Thiophene Systems. 11. The Synthesis of Novel Thieno[4,3,2-*de*] Tricyclic Ring Systems

Ronald K. Russell*, Richard A. Rampulla,
Caroline E. van Nievelt and Dieter H. Klaubert

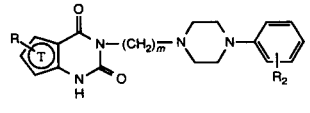
R. W. Johnson Pharmaceutical Research Institute, Division of Medicinal Chemistry,
Raritan, New Jersey 08869

Received January 16, 1990

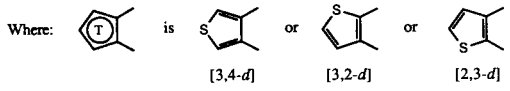
The synthesis of thieno[4,3,2-*de*] tricyclic compounds is described. The *N*-1 alkylation of **I** produced the alkanoic ester precursors. After hydrolysis, the corresponding carboxylic acids were cyclized to the title compounds **II**. This cyclization step was accomplished with 1:10 phosphorus pentoxide-methanesulfonic acid. The ketones **II** were further modified to introduce additional functionality onto this novel tricyclic ring system.

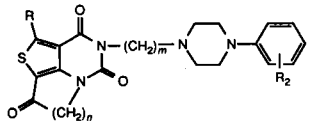
J. Heterocyclic Chem., **27**, 1761 (1990).

We recently reported the synthesis and antihypertensive activity of some thieno[3,4-*d*]-, thieno[3,2-*d*]-, and thieno[2,3-*d*]pyrimidine-2,4-diones **I** (m = 2 or 3) [1]. In this paper, we report our further synthetic efforts in preparing the thieno[3,4-*d*]pyrimidine-2,4-dione moiety and the conversion of this ring system to the novel thieno[4,3,2-*de*] tricyclic ring system **II**.



I

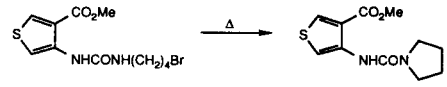




II

Chemistry.

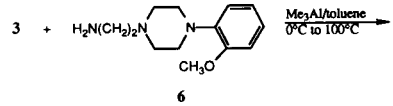
The starting materials for the preparation of **II** (m = 2 or 3) were the thieno[3,4-*d*]pyrimidine-2,4-diones whose syntheses have already been described [1]. The preparation of the tricyclic ring system **II** (m = 4) was envisioned to use bromobutyl urea **1** which was prepared in toluene at room temperature. In the course of preparing large amounts of **1**, it was found that when the reaction of methyl 4-aminothiophene-3-carboxylate and 4-bromobutyl isocyanate was carried out at 90° or higher [1] the urea **2** was isolated. The cyclization of **1** to **2** also occurred when **1** was dried in a vacuum oven at 55°. The structure of **2** was determined by ^{1}H nmr wherein the urea N*H*CH$_2$ proton absorption was missing and a symmetrical pattern for the methylene protons was observed.



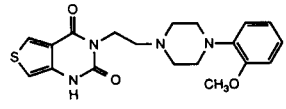
1 2

Since the intramolecular cyclization of **1** to **2** occurred at temperatures required to convert ureas such as **1** to its corresponding thieno[3,4-*d*]pyrimidine-2,4-dione [1], we decided to investigate an alternate synthesis. This synthesis did not use **1**, but relied on the reaction of urethane **3** with known amine **4** [2] (Scheme I). A toluene solution of trimethylaluminum and **4** [3] was treated with the urethane **3**. After briefly warming to reflux, the expected amide urethane was not isolated, but the desired ring-closed product **5** was obtained in a modest 20% yield. This trimethylaluminum procedure afforded analytically pure **7** [1] in 36% yield when **3** was reacted with the 4-(2-methoxyphenyl)-1-piperazineethanamine (**6**) [4].

