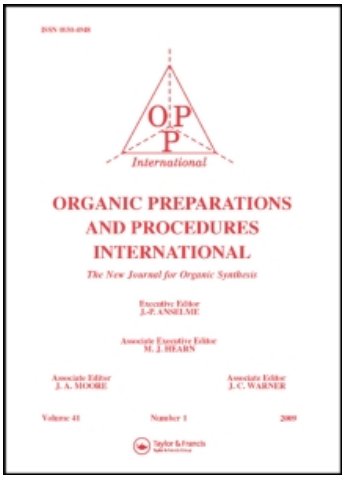

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THIOPHENO[3,2][1]BENZAZEPINE, BENZO[3,4]CYCLOHEPTA[2,1-b]THIOPHENES, THIAZOLO[5,4-d][1]BENZAZEPINE AND BENZO[3,4]CYCLOHEPTA[2,1-d]THIAZOLES

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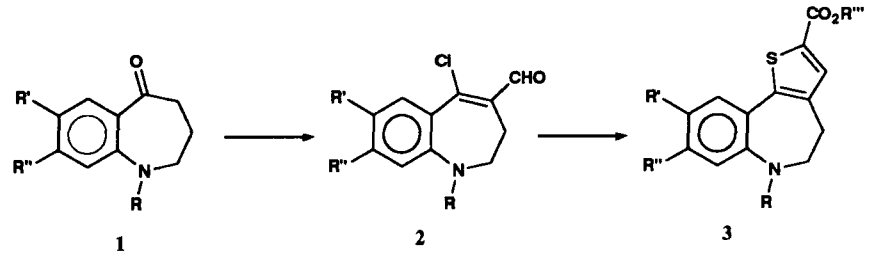
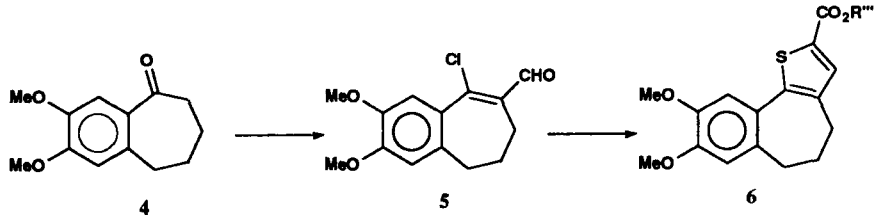
A number of biologically interesting polynuclear compounds incorporating a fused thiophene ring *viz.* thiasteroids,[1] analogues of indole alkaloids,[2] carcinogenic compounds,[3] etc. consist of six-membered rings annelated to thiophene. But examples of polycondensed systems incorporating a thiophene or thiazole ring fused to a seven-membered ring (*viz.* 1-benzazepines and benzosuberones) are sparse. In continuation of our interest in the synthesis of biologically active fused heterocycles,[4] we have synthesized the hitherto unreported thiophene and thiazole derivatives starting from the tetrahydro-1-benzazepin-5-one (**1a-c**)[5] and 1-benzosuberone (**4**)[6] analogues.

Reaction of the tetrahydro-1-tosyl-1-benzazepine-5-one (**1a**) with phosphoryl chloride in dimethylformamide at 0° gave 5-chloro-2,3-dihydro-1-tosylbenzazepin-2-carbaldehyde (**2a**, 82%) which cyclized to 2-carbethoxy-4,5,6-trihydro-6-tosylthiopheno[3,2-d][1]benzazepine (**3a**) in good yield (86%) upon treatment with ethyl mercaptoacetate and sodium ethoxide. Compound **3a** on vigorous hydrolysis in 50% aqueous sulfuric acid and acetic acid underwent simultaneous detosylation to yield the corresponding thiophene-2-carboxylic acid (**3e**) in 45% yield. The infrared spectrum contained a strong C=O peak at 1670 cm^{-1} and the ^1H NMR spectrum showed the isolated thiophene



1 2 3

a) R = Tos, R' = R'' = H, R''' = Et b)R = Tos, R' = H, R'' = Cl, R''' = Et c) R = Tos, R' = R'' = OMe, R''' = Et
e) R = R' = R'' = R''' = H f) R = R' = R''' = H, R'' = Cl



