Synthesis of Thieno[2,3-*b*]azepin-4-ones as Potential Antineoplastic Agents†

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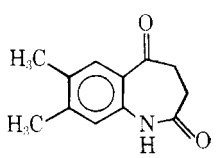
In view of the antitumor activity reported for 7,8-dimethylbenzo[*b*]azepine-2,5-dione, new isosteric thieno[2,3-*b*]-azepin-4-ones have been prepared by a Dieckmann ring closure reaction. Substituted 2-amino-3-carbethoxythiophenes were tosylated, or benzoylated, and the corresponding sodium salt was alkylated with ethyl 4-bromobutyrate. The resulting product was cyclized in the presence of sodium hydride, and the azepinones were detosylated with 40% sulfuric acid–acetic acid solution. Preliminary biological data do not indicate any significant antineoplastic activity.

Many benzazepines have been found to possess medicinal activities of varying types and degrees. These include weak to moderate hypoglycemic activity,[1] antifibrillatory action,[2] and clinically useful CNS activity.[3] Benzodiazepines are well known for their CNS action.[4]

A particular benzazepine, 7,8-dimethylbenzo[*b*]azepine-2,5-dione (**1**), has been found by James and Rees[5] to possess antitumor activity against Crocker's sarcoma comparable to the therapeutically active antitumor agent, triethylenemelamine (TEM). It has been suggested that these benzazepines act as potential antimetabolites of riboflavin and vitamin B_{12}, substances which play some role in certain forms of tumor growth.[6] It was in this regard that we initiated studies toward the synthesis of thiophene analogs of such compounds, which potentially may localize in specific organs or parts of the body and serve as CNS active antitumor agents. As part of our structure–activity relationship studies, this paper reports the synthesis and biological data for some thieno[2,3-*b*]azepin-4-ones (**2**). Results for the thieno[2,3-*b*]azepine-4,7-diones (**3**) will be the subject of a later communication. Results from the monocarbonyl (**2**) and dicarbonyl (**3**) series may aid in establishing some meaningful structure–activity relationships.



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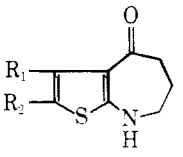

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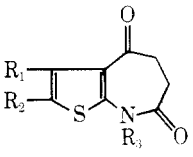

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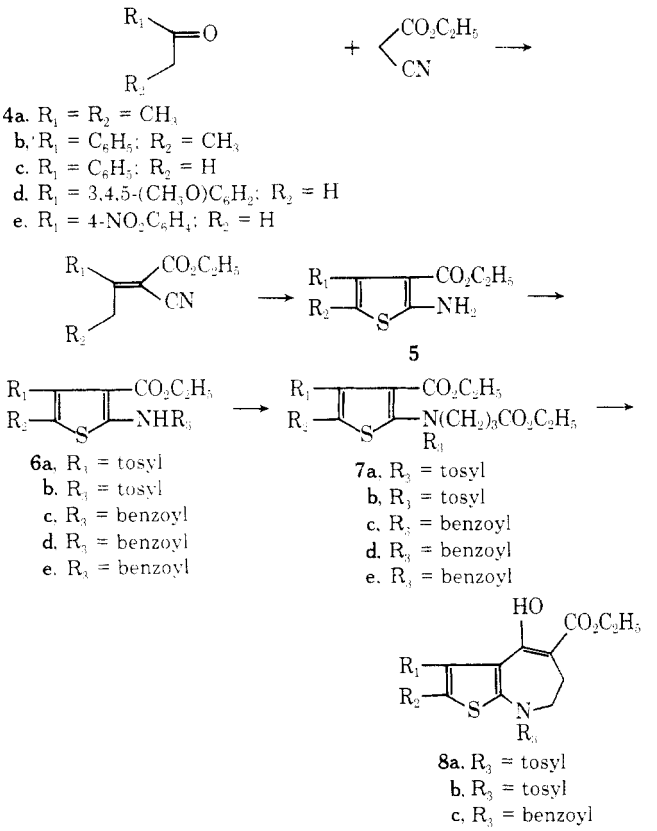
Chemistry. In contrast to the numerous reports which have appeared for the synthesis of benzazepines, few references are prevalent for the preparation of thienoazepines. Syntheses of thieno[3,2-*c*]azepin-4-one[7] and thieno[3,2-*b*]azepin-5-one,[8] in which the nitrogen atom in the seven-membered ring is also an amide nitrogen, were accomplished by ring expansions of the Schmidt and Beckmann types, respectively, on the corresponding fused thienocyclohexanones. Since our target compounds (**2**) did not possess such amide linkages, and the chemistry concerning the preparation of seven-membered heterocyclic systems onto thiophene moieties was virtually nonexistent, a general method has been developed whereby these compounds can be made by a Dieckmann cyclization on an appropriate diester intermediate.

