, the presence of five and not four adjacent hydrogen atoms [6] revealed the presence of an unsubstituted phenyl group (cf. mechanism [2b]).


Scheme 3.

Cyclization of the predominant ( $E$-) hemiester (11) using sodium acetate and acetic anhydride [7] gave 4-acetoxy-2-ethoxycarbonyl-1-phenyl-6-(tetrahydro-1,2-thiazin-1,1-dioxide-2-yl)-naphthalene (13). Compound $\mathbf{1 3}$ was hydrolyzed with aqueous sodium hydroxide ( $8 \%$ ) to give the phenolic acid 14. The latter acid was either treated with phenyl isothiocyanate in benzene to give $\mathbf{1 6}$ or methylated to give methoxy ester 15. The latter was hydrolyzed with sodium hydroxide ( 2 N ) to give 2 -carboxy-4-methoxy-1-phenyl-6-(tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)naphthalene (17) (cf. Scheme 3).

Saponification of the ( $E$-) hemiester 11 with 2 N sodium hydroxide $\left(a t 50-60^{\circ} \mathrm{C}\right.$ ) gave the dibasic acid $\mathbf{1 8}$ in $87 \%$ yield. Use more of concentrated alkali or alcoholic alkali was not successful. This may be due to the destruction of sultam ring. The dibasic acid was converted by refluxing with acetic anhydride to the corresponding cyclic anhydride which exhibited the expected carbonyl coupling bands (1830 and $1780 \mathrm{~cm}^{-1}$ ) [4,6].

Biological testing of all reported compounds, in particular for antitumor and antiepileptic activity, is currently under way and results will be published elsewhere.

## Experimental

## General

All melting points were determined on a Electrothermal melting point apparatus and are uncorrected. IR spectra ( KBr disks) were recorded on a Beckman IR 4220 spectrophotometer. ${ }^{1} \mathrm{H}-\mathrm{NMR}$ spectra were recorded on a Varian EM $390-90 \mathrm{MHz}$. spectrometer and chemical shifts are expressed in $\delta(\mathrm{ppm})$ units using TMS as internal reference. Electronic absorption spectra were recorded in ethanol solutions a Shimadzu graphic printer Pr-1 spectrophotometer. Mass spectra were recorded using a GCMS-QP 1000 EX Shimadzu spectrometer. The Microanalytical units of Cairo University and of the National Research Center performed elemental analyses.

## 4-(Trihydro-2H-1,2-thiazole-1,1-dioxide-2-yl)benzophenone (1)

4-Aminobenzophenone ( $1.97 \mathrm{~g}, 0.01 \mathrm{~mol}$ ) was fused with oxathiolan-2,2-dioxide ( $1.2 \mathrm{~g}, 0.01 \mathrm{~mol}$ ) at $90-100^{\circ} \mathrm{C}$ in oil bath for one hour. The reaction mixture changed to yellow, then brownish oil, which solidified. This solid was washed with hydrochloric acid and then with water. Yield $69 \%$. Compound 1 had mp. 230-32 ${ }^{\circ} \mathrm{C}$ (methanol), Found for $\mathrm{C}_{16} \mathrm{H}_{15} \mathrm{NO}_{3} \mathrm{~S}$ (301.36): C, 63.51; H, 4.80; N, 4.80 and S , 10.10. Calcd.: C, 63.77; H, 5.01; N, 4.65; S, 10.63. ${ }^{1} \mathrm{H}$ NMR: 1.7 (m, $2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{SO}_{2}$ ), 2.6 (t, 2 H , $\left.\mathrm{NCH}_{2}\right), 3.2\left(\mathrm{t}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{SO}_{2}\right)$ and 7.4-7.7 (m, 9H, ArH's)[8]. UV: $\lambda_{\text {max }} 218(\log \varepsilon=4.47), 285(\log \varepsilon=$ 4.32) and $332(\log \varepsilon=4.90) \mathrm{nm}$; IR $\left(\mathrm{cm}^{-1}\right) 1648(\mathrm{CO}), 1157\left(\mathrm{SO}_{2}\right), 1317\left(\mathrm{SO}_{2}\right.$ asym.), 1283 (sultam band) and 738-705 (5 phenylic adjacent H atoms).