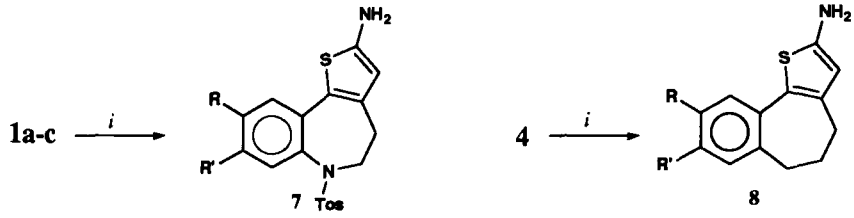
4 5 6

a) R'' = Et b) R = H

Scheme 1

proton (3-H) as a singlet at δ 7.55 and also the absence of tosyl and ethyl proton peaks at their respective places., Analogues **3f** and **6b** were similarly obtained by the same procedure, but attempts to decarboxylate or detosylate compound **3c** were unsuccessful. The structures of the compounds were established on the basis of their analytical, ir, nmr and mass spectral data.

The observation that ketones react with thiourea and halogens to give substituted 2-aminothiazoles,[10] coupled with the availability of 1-benzazepin-5-ones (**1a-c**) and 1-benzosuberone (**4**) obtained in this work provided a further opportunity to examine the fusion of thiazole nucleus onto these systems. Reaction of tetrahydro-1-benzazepin-5-one (**1a**) with thiourea and iodine gave the expected 2-aminothiazolo[5,4-d][1]benzazepine (**7a**) as colorless needles *(65%)*. The ^{1}H nmr spectrum of **7a** showed NH_2 as a broad singlet at δ 5.35 in DMSO-d_6, which underwent deuterium exchange readily, and the infrared spectrum contained NH_2 bands at 3380 and 3100 cm^{-1}.



a) R = R' = H
b) R = H, R' = Cl
c) R = R' = OMe

i) NH_2CSNH_2, I_2

Scheme 2

As with **1a**, condensation of **1b**, **1c** and **4** with thiourea proceeded satisfactorily yielding the corresponding thiazole derivatives **7a**, **7c** and **8**, respectively. Their structures were confirmed by ir, nmr, mass spectra and elemental analysis.

EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries on a Metler FP5 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian (80 MHz) and Gemini (200 MHz) spectrometers and chemical shifts are recorded in ppm, internal standard was TMS (δ scale). Mass spectra were taken on VG micromass 7070H and Finnigan Met 1020B mass spectrometers. IR spectra were recorded using a Shimadzu 470 spectrophotometer. UV spectra were measured with a Shimadzu 240 spectrometer in methanol solution. Elemental analyses were performed by the physical department of the Indian Institute of Chemical Technology, Hyderabad, India.

Preparation of 2a-c and 5:

Typical Procedure for the Formylation Reaction. Synthesis of 5-Chloro-2,3-dihydro-1-tosyl-1-benzazepin-2-carbaldehyde (2a).- Phosphoryl chloride (0.75 g, 0.005 mole) was added dropwise with stirring and cooling to dry dimethylformamide (10 mL), at such a rate that the temperature did not exceed 5°. 1,2,3,4-Tetrahydro-1-tosyl-1-benzazepin-5-one[5a] (1.67 g, 0.005 mole) was added drop-

wise to the resulting solution at 0-5° and the mixture was stirred for 0.5 hr at 0° and for 1.5 hr at 80°, then poured into cold aqueous sodium acetate (20% w/v, 25 mL). Extraction with ether, drying over $MgSO_4$ and removal of the solvent under vacuum afforded **2a** (1.7 g, 82%) as a pale yellow oil, which later solidified. The product (**2a**) crystallized from ether as pale yellow crystals, mp. 176-177°. ^1H NMR ($CDCl_3$): δ 2.37 (2H, t, 3-H), 4.31 (2H, t, 2-H), 2.62 (3H, s, ArMe), 7.31-7.81 (8H, aromatic H) and 10.00 (1H, s, CHO). IR (KBr): 1660 cm^{-1} (C=O). MS: *m/z* $(M)^+$ Calcd. (for $C_{18}H_{16}{}^{35}ClNO_3S$) 361.8501; obsd 361.8511.

Anal. Calcd for $C_{18}H_{16}ClNO_3S$: C, 59.83; H, 4.43; N, 3.87. Found: C, 59.80; H, 4.41; N, 3.83

Compound 2b: Yield 88%, colorless crystals, mp. 255-256°. ^1H NMR ($CDCl_3$): δ 2.35 (2H, t, 3-H), 4.15 (2H, t, 2-H), 2.20 (3H, s, ArMe), 7.15-7.65 (7H, m, aromatic H) and 9.75 (1H, s, CHO). IR (KBr): 1665 cm^{-1} (C=O). MS: *m/z* $(M)^+$ Calcd. (for $C_{18}H_{15}{}^{35}Cl_2NO_3S$) 396.2874, obsd 396.2879.