Precedent for a synthesis of this type has been provided by a benzene model. Astill and Boekelheide[9] successfully cyclized methyl *N*-methyl-*N*-(γ-carbomethoxypropyl)anthranilate with potassium *tert*-butoxide to produce an *N*-methyl-4-carbomethoxybenzo[*b*]azepin-5-one. After some modifications, this reaction was applied to specially suited thiophene derivatives (Scheme I).

†This work was presented in part at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, MEDI 54.

Scheme I



4a, $R_1 = R_2 = CH_3$
b, $R_1 = C_6H_5$; $R_2 = CH_3$
c, $R_1 = C_6H_5$; $R_2 = H$
d, $R_1 = 3,4,5\text{-}(CH_3O)C_6H_2$; $R_2 = H$
e, $R_1 = 4\text{-}NO_2C_6H_4$; $R_2 = H$

5

6a, R_3 = tosyl
b, R_3 = tosyl
c, R_3 = benzoyl
d, R_3 = benzoyl
e, R_3 = benzoyl

7a, R_3 = tosyl
b, R_3 = tosyl
c, R_3 = benzoyl
d, R_3 = benzoyl
e, R_3 = benzoyl

8a, R_3 = tosyl
b, R_3 = tosyl
c, R_3 = benzoyl

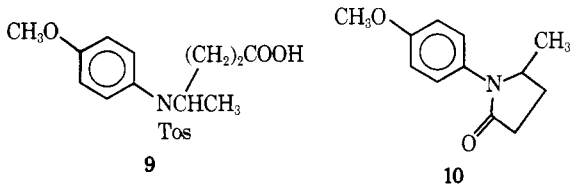
Condensation of suitably substituted ketones **4** with ethyl cyanoacetate, followed by reaction of the adduct with sulfur and base, according to the method of Gewald and coworkers[10] afforded 2-amino-3-carbethoxythiophene compounds **5**. Attempts to alkylate **5** with ethyl 4-bromobutyrate proved useless due to poor nucleophilicity at nitrogen. The nitrogen atom was activated toward alkylation by first converting compounds **5** into either their tosyl or benzoyl derivatives. For those derivatives of **5** in which the 5 position contains a hydrogen atom, we have noted that the benzamide was produced in a cleaner reaction from the amine, and was also easier to purify than the corresponding sulfonamide derivatives. Subsequently, treatment of the amides **6** with sodium hydride in anhydrous dimethylformamide, followed by reaction with excess ethyl 4-bromobutyrate, neutralization, and extraction, gave good yields of crystalline diesters **7**, except for the case with **7d** which was an oil.