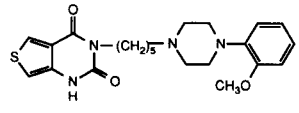
Later, we reexamined the synthesis of **5** and found that **1** could be reacted with 1-(2-methoxyphenyl)piperazine hydrochloride, sodium bicarbonate, and sodium iodide in 2-propanol at reflux to produce **5** in 84% yield *without* significant amounts of **2** detected. These same isopropanol reaction conditions allowed the preparation of the pentamethylene spaced thieno[3,4-*d*]pyrimidine-2,4-dione **8** in 91% yield.



6



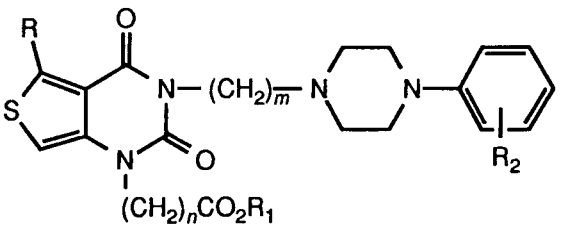
7



8

Table I

Thieno[3,4-*d*]pyrimidine-2,4-dione Carboxylic Ester/Acid Intermediates



Compd No.	R	*n*	R_1	*m*	R_2	Method [a]	Yield (%)[b]	Mp (°C)	Formula	Analysis (%) Calcd.(Found) C	H	N
10	H	2	CH_3	2	2-OCH_3	A	75	140-140.5[c]	$C_{23}H_{28}N_4O_5S$	58.45(58.21)	5.97(6.08)	11.86(11.89)
11	H	2	H	2	2-OCH_3	C	28	186-187.5[d]	$C_{22}H_{26}N_4O_5S$	57.62(57.54)	5.72(5.71)	12.22(12.27)
12	H	2	CH_3	2	2-CH_3	A	70	149-150[e]	$C_{23}H_{28}N_4O_4S$	60.50(60.28)	6.18(6.25)	12.27(12.24)
13	H	2	Na	2	2-CH_3	C	62	163-166 dec[f]	$C_{22}H_{25}NaN_4O_4S{\cdot}H_2O$	54.76(54.66)	5.84(5.90)	11.61(11.43)
14	H	2	CH_3	2	2-Cl	A	71	142.5-144[e]	$C_{22}H_{25}ClN_4O_4S$	55.39(54.97)	5.28(5.34)	11.75(11.66)
15	H	2	Na	2	2-Cl	C	94	213-223[d]	$C_{21}H_{22}ClNaN_4O_4S{\cdot}H_2O$	50.15(50.21)	4.82(4.68)	11.14(11.10)
16	H	2	CH_3	2	H	A	85	133-134.5[e]	$C_{22}H_{26}N_4O_4S$	59.71(59.51)	5.92(6.01)	12.66(12.76)
17	H	2	Na	2	H	C	93	199-201 dec[d]	$C_{21}H_{23}NaN_4O_4S$	55.99(55.65)	5.15(5.44)	12.44(12.30)
18	H	2	CH_3	2	3-OCH_3	A	68	136-137[e]	$C_{23}H_{28}N_4O_5S$	58.45(58.15)	5.97(6.03)	11.86(11.75)
19	H	2	H	2	3-OCH_3	C	67		not purified			
20	H	2	CH_3	2	3-Cl	A	37	150[e]	$C_{22}H_{25}ClN_4O_4S$	55.39(55.35)	5.28(5.28)	11.75(11.64)
21	H	2	H	2	3-Cl	C	61		not purified			
22	H	2	CH_3	2	4-OCH_3	A	94[g]	151-152[e]	$C_{23}H_{28}N_4O_5S$	58.45(58.17)	5.97(5.83)	11.86(11.55)
23	H	2	Na	2	4-OCH_3	C	90	220-223 dec[d]	$C_{22}H_{25}NaN_4O_5S{\cdot}1/2H_2O$	53.97(54.01)	5.76(5.61)	11.44(11.32)
24	H	2	CH_3	2	4-F	A	66	165-165.5[h]	$C_{22}H_{25}FN_4O_4S$	57.38(57.36)	5.47(5.47)	12.17(12.09)
25	H	2	H	2	4-F	C	88[g]	202-203[d]	$C_{21}H_{23}FN_4O_4S{\cdot}1/4H_2O$	55.92(55.67)	5.25(5.20)	12.42(12.23)