Anal. Calcd for $C_{18}H_{15}Cl_2NO_3S$: C, 54.68; H, 3.79; N, 3.54. Found: C, 54.65; H: 3.72; N, 3.50

Compound 2c: Yield 75%, yellow crystals, mp. 203.3°. ^1H NMR ($CDCl_3$): δ 2.93 (2H, t, 3-H), 4.15 (2H, t, 2-H), 3.95 (3H, s, OMe); 4.00 (3H, s, OMe), 6.95-7.45 (6H, m, aromatic H) and 9.70 (1H, s, CHO). IR (KBr): 1660 cm^{-1} (C=O). MS: *m/z* $(M)^+$ Calcd. (for $C_{20}H_{20}{}^{35}ClNO_5S$) 421.8947, obsd 421.8952.

Anal. Calcd for $C_{20}H_{20}ClNO_5S$: C, 57.00; H, 4.75; N, 3.32. Found: C, 56.92; H, 4.74; N, 3.30

Compound 5: Yield: 76%, pale yellow crystals, mp. 105-106°. ^1H NMR ($CDCl_3$): δ 2.25-2.18 (2H, m, 4-H), 2.62-2.43 (4H, m, 3 & 5-H), 3.93 (3H, s, OMe), 3.95 (3H, s, OMe), 6.68 (1H, s, 6-H), 7.18 (1H, s, 9-H) and 10.37 (1H, s, CHO). IR (KBr): 1665 cm^{-1} (C=O). MS: *m/z* $(M)^+$ Calcd. (for $C_{14}H_{15}{}^{35}ClO_3$) 266.7237, obsd 266.7240.

Anal. Calcd for $C_{14}H_{15}ClO_3$: C, 63.15; H, 5.63. Found: C, 63.10; H, 5.60

Preparation of 3a-c and 6:

Typical Procedure for Cyclization Reaction. Synthesis of 2-carbethoxy-4,5,6-trihydro-6-tosyl-thiopheno[3, 2-d][1]benzazepin (3a).- Ethyl mercaptoacetate (0.6 g, 0.005 mole) was added to a cooled, stirred solution from the reaction sodium (0.25 g, 0.01 g atom) with dry ethanol (30 mL). A solution of 5-chloro2,3-dihydro-1-tosyl[1]benzazepin-2-carbaldehyde (**2a**) (1.9 g, 0.005 mole) in ethanol (25 mL) was then added dropwise during O.5 hr at 0-5°, and the mixture was stirred overnight at room temperature, boiled for 0. 5 hr, cooled, and poured into water. The ester (**3a**) was collected and obtained as pale yellow prisms [from light-petroleum (bp. 60-80°)] mp. 86.5°. ^1H NMR ($CDCl_3$): δ 3.00 (2H, t, 3-H), 4.15 (2H, t, 2-H), 1.35 (3H, t, $-CH_2-CH_3$), *4.35* (2H, q, $-OCH_2-$), 2.25 (3H, s, ArMe), 7.55 (1H, s, 3-H) and 6.90-7.75 (8H, m, aromatic H). IR (KBr): 1700 cm^{-1} (ester C=O). MS: *m/z* $(M)^+$ Calcd. (for $C_{22}H_{21}NO_4S_2$) 427.5322, obsd 427.5324. UV λ_{max}: 201 (log ε = 4.90), 315 nm (4.55).

Anal. Calcd. for $C_{22}H_{21}NO_4S_2$: C, 61.82; H, 4.91: N, 3.27. Found: C, 61.80; H, 4.90; N, 3.24

Compound 3b: Yield 90%, yellow prisms, mp. 108-109°. ^1H NMR ($CDCl_3$): δ 3.15 (2H, t, 4-H), 4.15 (2H, t, 5-H), 1.45 (3H, t, $-CH_2-CH_3$), 4.45 (2H, q, OCH_2-), 2.25 (3H, s, ArMe), 7.50 (1H, s, 3-H) and 6.95-7.75 (7H, m, aromatic H). IR (KBr): 1700 cm^{-1} (ester C=O). MS: *m/z* $(M)^+$ Calcd. (for

$C_{22}H_{20}{}^{35}ClNO_4S_2$) 461.9773, obsd 461.9775. UV λ_{max}: 201 (log ε = 4.94), 320 nm (4.56).