Cyclization of diesters **7** to the thieno[2,3-*b*]azepin-4-ones **8** was accomplished only after a considerable amount of experimentation into optimum reaction conditions. Bases that could also act as nucleophiles (*e.g.*, ethoxide, methoxide, sodamide) were not considered well suited, since prolonged heating of the reaction solution, containing a deactivated thiophene ring system, might produce un-

wanted side reactions. Further, the hindered base, potassium *tert*-butoxide, seemed to be quite ineffective, producing ring closures in low yields. Sodium hydride in refluxing benzene was shown to be the reagent of choice, and optimum yields were obtained when high dilution was not used and hydrolyses were performed with strong acid solutions. (Intermediates **7d** and **7e** were not cyclized by this general procedure and further study was not initiated.) The tosylated thienoazepinones **8** have been found to exist predominately in the enol form, whereas the benzoylated derivatives show more ketonic character. Enolic behavior of this type has also been demonstrated by MacPhillamy[11] and coworkers.

Many of the standard procedures were considered for detosylation of **8a** and **8b**, as well as methods for hydrolysis and decarboxylation of the 5-carbethoxy group. All of these were unsuccessful. However, with Carpenter and Lennon's method[12] of heating tosylated azepines in 40% sulfuric acid–acetic acid solution, the detosylation was successful. In addition, the 5-carbethoxy group was hydrolyzed, and decarboxylation occurred simultaneously to produce **2a** and **2b**.

During the course of these experiments, some interesting reactivity differences were observed among intermediates **7a**, **8a**, and **9**, a compound used in an early model reaction. In excess concentrated sulfuric acid or polyphosphoric acid, **9** underwent hydrolysis with detosylation and ring closure to the pyrrolidinone **10**. Similar results were obtained by Collins.[13] Under the same conditions, diester **7a** underwent hydrolysis at the side chain ester only producing **11**, but with no detosylation or accompanying pyrrolidinone formation. **8a** remained inert to either condition.



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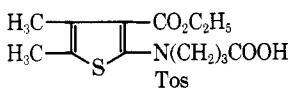

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Biological Results. The compounds prepared in this study were tested in mice against L1210 and P388 leukemia and B16 melanocarcinoma according to the standard protocol of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.‡ For general screening procedure and data interpretation see Geran and coworkers[14a] and Instruction Booklet 14.[14b] The test compounds were administered at 400, 200, 100, 50, and, in a few cases, 25 mg/kg body weight intraperitoneally in sonified saline with polysorbate 80. Doses were administered, beginning on day 1, either daily for five or nine doses, or every fourth day for three doses, and test results were evaluated at day 30. Evaluations were made as mean survival time and are expressed as % *T/C* (test/control), with a value of 125 or greater representing activity in these systems. Compound **2b** had a *T/C* of 128 at 400 mg/kg administered daily for five doses in the P388 system. Compound **7a** had a *T/C* of 130 at 25 mg/kg in the B16 melanocarcinoma system. Compounds **7c** and **8c** did not exhibit any cytotoxicity (cell culture, KB).[14] None of the thienoazepinones (**2**, **8**) or the diester intermediates (**7**) screened exhibited anticancer activity patterns adequate to justify expanded testing or further extension of the present group.

‡The biological data were made available through the courtesy of Drs. H. B. Wood, Jr., and J. S. Driscoll, Drug Development Branch, Drug Research and Development, Division of Cancer Treatment, National Cancer Institute.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and results were within ±0.4% of the calculated values. Satisfactory ir (Perkin-Elmer 467 grating spectrophotometer, KBr) and nmr (Hitachi Perkin-Elmer R20A high-resolution nmr spectrophotometer and Me_4Si as internal reference) spectra were obtained for all new compounds. Tlc was performed on plates coated with silica gel G or Eastman chromatogram sheets, type 6060 (silica gel).

Ketones 4. Methyl ethyl ketone (**4a**), ethyl phenyl ketone (**4b**), methyl phenyl ketone (**4c**), methyl 3,4,5-trimethoxyphenyl ketone (**3d**), and methyl 4-nitrophenyl ketone (**4e**) were purchased from the Aldrich Chemical Co., Inc., and used without further purification.