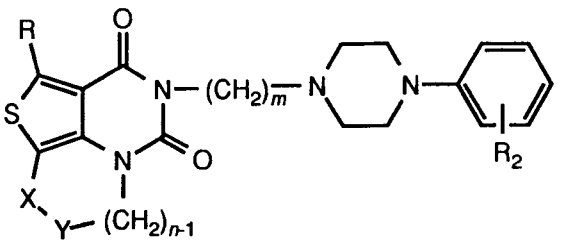
Table I (continued)

Compd No.	R	*n*	R_1	*m*	R_2	Method [a]	Yield (%)[b]	Mp (°C)	Formula	Analysis (%) Calcd.(Found) C	H	N
26	H	2	CH_3	3	2-OCH_3	A	87[g]	184-192[i]	$C_{24}H_{30}N_4O_5S \cdot HCl \cdot H_2O$	53.27(53.37)	6.15(5.94)	10.36(10.31)
27	H	2	H	3	2-OCH_3	C	87[j]	201-203.5 dec[k]	$C_{23}H_{28}N_4O_5S$	58.45(58.16)	5.97(5.91)	11.86(11.74)
28	H	2	CH_3	4	2-OCH_3	A	59		not purified			
29	H	2	H	4	2-OCH_3	C	96		not purified			
30	H	2	CH_3	5	2-OCH_3	A	24	97-102[i]	$C_{26}H_{34}N_4O_5S \cdot HCl \cdot 3/4H_2O \cdot 1/3$ IPA	55.04(55.34)	6.78(6.68)	9.51(9.85)
31	H	2	H	5	2-OCH_3	C	71		not purified			
32	H	3	C_2H_5	2	2-OCH_3	B	65	108-109.5[c]	$C_{25}H_{32}N_4O_5S$	59.98(60.08)	6.44(6.47)	11.19(11.27)
33	H	3	H	2	2-OCH_3	C	70		not purified			
34	H	4	C_2H_5	2	2-OCH_3	B	88[g]	108-110[e]	$C_{26}H_{34}N_4O_5S$	60.68(60.79)	6.66(6.65)	10.89(10.74)
35	H	4	H	2	2-OCH_3	C	62	211-213[d]	$C_{24}H_{30}N_4O_5S$	59.24(59.13)	6.21(6.19)	11.52(11.49)
36	CH_3	2	CH_3	2	2-OCH_3	A	90	127-128[e]	$C_{24}H_{30}N_4O_5S$	59.24(59.14)	6.21(6.25)	11.52(11.54)
37	CH_3	2	Na	2	2-OCH_3	C	96	218-224 dec[d]	$C_{23}H_{27}NaN_4O_5S$	55.86(55.52)	5.50(5.72)	11.32(11.27

[a] See the Experimental Section. [b] Yields are not optimized and represent recrystallized material except where noted. [c] Recrystallized from ether. [d] Recrystallized from EtOH. [e] Recrystallized from CH_2Cl_2/hexane. [f] Triturated with ether. [g] Yield was determined after column chromatography. [h]Recrystallized from CH_2Cl_2/ether. [i] Recrystallized from 2-propanol/HCl. [j] Yield of crude material. [k] Recrystallized from CH_2Cl_2/ether/MeOH.