Anal. Calcd. for $C_{22}H_{20}ClNO_4S_2$: C, 57.26, H, 4.33, N, 3.03. Found: C, 57.18; H, 4.30; N, 3.00

Compound 3c: Yield 79%, thick brown oil bp. 132-134°/2mm. ^1H NMR ($CDCl_3$): δ 3.00 (2H, t, 4-H), 4.15 (2H, t, 5-H), 1.39 (3H, t, $-CH_2-CH_3$), 4.45 (2H, q, $-OCH_2-$), 2.21 (3H, s, ArMe), 3.95 (3H, s, OMe), 4.00 (3H, s, OMe), 7.65 (1H, s, 3-H) and 6.95-7.60 (6H, m, aromatic H). IR (neat): 1700 cm^{-1} (ester C=O). MS: *m/z* $(M)^+$ Calcd. (for $C_{24}H_{25}NO_6S_2$) 487.5846, obsd 487.5845. UV λ_{max}: 201 (log ε = 4.91), 310 nm (4.61).

Anal. Calcd. for $C_{24}H_{25}NO_6S_2$: C, 59.13; H, 5.13; N, 2. 85. Found: C, 59.00; H, 5.11; N, 2.85

Compound 6a: Yield 76%, thick brown oil bp. 112-115°/2mm. ^1H NMR ($CDCl_3$): δ 2.25-2.10 (2H, m, 5-H), 2.85-2.62 (4H, m, 4 & 6-H), 3.95 (3H, s, OMe), 4.00 (3H, s, OMe), 1.35 (3H, t, $-CH_2-CH_3$), 4.18 (2H, q, $-OCH_2-$), 6.50 (1H, s, 7-H), 7.25 (1H, s, 10-H) and 7.65 (1H, s, 3-H). IR (neat): 1700 cm^{-1} (ester CO). MS: *m/z* $(M)^+$ Calcd. (for $C_{18}H_{20}O_4S$) 332.4136, obsd 332.4138. UV λ_{max}: 211 (logε = 4.74), 260 nm (4.39), 294 nm (4.17).

Anal. Calcd. for $C_{18}H_{20}O_4S$: C, 65.06; H, 6.02. Found: C, 65.00; H, 6.00.

Preparation of 3e, f and 6b:

General Procedure for Hydrolysis and Detosylation. Synthesis of 2-Carboxy-4,5,6-trihydro-6-tosyl-thiopheno[3,2-d][1]benzazepine (3e).- Sulfuric acid (50%, v/v 5 mL) was added dropwise to a boiling, stirred solution of the ethyl ester (**3a**, 0.5 g) in acetic acid (10 mL), then the mixture was boiled for 6 hrs and cooled. The detosylated acid was collected and purified by preparative thin-layer chromatography (chloroform:methanol 95:5) gave colorless needles (0.1 g, 45%), mp. 260° (from pet. ether). IR (KBr): 1670 (CO) and 3380 cm^{-1} (NH).

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.67; H, 4.49; N, 5.71. Found: C, 63.63; H, 4.31; N, 5.70

Compound 3f: Yield 40%, cream prisms, mp. 272° (dec.). IR (KBr): 1670 (CO) and 3380 cm^{-1} (NH).

Anal. Calcd. for $C_{13}H_{10}ClNO_2S$, C, 55.91; H, 3.58; N, 5.01. Found: C, 55.89; H, 3.55; N, 5.00

Compound 6b: Yield 35%, colorless prisms, mp. 213°. IR (KBr): 1670 cm^{-1} (CO).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 63.15: H, 5.26. Found: 63.10; H, 5.11

Preparation of 7a-c and 8:

Typical Procedure for Condensation Reaction with Thiourea. Synthesis of 2-Amino8,9,10-trihydro-8-tosyl-thiazolo[5,4-d][1]benzazepine (7a).- A mixture of **1a** (1.6 g, 0.005 mole), thiourea (0.76 g, 0.01 mole) and iodine (1.27 g, 0.005 mole) was refluxed for 48 hrs in absolute ethanol (50 mL). At this point thin layer chromatography (TLC) showed only a slight change in the substrate. After prolonged refluxing (4 to 5 days until thin layer chromatography showed the absence of the ketone **1a**), the resulting hydroiodide was dissolved in hot water. The solution was filtered while hot and the clear filtrate was neutralized with a strong solution of ammonia. The precipitate was washed with water and recrystallization from ethanol gave **7a** (65%) as colorless crystals, mp. >290°. ^1H NMR (DMSO-d_6): δ 2.31 (2H, t, 10-H), 4.00 (2H, t, 9-H), 2.25 (3H, s, ArMe), 5.35 (br, s, 2H, D_2O exchangeable) and 7.25-7.70 (8H, m, aromatic H). IR (KBr): 3385 cm^{-1} (NH). MS: *m/z* $(M)^+$: Calcd. (for $C_{18}H_{17}N_3O_2S_2$) 371.4712, obsd 371.4715.