## 4-(3,5-Dimethyl-1',2'-thiazine-1',1'-dioxide-2-yl)benzophenone (2)

4-Aminobenzophenone ( $1.97 \mathrm{~g}, 0.01 \mathrm{~mol}$ ) was fused with 4,6-dimethyl-1,2-oxathiin-2,2-dioxide $(1.6 \mathrm{~g}, 0.01 \mathrm{~mol})$ at $110^{\circ} \mathrm{C}$ for one hour in an oil bath. The solid formed was washed with dil. hydrochloric acid and then with water. Yield: $35 \%$. Compound 2 had mp. 185-86 ${ }^{\circ} \mathrm{C}$ (methanol), Found for $\mathrm{C}_{19} \mathrm{H}_{17} \mathrm{NO}_{3} \mathrm{~S}$ (339.41): C, 66.80; H, 5.00; N, 3.90; S, 9.50. Calcd.: C, 67.23; H, 5.40; N, 4.12; S, 9.44. $\mathrm{UV} \lambda_{\max } 245(\log \varepsilon=4.00)$ and $334(\log \varepsilon=4.03)$; IR $\left(\mathrm{cm}^{-1}\right) 1658(\mathrm{CO}), 1581$ (conjugated double bond of the sultam ring), 1280 (sultam ring).

## 4-Aminobenzophenone cyanoacetohydrazone (3)

To a mixture of 4-aminobenzophenone ( $1.97 \mathrm{~g}, 0.01 \mathrm{~mol}$ ) and cyanoacetohydrazide [8] ( $0.99 \mathrm{~g}, 0.01$ mol ) in ethanol ( 50 mL ), 3 drops of hydrochloric acid are added. The mixture was left at room temperature for 72 hrs. Yield: $99 \%$. Compound 3 had mp., $145-46^{\circ} \mathrm{C}$. Found for $\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{~N}_{4} \mathrm{O}$ (278.31): C, 69.10; H, 5.10; N, 20.04. Calcd.: C, 69.05, H, 5.07; N, 20.13. ${ }^{1} \mathrm{H}$ NMR: 3.8 (s, 2H, NH2), 4.2 (d, 2H, $\left.\mathrm{CH}_{2} \mathrm{CN}\right)$, 6.5-7.6 (m, 9H, ArH's) and $9.6(\mathrm{~s}, 1 \mathrm{H}, \mathrm{NH})$. IR $\left(\mathrm{cm}^{-1}\right), 3460,3375\left(\mathrm{NH}_{2}\right), 2260(\mathrm{CN}), 1687$ ( CONH ), $1140\left(\mathrm{SO}_{2}\right), 1322\left(\mathrm{SO}_{2}\right.$ asym).

## 4-(Phenyl thioureido)benzophenone (4)

A mixture of 4-aminobenzophenone ( $1.97 \mathrm{~g}, 0.01 \mathrm{~mol}$ ), phenyl isothiocyanate $(1.35 \mathrm{~g}, 0.01 \mathrm{~mol})$ and triethylamine ( 3 drops) in benzene ( 50 mL ) was refluxed for 5 hrs . The solvent was evaporated under vacuum to give an oily residue. It was triturated with light petroleum $\left(60-80^{\circ} \mathrm{C}\right)$ to afford a solid. Yield: $45 \%$. Compound 4 had mp. $156-57^{\circ} \mathrm{C}$ (benzene-acetone). Found for $\mathrm{C}_{20} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{OS}$ (332.426): C, 72.50 ; H, 4.50; N, 8.00; S, 9.20. Calcd.: 72.26; H, 4.85; N, 8.42; S, 9.64. (UV $\lambda_{\max } 217,274 \mathrm{~nm}(\log \varepsilon=$ 4.16 and 4.06, respectively). IR $\left(\mathrm{cm}^{-1}\right), 3322-3029(\mathrm{NH}), 1690(\mathrm{CO}), 1253-1023(\mathrm{CS})$.