Table II

Thieno[4,3,2-*de*] Tricyclics



Compd No.	R	*n*	X	Y	*m*	R_2	Method [a]	Yield (%)[b]	Mp (°C)	Formula	Analysis (%) Calcd.(Found) C	H	N
38	H	2	CO	CH_2	2	2-OCH_3	D	61	158-160[c]	$C_{22}H_{24}N_4O_4S$	59.98(59.74)	5.49(5.44)	12.72(12.69)
39	H	2	CO	CH_2	2	2-CH_3	D	60	156.5-157.5[d]	$C_{22}H_{24}N_4O_3S$	62.24(62.52)	5.70(5.72)	13.20(13.18)
40	H	2	CO	CH_2	2	2-Cl	D	55	183.5-184.5[d]	$C_{21}H_{21}ClN_4O_3S$	56.68(56.72)	4.76(4.76)	12.59(12.41)
41	H	2	CO	CH_2	2	H	D	57	178.5-180[d]	$C_{21}H_{22}N_4O_3S$	61.44(61.40)	5.40(5.39)	13.65(13.53)
42	H	2	CO	CH_2	2	3-OCH_3	D	73	190-191[e]	$C_{22}H_{24}N_4O_4S$	59.98(59.74)	5.49(5.51)	12.72(12.60)
43	H	2	CO	CH_2	2	3-Cl	D	64	187-191[d]	$C_{21}H_{21}ClN_4O_3S$	56.68(56.36)	4.76(4.85)	12.59(12.45)
44	H	2	CO	CH_2	2	4-OCH_3	D	59	195-196[e]	$C_{22}H_{24}N_4O_4S$	59.98(59.89)	5.49(5.42)	12.72(12.74)
45	H	2	CO	CH_2	2	4-F	D	44	196-197[d]	$C_{21}H_{21}FN_4O_3S$	58.86(59.02)	4.94(4.94)	13.08(13.35)
46	H	2	CO	CH_2	3	2-OCH_3	D	63[f]	163-164[g]	$C_{23}H_{26}N_4O_4S$	60.77(60.46)	5.77(5.78)	12.33(12.28)
47	H	2	CO	CH_2	4	2-OCH_3	D	18	136.5-138[d]	$C_{24}H_{28}N_4O_4S$	61.52(61.45)	6.02(5.99)	11.96(12.12)
48	H	2	CO	CH_2	5	2-OCH_3	D	16	168-170[h]	$C_{25}H_{30}N_4O_4S\cdot 1/4H_2O$	61.64(61.76)	6.31(6.34)	11.50(11.49)
49	H	3	CO	CH_2	2	2-OCH_3	D	70	171-173[d]	$C_{23}H_{26}N_4O_4S$	60.77(60.39)	5.77(5.77)	12.33(12.35)
50	H	4	CO	CH_2	2	2-OCH_3	D	73	162.5-164[c]	$C_{24}H_{28}N_4O_4S$	61.52(61.14)	6.02(6.10)	11.96(11.55)
51	CH_3	2	CO	CH_2	2	2-OCH_3	D	83	173-174[d]	$C_{23}H_{26}N_4O_4S$	60.77(60.47)	5.77(5.86)	12.33(12.33)
52	H	2	HOCH	CH_2	2	2-OCH_3	E	58	210-211.5[i]	$C_{22}H_{26}N_4O_4S$	59.71(59.69)	5.92(5.86)	12.66(12.59)
53	H	3	HOCH	CH_2	2	2-OCH_3	E	92[j]	148-149.5[d]	$C_{23}H_{28}N_4O_4S$	60.50(60.36)	6.18(6.15)	12.27(12.24)

Table II (continued)