2-Amino-3-carbethoxythiophenes (5). The thiophene precursors were prepared by the procedure of Gewald[10] in 50–60% yield.

2-(*p*-Toluenesulfonamido)thiophene (6a and 6b). The tosylated thiophenes were prepared by the routine procedure in pyridine solution.[15] Yields were from 60 to 90%.[16]

2-Benzamido-3-carbethoxy-4-phenylthiophene (6c). A reaction mixture containing 30 g (0.126 mol) of **5c**, 18 g (0.126 mol) of benzoyl chloride, and 13.2 g (0.126 mol) of triethylamine, dissolved in 300 ml of THF, was stirred 24 hr at room temperature, and poured onto 1 l. of ice. The mixture was allowed to come to room temperature and the yellow solid filtered. Recrystallization from $CHCl_3$–ligroine gave 42.5 g (99%) of a light yellow solid: mp 158–159°. *Anal.* ($C_{20}H_{17}NO_3S$) C, H, N, S.

2-Benzamido-3-carbethoxy-4-(3,4,5-trimethoxyphenyl)thiophene (6d). A reaction mixture containing 41.6 g (0.124 mol) of **5d**, 17.5 g (0.124 mol) of benzoyl chloride, and 12.6 g (0.124 mol) of triethylamine, in 290 ml of THF, was stirred at room temperature 24 hr. Precipitated triethylammonium chloride was filtered and washed with solvent, and the filtrate was evaporated to dryness. The resulting green solid was triturated with a mixture of ether–petroleum ether, filtered, and recrystallized from $CHCl_3$–ligroine (Norit). The yield of white solid was 54 g (100%): mp 145–148°. *Anal.* ($C_{23}H_{23}NO_6S$) C, H, N, S.

2-Benzamido-3-carbethoxy-4-(4-nitrophenyl)thiophene (6e). This compound was prepared as **6d** in 95% yield. The yellow solid melted at 169–172°. *Anal.* ($C_{20}H_{16}N_2O_5S$) C, H, N, S.

3-Carbethoxy-2-[*N*-(3-carbethoxypropyl)-*p*-toluenesulfonamido]-4,5-dimethylthiophene (7a). Sodium hydride dispersion, 4.88 g (0.116 mol of 57% dispersion), was washed with three 50-ml portions of anhydrous Et_2O and covered with 233 ml of anhydrous DMF. To this slurry, stirred under N_2, was added 33 g (0.0935 mol) of **6a**, dissolved in 78 ml of solvent, over a 45-min period. When hydrogen evolution had ceased, a dark solution was obtained. This solution was heated to 60°, and 45.6 g (0.234 mol) of ethyl 4-bromobutyrate, dissolved in 78 ml of solvent, was then added dropwise over a 1-hr period. After the addition was complete, stirring was continued an additional 3 hr at 60° and overnight at room temperature. Then, the reaction mixture was poured into 1 l. of H_2O, the oil was extracted three times with 200-ml portions of Et_2O, and the extracts were dried ($MgSO_4$). Filtration and evaporation *in vacuo* gave a red oil. This residue was fractionated, and excess bromo ester was collected at 0.1 mm from a heating bath not exceeding 120°. The resultant thick red oil was crystallized from Et_2O–ligroine to give a light yellow solid and recrystallized from the same solvents to give 40 g (92%) of a white solid: mp 70–73°. *Anal.* ($C_{22}H_{29}NO_6S_2$) C, H, N, S.

3-Carbethoxy-2-[*N*-(3-carbethoxypropyl)-*p*-toluenesulfonamido]-5-methyl-4-phenylthiophene (7b). This diester (**7b**) was prepared by the procedure described for **7a** in 91% yield. Recrystallization from Et_2O–petroleum ether (Norit) gave a white solid: mp 70–72°. *Anal.* ($C_{27}H_{31}NO_6S_2$) C, H, N, S.