## 4-(Tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenone (6)

4-chloro-1-butanesulfonyl chloride ( 0.01 mol ) was added dropwise at room temperature over 0.5 hr to a stirred solution of 4 -aminobenzophenone ( $1.97 \mathrm{~g}, 0.01 \mathrm{~mol}$ ) in benzene ( 20 mL ) and pyridine ( 3 mL ) to give 4-benzoyl-4-chlorobutanesulfonanilide (5). Compound 5 had mp., $105-106^{\circ} \mathrm{C}$ (benzenepetroleum ether). Found for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{ClNO}_{3}$ (351.85): C, 58.30 ; H, 5.20 ; N, 3.92; S, 9.00. Calcd.: C, 58.03; H, 5.12; N; 3.98; S, 9.11. Its 2,4-DNP derivative, mp. 233-34 ${ }^{\circ} \mathrm{C}$ (acetic acid, $60 \%$ ). Found for $\mathrm{C}_{23} \mathrm{H}_{22} \mathrm{ClN}_{5} \mathrm{O}_{6} \mathrm{~S}$ (531.98): C, 52.00; H, 4.10; N, 13.20; S, 6.00. Calcd.: C, 51.93; H, 4.16; N, 13.16; S, 6.03 .

A solution of 5 was warmed at $40-50^{\circ} \mathrm{C}$ for 3 hrs with sodium hydroxide ( 2 N ) to give $\mathbf{6}$ [4]. Yield: $63 \%$, mp. $136-37^{\circ} \mathrm{C}$ (benzene). Found for $\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{NO}_{3} \mathrm{~S}$ (315.39): C, $64.70 ; \mathrm{H}, 5.30 ; \mathrm{N}, 4.40 ; \mathrm{S}, 9.90$. Calcd., C, 64.74; H, 5.43; N, 4.44; S, 10.15. ${ }^{1} \mathrm{H}$ NMR: 1.8 (m, $2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{SO}_{2}$ ), 2.3 (m, 2 H ,
$\left.\mathrm{SO}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2}\right), 3.2\left(\mathrm{t}, 2 \mathrm{H}, \mathrm{SO}_{2} \mathrm{CH}_{2}\right), 3.8\left(\mathrm{t}, 2 \mathrm{H}, \mathrm{NCH}_{2}\right)$ and 7.2-7.7 (m, $9 \mathrm{H}, \mathrm{ArH}$ 's. IR $\left(\mathrm{cm}^{-1}\right), 1690$ (CO), $1325\left(\mathrm{SO}_{2} \mathrm{~N}\right), 1280$ (sultam) and 770-700 (five adjacent hydrogen atoms). UV $\lambda_{\text {max }} 235$, 305 nm ( $\log \varepsilon=4.68$ and 4.89 , respectively). Its DNP had mp. 275-76 ${ }^{\circ} \mathrm{C}$ (acetic acid). Found for $\mathrm{C}_{23} \mathrm{H}_{21} \mathrm{~N}_{5} \mathrm{O}_{6} \mathrm{~S}$ (495.52); C, 56.10; H, 4.40; N, 13.60; S, 6.20. Calcd.: C, 55.75; H, 4.26; N, 14.19; S, 6.67.