Anal. Calcd for $C_{18}H_{17}N_3O_2S_2$: C, 58.22; H, 4.58; N, 11.32. Found: C, 58.20; H, 4.66; N, 11.21

Compound 7b: Yield 62%, colorless crystals, mp. >290°. ^{1}H NMR (DMSO-d_6): δ 3.00 (2H, t, 10-H), 4.31 (2H, t, 9-H), 2.25 (3H, s, ArMe), 5.35 (br, s, 2H, D_2O exchangeable) and 7.15-7.70 (7H, m, aromatic H). IR (KBr): 3380 cm^{-1} (NH). MS: *m/z* (M)$^+$: Calcd. (for $C_{18}H_{16}{}^{35}ClN_3O_2S_2$) 405.9153, obsd 405.9163.

Anal. Calcd for $C_{18}H_{16}ClN_3O_2S_2$: C, 53.33; H, 3.95; N, 10.37. Found: C, 53.30; H, 3.95; N, 10.33

Compound 7c: Yield 60%, colorless crystals, mp. >290°. ^{1}H NMR (DMSO-d_6): δ 2.95 (2H, t, 10-H), 4.15 (2H, t, 9-H), 3.95 (3H, s, OMe), 4.00 (3H, s, OMe), 5.30 (br, s, 2H, D_2O exchangeable) and 6.91-7.63 (6H, m, aromatic H). IR (KBr): 3380 cm^{-1} (NH). MS: *m/z* (M)$^+$: Calcd. (for $C_{20}H_{21}N_3O_4S_2$) 431.5236, obsd 31. 5239.

Anal. Calcd for $C_{20}H_{21}N_3O_4S_2$: C, 55.68; H, 4..87; N, 9.74. Found: C, 55.66; H, 4.84; N, 9.70

Compound 8: Yield 60%, colorless crystals, mp. >290% ^{1}H NMR (DMSO-d_6): δ 2.30-2.15 (2H, m, 9-H), 2.85-2.60 (4H, m, 8 and 10-H), 6.50 (1H, s, 7-H), 7.25 (1H, s, 4-H), 5.35 (br, s, 2H, D_2O exchangeable), 3.90 (3H, s, OMe) and 3.95 (3H, s, OMe). IR (KBr): 3380 cm^{-1} (NH). MS: *m/z* (M)$^+$: Calcd. (for $C_{14}H_{16}N_2O_2S$) 276.3526, obsd 276.3529.

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.79; N, 10.14. Found: C, 60.84; H, 5.72; N, 10.11

REFERENCES

1. S. R. Ramadas, P. C. Chennaiah, N. S. Chandrakumar, M. V. Krishna, P. S. Srinivasan, V. Sastry and J. Apparao, *Heterocycles*, **19**, 861 (1982).

2. a) T. R. Bosin and E. Campaigne, *Adv. Drug Res.*, **12**, 191 (1977); b) E. Campaigne, D. R. Knapp, E. S. Neiss and T. R. Bosin, *ibid.*, **5**, 1 (1970).

3. B. D. Tilak, *Tetrahedron*, **9**, 76 (1960).

4. J. McLean, V. Peesapati and G. R. Proctor, *J. Chem. Soc. Perkin I*, 98 (**1979**); V. Peesapati and N. Lingaiah, *Org. Prep. Proced. Int.*, **24**, 27 (1992).

5. I. McCall, G. R. Proctor and L. Purdie, *J. Chem. Soc. (C)*, 1126 (**1970**); A. Cromarty, G. R. Proctor and M. Shabbir, *J. Chem. Soc. Perkin I*, 2012 (**1972**); P. D. Carpenter, V. Peesapati and G. R. Proctor, *ibid.*, 103 (**1979**).

6. G. R. Proctor, *J. Chem. Soc.*, 4274 (**1964**).

7. R. M. Dodson and L. C. King, *J. Am. Chem. Soc.*, **67**, 2242 (1945).