3-Carbethoxy-2-[*N*-(3-carbethoxypropyl)benzamido]-4-phenylthiophene (7c). Sodium hydride (1.20 g of 57% dispersion, 0.05 mol) was washed with anhydrous Et_2O, covered with 90 ml of dry DMF, placed under N_2, and brought to 60°. Then powdered benzamide **6c** (14.04 g, 0.04 mol) was added portionwise over a 30-min period. Stirring was continued for 30 min and 15.6 g (0.08 mol) of ethyl 4-bromobutyrate, dissolved in 30 ml of solvent, was added over another 30-min period. The resulting mixture was stirred at 80–85° for 3 hr and at room temperature 3 days. After neutraliza-

tion with H_2O, extraction with Et_2O, and drying of the extracts ($MgSO_4$), as in the preparation of **7a** and **7b**, the oily residue was chromatographed on 200 g of silica gel. Elution with 20% Et_2O in petroleum ether separated unreacted excess bromo ester. Elution with 40% Et_2O in petroleum ether produced a light yellow oil, which was crystallized as a white solid from $CHCl_3$–ligroine. Recrystallization from Et_2O–petroleum ether gave 8.6 g (46%) of a white solid: mp 81–83°. *Anal.* ($C_{26}H_{27}NO_5S$) C, H, N, S.

3-Carbethoxy-2-[*N*-(3-carbethoxypropyl)benzamido]-4-(3,4,5-trimethoxyphenyl)thiophene (7d). This diester was prepared by the procedure given for **7c**. The oil obtained from column chromatography was not submitted for elemental analysis.

3-Carbethoxy-2-[*N*-(carbethoxypropyl)benzamido]-4-(4-nitrophenyl)thiophene (7e). This diester was prepared by the procedure given for **7c**. After column chromatography of the crude reaction mixture, the white solid was recrystallized from Et_2O–petroleum ether to give a 46% yield: mp 83–84°. *Anal.* ($C_{26}H_{26}N_2O_7S$) C, H, N, S.

5-Carbethoxy-2,3-dimethyl-*N*-tosylthieno[2,3-*b*]azepin-4-one (8a). Sodium hydride dispersion (0.053 g, 0.0022 mol of 57%) was washed with anhydrous Et_2O and covered with 5 ml of anhydrous benzene. To the slurry, stirring under N_2, was added diester **7a** (1.0 g, 0.0021 mol), dissolved in 12–15 ml of solvent, over a 10-min period. The mixture was refluxed at a bath temperature of 95–100° for 4.5 hr. The mixture was cooled to room temperature, and 5 ml of 10 *N* H_2SO_4 was added carefully over a 15-min period. The mixture was stirred for 10 min, the layers were separated, and the aqueous layer was washed twice with 50-ml portions of benzene. The combined extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* and yielded 0.700 g of a light yellow oil. This oil was chromatographed on 10 g of silica gel. Product eluted with 20% Et_2O in petroleum ether as a colorless oil which crystallized on standing. The solid was recrystallized from Et_2O–ligroine and gave 0.500 g (56%) of a white crystalline solid: mp 105–106°; nmr ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.0 Hz, CH_3 of ester), 2.20 (m, 2 H, C-6 CH_2), 2.10 (s, 3 H, tosyl CH_3), 2.35 (s, 3 H, C-3 CH_3), 2.42 (s, 3 H, C-2 CH_3), 4.08 (t, 2 H, J = 6.0 Hz, C-7, CH_2), 4.15 (q, 2 H, J = 7.0 Hz, CH_2 of ester), 7.50 (q, 4 H, phenyl H), and 11.95 (s, 1 H, enol H). *Anal.* ($C_{20}H_{23}NO_5S_2$) C, H, N, S.

5-Carbethoxy-2-methyl-5-phenyl-*N*-tosylthieno[2,3-*b*]azepin-4-one (8b). This azepinone was prepared by the procedure described for **8a**. After recrystallization from $CHCl_3$–ligroine, a white solid was obtained in 43% yield: mp 157–160°; nmr ($CDCl_3$) δ 11.49 (s, 1 H, enol H). *Anal.* ($C_{25}H_{25}NO_5S_2$) C, H, N, S.