## 4-(Tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)benzophenonecyanoacetohydrazone (7)

Prepared from 6 in a similar fashion as above, yield $75 \%$. Mp. $122-23^{\circ} \mathrm{C}$ (ethanol). Found for $\mathrm{C}_{20} \mathrm{H}_{20} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S}$ (396.47): C, 60.50; H, 5.10; N, 14.00; S, 8.20. Calcd.: C, 60.59; H, 5.08; N, 14.13, S, 8.08. ${ }^{1} \mathrm{H}$ NMR: $1.8\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{SO}_{2} \mathrm{CH}_{2} \underline{\mathrm{CH}}_{2}\right), 2.3\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{SO}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2} \underline{\mathrm{CH}}_{2}\right), 3.2\left(\mathrm{t}, \mathrm{SO}_{2} \underline{\mathrm{CH}}_{2}\right), 3.8(\mathrm{t}$, $\mathrm{NCH}_{2}$ ), 7.4-7.7 (m, 9H, ArH's), 9.3 (s, 1H, NHCO).
(a) The hydrazone derivative $7(0.01 \mathrm{~mol})$ was coupled with benzenediazonium chloride ( 0.01 mol ) to give 8, yield at room temperature $64 \%$, mp. $130-31^{\circ} \mathrm{C}$ (acetic acid). Found for $\mathrm{C}_{26} \mathrm{H}_{24} \mathrm{~N}_{6} \mathrm{O}_{3} \mathrm{~S}$ (500.58): C, $61.40 ; \mathrm{H}, 4.80 ; \mathrm{N}, 16.80$; S, 6.40. Calcd.: C, 61.38 ; H, 4.83 ; N, 16.78; S, 6.40. IR ( $\mathrm{cm}^{-1}$ ), 2152 (CN), 1648 (CONH) and 1280 (sultam).
(b) To hydrazone derivative $7(0.01 \mathrm{~mol})$, benzaldehyde $(0.01 \mathrm{~mol})$ in ethanol ( 20 mL ) and 2 drops of piperidine were added. The mixture was refluxed for 30 minutes on a water bath. After cooling, the solid was collected and crystallized to give 9 ( $73.5 \%$ ), mp. $230-31^{\circ} \mathrm{C}$ (ethanol). Found for $\mathrm{C}_{26} \mathrm{H}_{24} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S}$ (472.57): C, 66.30; H, 5.10; N, 11.70; S, 6.40. Calcd.: C, 66.08; H, 5.12; N, 11.85; S, 6.76. IR ( $\mathrm{cm}^{-1}$ ), 2152 (CN), 1648 (CONH) and 1280 (sultam).
(c) To hydrazone derivative $7(0.01 \mathrm{~mol})$, salicylaldehyde ( 0.01 mol ) in ethanolic sodium ethoxide solution [prepared from sodium metal ( 1.1 g -atom) in ethanol ( 20 mL )] was added. The mixture was refluxed for 2 hrs ., then cooled. The reaction mixture was acidified with hydrochloric acid to give $\mathbf{1 0}$, yield $55 \%$, mp. $243-44^{\circ} \mathrm{C}$ (ethanol). Found for $\mathrm{C}_{27} \mathrm{H}_{23} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}$ (501.56): C, 64.50; H, 4.60; N, 8.80, S, 6.70. Calcd.: C, 64.65 ; H, 4.62; N, 8.38; S, 6.39. IR $\left(\mathrm{cm}^{-1}\right) 3446$ (NH), 1700, 1648 (two CO) and 1282 (sultam).

## 3-Ethoxycarbonyl-4-phenyl-4-(4'-tetrahydro-1,2-thiazine-1,1-dioxide-2-yl)phenyl-3-butenoic acids (11 and 12)

To a cooled stirred mixture of ketone $6(0.01 \mathrm{~mol})$ and diethyl succinate $(0.02 \mathrm{~mol})$ in t-butanol ( 15 mL ), potassium t-butoxide was added dropwise [prepared from 1.2 g -atom potassium and t-butanol ( 50 $\mathrm{mL})$ ]. After 72 hrs , the reaction mixture was heated at $65-70^{\circ} \mathrm{C}$ for one hour, then worked up as usual [2b] to give an acidic brown viscous oily product (yield $\sim 7.3 \mathrm{~g}, 82 \%$ ). The ( $E-$ ) (11) and ( $Z-$ ) (12) isomeric hemiesters were separated by fractional crystallization.

Compound 11 had mp. 144-45 ${ }^{\circ} \mathrm{C}$ (benzene-acetone). Found for $\mathrm{C}_{23} \mathrm{H}_{25} \mathrm{NO}_{6} \mathrm{~S}$ (443.52): C, 62.00; H, 5.50 ; N, 3.30; S, 7.60. Calcd.: C, 62.28; H, 5.64; N, 3.16; S, 7.23. IR $\left(\mathrm{cm}^{-1}\right), 3300-2600(\gamma \mathrm{OH}), 1700-$ 1620 (CO), 1270 (sultam).

Compound 12 had m.p. $108-109^{\circ} \mathrm{C}$ (benzene). Found for $\mathrm{C}_{23} \mathrm{H}_{25} \mathrm{NO}_{6} \mathrm{~S}$ (443.52): C, $62.40 ; \mathrm{H}, 5.50$;

N, 3.30; S, 7.50. Calcd.: C, 62.28; H, 5.64, N, 3.16; S, 7.23. IR ( $\mathrm{cm}^{-1}$ ), 3600-2500 (OH), 1700-1640 (CO), 1280 (sultam).

Determination of the relative ratio of the two (E-) and (Z-) hemiesters by electronic absorption spectroscopy [5]

Values for $\mathrm{E}_{\text {obs }} / \mathrm{E}_{1}$ were plotted vs. the values for $\mathrm{E}_{2 \mathrm{~s}} / \mathrm{E}_{1}$ where $\mathrm{E}_{\text {obs }}$ is the observed optical density of the mixture and $\mathrm{E}_{1}$ and $\mathrm{E}_{2}$ are the optical densities of the hemiesters $\mathbf{1 1}$ and $\mathbf{1 2}$ respectively, at the same wavelength. A straight line was obtained from which the ratio of $5.9 / 1$ was calculated. This is almost the same ratio as that obtained experimentally by fractional crystallization.

## Cyclization of the ( $E$-) hemiester

A mixture of the $(E-)$ hemiester ( 1 mol ) fused sodium acetate ( 1.2 mol ) and acetic anhydride (30 $\mathrm{mL} / 1 \mathrm{~g}$ sodium acetate) was left overnight with occasional shaking at room temperature. The temperature was gradually raised to $70-80^{\circ} \mathrm{C}$ for 3 hrs . The neutral cyclized product $\mathbf{1 3}$ was isolated and had mp. 122-23 ${ }^{\circ} \mathrm{C}$ (ethanol). Found for $\mathrm{C}_{25} \mathrm{H}_{25} \mathrm{NO}_{6} \mathrm{~S} . \mathrm{H}_{2} \mathrm{O}$ (485.56): C, $62.00 ; \mathrm{H}, 5.40 ; \mathrm{N}, 3.00 ; \mathrm{S}, 6.80$. Calcd.: C, 61.84; H, 5.19; N, 2.88; S, 6.61. Mass spectrum, m/e $=485$ and ${ }^{1} \mathrm{H}$ NMR: $1.2(\mathrm{t}, 3 \mathrm{H}$, $\mathrm{CH}_{3} \mathrm{CH}_{2} \mathrm{O}$ ), $1.8\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{SO}_{2} \mathrm{CH}_{2} \mathrm{CH}_{2}\right), 2.3\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2}\left(\mathrm{CH}_{2}\right)_{2} \mathrm{SO}_{2}, 3.2\left(\mathrm{t}, 2 \mathrm{H}, \mathrm{SO}_{2} \mathrm{CH}_{2}\right), 3.5(\mathrm{t}, 2 \mathrm{H}\right.$, $\mathrm{NCH}_{2}$ ), and 7.0-7.8 (m, 9H, ArH's) ${ }^{9}$. IR $\left(\mathrm{cm}^{-1}\right), 1760(\mathrm{CO}), 1290$ (sultam ring), 740-700 (five adjacent hydrogen atoms).

## Conversion of the acetoxy ester $\mathbf{1 3}$ into methoxy acid $\mathbf{1 7}$

The acetoxy ester was hydrolysed with 2 N sodium hydroxide on water-bath $\left(70-80^{\circ} \mathrm{C}\right)$ for two hrs. The hydroxy acid $\mathbf{1 4}(1 \mathrm{~mol})$ was methylated by refluxing for 10 hrs with dimethyl sulphate ( 5 mol ) and potassium carbonate ( 6 mol ) in dry acetone. The methoxy ester was hydrolyzed to the corresponding acid by warming for 3 hrs with $8 \%$ sodium hydroxide, followed by cooling and acidification.

Compound 14 had mp. $225-26^{\circ} \mathrm{C}$ (acetic acid). Found for $\mathrm{C}_{21} \mathrm{H}_{19} \mathrm{NO}_{5} \mathrm{~S}$ (397.45): C, 63.20; H, 5.10; N, 3.40; S, 7.70. Calcd.: C, 63.47; H, 4.81; N, 3.52; S, 8.06.

Compound 15 had mp. 167-68 (methanol). Found for $\mathrm{C}_{23} \mathrm{H}_{23} \mathrm{NO}_{5} \mathrm{~S}$ (425.50): C, 64.70; H, 5.00; N, 3.60, S, 7.90. Calcd.: C, 64.92; H, 5.44; N, 3.29; S, 7.52.

Compound 17 had mp., $120-21^{\circ} \mathrm{C}$ (acetic acid). Found for $\mathrm{C}_{22} \mathrm{H}_{21} \mathrm{NO}_{5} \mathrm{~S}$ (411.48): C, 63.90; H, 5.30; N, 3.40; S, 7.60. Calcd.: C, 64.23; H, 5.14; N, 3.40; S, 7.78. IR ( $\mathrm{cm}^{-1}$ ), 1725 (CO), 1295 (sultam) and 740-700 (five adjacent hydrogen atoms).