5-Carbethoxy-3-phenyl-*N*-benzoylthieno[2,3-*b*]azepin-4-one (8c). This azepinone was prepared by the procedure described for **8a**. After recrystallization from $CHCl_3$–ligroine, a light yellow solid was obtained in 28% yield: mp 110–112°. The nmr in $CDCl_3$ confirmed structural assignment, but no enol H was discernible in this case. *Anal.* ($C_{23}H_{21}NO_4S$) C, H, N, S.

2-Methyl-3-phenylthieno[2,3-*b*]azepin-4-one (2b). To 9 g (0.0185 mol) of **8b** was added 150 ml of 40% H_2SO_4 in HOAc.[12] This mixture was stirred and heated at 50° for 14 hr. Complete solution had not occurred at the end of this time, and an additional 150 ml of the acid solution was added. After heating and stirring for an additional 9 hr, this mixture was cooled and poured onto ice. The pH of this solution was adjusted to approximately 8 with solid NaOH, extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated *in vacuo*. Tlc indicated one major product with a small amount of starting material. This product was dissolved in the minimum amount of CH_2Cl_2, preadsorbed on 7 g of 60–200 mesh silica gel, and chromatographed through an additional 50 g of silica gel using petroleum ether and increasing amounts of Et_2O as eluents. Fractions from 15 to 100% Et_2O were combined yielding 3.1 g (65%) of yellow solid. The analytical sample was prepared by recrystallization from Et_2O–petroleum ether: mp 158.5–159°; nmr ($CDCl_3$) δ 2.03 (s, 3 H, C-2 CH_3), 2.14 (m, 2 H, C-6 CH_2), 2.71 (t, 2 H, C-5 CH_2), 3.28 (m, 2 H, C-7 CH_2), 5.50 (broad, 1 H, NH), 7.3 (m, 5 H, phenyl H). *Anal.* ($C_{15}H_{15}NOS$) C, H, N, S.

2,3-Dimethylthieno[2,3-*b*]azepin-4-one (2a). This azepinone was prepared by the procedure described for **2b**. After recrystallization from $CHCl_3$–petroleum ether, the yellowish tan solid melted at 118–120°. *Anal.* ($C_{10}H_{13}NOS$) C, H, N, S.

***N*-(4-Methoxyphenyl)-5-methylpyrrolidin-2-one (10).** 4-[*N*-(*p*-Methoxyphenyl)-*p*-toluenesulfonamido]pentanoic acid (**9**, 1.0 g, 0.0026 mol), which was prepared from levulinic acid and *p*-anisidine, was dissolved in 7.5 g of polyphosphoric acid and heated on a steam bath for 3.5 hr. The syrup was cooled and diluted with ice water. The aqueous acid solution was neutralized with concentrated NH_4OH and extracted with 40 ml of Et_2O. The extract was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give 0.5 g of a nearly colorless oil. This material crystallized from $CHCl_3$–ligroine to yield 0.4 g (75%) of a white solid: mp 56–58°. *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

3-Carbethoxy-2-[*N*-(carboxypropyl)-*p*-toluenesulfonamido]-4,5-dimethylthiophene (11). 6a (5.0 g, 0.011 mol) was heated with 35 ml of 75% H_2SO_4 for 3 hr. The hot solution was poured onto 500 ml of ice–H_2O and extracted with $CHCl_3$. The extract was dried ($MgSO_4$), filtered, and evaporated to dryness. A blue-green solid resulted (3.5 g, 78%) which was recrystallized from Me_2CO–H_2O as white needles: mp 141–143° dec. (Compound turns blue-gray on standing.) *Anal.* ($C_{20}H_{25}NO_6S_2$) C, H, N, S.

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