2-Carboxy-4(N-phenylthiocarbamoyl)-1-phenyl-6-(tetrahydro-2H-1,2-thiazine-1,1-dioxide-2-yl)naphthalene (16)

A mixture of hydroxynaphthoic acid derivative $14(0.01 \mathrm{~mol})$, phenyl isothiocyanate ( 0.01 mol ) and

3 drops of triethylamine in dry benzene ( 30 mL ) was refluxed for 5 hrs . The benzene was evaporated under reduced pressure to give yellow solid 16, yield $71 \%$. It had mp. 133-34 ${ }^{\circ} \mathrm{C}$ (benzene-acetone). Found for $\mathrm{C}_{28} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{O}_{5} \mathrm{~S}_{2}$ (532.64): 62.90; H, 4.90; $\mathrm{N}, 5.40 ; \mathrm{S}, 11.90$. Calcd.: C, 63.14; H, 4.54; N , $5.26 ; \mathrm{S}, 12.01$. IR $\left(\mathrm{cm}^{-1}\right), 3247-2800(\mathrm{OH}), 1725(\mathrm{CO}), 1290$ (sultam) and 744-701 (five adjacent hydrogen atoms).

Saponification of the ( $E-$ ) hemiester to the corresponding dibasic acid 18 and anhydride 19
The ( $E$-) hemiester ( 0.1 mol ) was left in $\mathrm{NaOH}\left(2 \mathrm{~N}, 50 \mathrm{~mL}\right.$ ) for about 72 hrs ., then kept $60-80^{\circ} \mathrm{C}$ for one hour. The dibasic acid $\mathbf{1 8}$ was refluxed with a mixture of acetic anhydride ( 7 mL ) and acetyl chloride ( 5 mL ) on a sand bath for 30 minutes, to give the corresponding anhydride (19).

Compound 18 had mp., $175-76^{\circ} \mathrm{C}$ (benzene-acetone). Found for $\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{NO}_{6} \mathrm{~S}$ (415.47): C, 60.20; H, 5.10; N, 3.90; S, 7.20. Calcd.: 60.72; H, 5.08; N, 3.37; S, 7.85. ${ }^{1} \mathrm{H}$ NMR: $1.7\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{2} \mathrm{CH}_{2} \mathrm{SO}_{2}\right.$ ), 2.3 (m, $2 \mathrm{H}, \mathrm{CH}_{2}\left(\mathrm{CH}_{2}\right) 2 \mathrm{SO}_{2}$ ), $3.2\left(\mathrm{t}, 2 \mathrm{H}, \mathrm{SO}_{2} \mathrm{CH}_{2}\right.$ ), $3.5\left(\mathrm{t}, 2 \mathrm{H}, \mathrm{NCH}_{2}\right), 7.1-7.4(\mathrm{~m}, 9 \mathrm{H}, \mathrm{ArH}$ 's) and $12.5(\mathrm{~s}$, $2 \mathrm{H},(\mathrm{COOH})_{2}$. IR $\left(\mathrm{cm}^{-1}\right), 3446-2500(\gamma \mathrm{OH}), 1720-1656(\mathrm{CO}), 1276$ (sultam), 745-707 (five adjacent hydrogen atoms).

Compound 19 had mp. 137-38 ${ }^{\circ} \mathrm{C}$ (benzene-peteroleum ether). Found for $\mathrm{C}_{21} \mathrm{H}_{19} \mathrm{NO}_{5} \mathrm{~S}$ (397.45): C, 63.20; H, 5.00; N, 3.90; S, 8.30. Calcd.: C, 63.46; H, 4.81; N, 3.52; S, 8.07. IR (cm-1), 1840,1780 (CO-O-CO), 1280 (sultam ring) and 750-700 (five adjacent hydrogen atoms).

Table 1. Mass spectra of compounds 1, 3, 6, 11, $\mathbf{1 2}$ and 13.

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\(1 \quad 301\left(20, \mathrm{C}_{16} \mathrm{H}_{15} \mathrm{NSO}_{3}{ }^{+}\right) ; 224\left(12, \mathrm{C}_{10} \mathrm{H}_{10} \mathrm{NSO}_{3}{ }^{+}\right) ; 197\left(100, \mathrm{C}_{9} \mathrm{H}_{10} \mathrm{NSO}_{2}^{+1}\right) ; 180\left(5, \mathrm{C}_{13} \mathrm{H}_{9} \mathrm{O}^{+1}\right)\);
        \(120\left(8, \mathrm{C}_{3} \mathrm{H}_{6} \mathrm{NSO}_{2}{ }^{+}\right) ; 77\left(16, \mathrm{C}_{6} \mathrm{H}_{5}{ }^{+}\right)\).
\(3278\left(100, \mathrm{C}_{16} \mathrm{H}_{14} \mathrm{ON}_{4}^{+}\right) ; 238\left(21.69, \mathrm{C}_{14} \mathrm{H}_{12} \mathrm{ON}_{3}{ }^{+}\right) ; 210\left(37.08, \mathrm{C}_{13} \mathrm{H}_{12} \mathrm{~N}_{3}{ }^{+}\right)\), 180 (29.44,
        \(\mathrm{C}_{13} \mathrm{H}_{10} \mathrm{~N}^{+}\)); \(119\left(1.87, \mathrm{C}_{7} \mathrm{H}_{5} \mathrm{ON}^{+}\right) ; 77\left(16.64, \mathrm{C}_{6} \mathrm{H}_{5}^{+}\right)\).
\(6315\left(100, \mathrm{C}_{17} \mathrm{H}_{17} \mathrm{NSO}_{3}{ }^{+} ; 238\left(47.13, \mathrm{C}_{11} \mathrm{H}_{12} \mathrm{NSO}_{3}{ }^{+}\right) ; 210\left(14.93 \mathrm{C}_{10} \mathrm{H}_{12} \mathrm{NSO}_{2}{ }^{+}\right) ; 132\right.\) (19,
        \(\left.\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{~N}^{+}\right) ; 105\left(19, \mathrm{C}_{7} \mathrm{H}_{5} \mathrm{O}^{+}\right) ; 77\left(16, \mathrm{C}_{6} \mathrm{H}_{5}{ }^{+}\right)\).
11443 (12.1, \(\mathrm{C}_{23} \mathrm{H}_{25} \mathrm{NSO}_{6}{ }^{+}\)); 339 (33.6, \(\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{NSO}_{4}{ }^{+1}\) ); 379 (1.8, \(\mathrm{C}_{23} \mathrm{H}_{25} \mathrm{NO}_{4}^{+}\)); 365 (14.4,
        \(\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{NO}_{4}{ }^{+}\)); \(325\left(100, \mathrm{C}_{19} \mathrm{H}_{18} \mathrm{NO}_{4}{ }^{+1}\right) ; 308\left(7.9, \mathrm{C}_{19} \mathrm{H}_{16} \mathrm{O}_{4}^{+}\right) ; 144\) (1.6, \(\left.\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{4}^{+}\right) ; 134\) (0.7,
        \(\mathrm{C}_{4} \mathrm{H}_{8} \mathrm{NSO}_{2}{ }^{+}\)); \(77\left(1.5, \mathrm{C}_{6} \mathrm{H}_{5}{ }^{+}\right)\).
12443 (12.80, \(\left.\mathrm{C}_{23} \mathrm{H}_{25} \mathrm{NSO}_{6}^{+}\right) ; 325\) (100, \(\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{O}_{4} \mathrm{~N}^{+1}\) ); 308 (13.4, \(\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{O}_{4}^{+}\)); 139 (5.2,
        \(\mathrm{C}_{6} \mathrm{H}_{2} \mathrm{O}_{4}{ }^{+1}\) ); \(134\left(3.4, \mathrm{C}_{4} \mathrm{H}_{8} \mathrm{NSO}_{2}{ }^{+}\right) ; 77\left(7.9, \mathrm{C}_{6} \mathrm{H}_{5}{ }^{+}\right)\).
\(13485\left(100, \mathrm{C}_{25} \mathrm{H}_{25} \mathrm{NSO}_{6} \cdot \mathrm{H}_{2} \mathrm{O}^{+}\right)\); \(467\left(5, \mathrm{C}_{25} \mathrm{H}_{25} \mathrm{NSO}_{6}{ }^{+}\right) ; 404\left(5, \mathrm{C}_{25} \mathrm{H}_{25} \mathrm{NO}_{4}{ }^{+1}\right) ; 361\) (5,
        \(\mathrm{C}_{23} \mathrm{H}_{22} \mathrm{NO}^{+1}\) ).
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