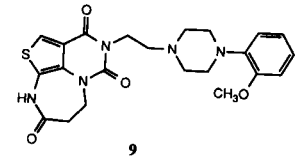
Compd No.	R	*n*	X	Y	*m*	R_2	Method [a]	Yield (%)[b]	Mp (°C)	Formula	Analysis (%) Calcd.(Found) C	H	N
54	CH_3	2	HOCH	CH_2	2	2-OCH_3	E	96	162-164[k]	$C_{23}H_{28}N_4O_4S$	60.50(60.24)	6.18(6.19)	12.27(12.38)
55	H	2	CH = CH		2	2-OCH_3	G	50	180-181[g]	$C_{22}H_{24}N_4O_3S$	62.24(61.86)	5.70(5.73)	13.20(13.04)
56	H	2	CH_3CO_2CH	CH_2	2	2-OCH_3	F	52	120-122[c]	$C_{24}H_{28}N_4O_5S$	59.48(59.87)	5.82(5.83)	11.56(11.89)
57	H	2	$C_5H_{11}CO_2CH$	CH_2	2	2-OCH_3	F	31	99-100[h]	$C_{28}H_{36}N_4O_5S$	62.20(62.32)	6.71(6.79)	10.36(10.39)
58	H	2	$(CH_3)_2CHCO_2CH$	CH_2	2	2-OCH_3	F	68	166-167[g]	$C_{26}H_{32}N_4O_5S$	60.92(60.71)	6.29(6.25)	10.93(10.70)
59	H	2	$(CH_3)_3CCO_2CH$	CH_2	2	2-OCH_3	F	73	185.5-187[g]	$C_{27}H_{34}N_4O_5S$	61.57(61.86)	6.51(6.59)	10.64(10.61)
60	H	2	$C_6H_5CO_2CH$	CH_2	2	2-OCH_3	F	46	174-176[d]	$C_{29}H_{30}N_4O_5S$	63.72(63.85)	5.53(5.47)	10.25(10.03)
61	H	2	4-MeO-$PhCO_2CH$	CH_2	2	2-OCH_3	F	59	120-122[k]	$C_{30}H_{32}N_4O_6S$	62.48(62.15)	5.59(5.63)	9.72(9.70)
62	H	2	4-Cl-$PhCO_2CH$	CH_2	2	2-OCH_3	F	78	128-130[k]	$C_{29}H_{29}ClN_4O_5S$	59.94(59.84)	5.03(5.05)	9.64(9.62)
63	H	2	HON=C	CH_2	2	2-OCH_3	H	86		not purified			
64	H	2	CH_3ON=C	CH_2	2	2-OCH_3	H	74	165-168[l]	$C_{23}H_{27}N_5O_4S$	58.83(58.94)	5.80(5.90)	14.92(14.75)
65	H	3	CH_3ON=C	CH_2	2	2-OCH_3	H	85	185.5-187[d]	$C_{24}H_{29}N_5O_4S$	59.61(59.63)	6.04(5.98)	14.48(14.47)
66	H	2	CH_3ON=C	CH_2	3	2-OCH_3	H	19[f]	164-166.5[g]	$C_{24}H_{29}N_5O_4S$	59.61(59.41)	6.04(6.09)	14.48(14.46)
67	CH_3	2	CH_3ON=C	CH_2	2	2-OCH_3	H	57	152-153[d]	$C_{24}H_{29}N_5O_4S$	59.61(59.44)	6.04(6.01)	14.48(14.32)
68	H	3	CO	NH	2	2-OCH_3	I	18	197-199[g]	$C_{22}H_{25}N_5O_4S$	58.00(57.94)	5.53(5.55)	15.38(15.19)
69	H	2	H_2NCH	CH_2	2	2-OCH_3	J	98[j]	152-155[g]	$C_{22}H_{27}N_5O_3S$	59.84(59.42)	6.16(6.12)	15.86(16.08)
70	H	2	$CH_3CONHCH$	CH_2	2	2-OCH_3	K	67	193.5-196.5[g]	$C_{24}H_{29}N_5O_4S$	59.61(59.43)	6.04(6.16)	14.48(14.41)
71	H	2	$C_6H_5CONHCH$	CH_2	2	2-OCH_3	K	66	202-203[g]	$C_{29}H_{31}N_5O_4S$	63.83(63.85)	5.73(5.86)	12.84(12.82)

[a] See the Experimental Section. [b] Yields are not optimized and represent recrystallized material except where noted. [c] Recrystallized from ether. [d] Recrystallized from CH_2Cl_2/hexane. [e] Recrystallized from $CHCl_3$/hexane. [f] Yield determined after chromatography. [g] Recrystallized from CH_2Cl_2/ether. [h] Recrystallized from ether/hexane. [i] Recrystallized from $CHCl_3$/EtOH/ether. [j] Yield of crude material. [k] Triturated with hexane. [l] Recrystallized from CH_2Cl_2/ether/hexane.

Scheme II shows the transformation of thienopyrimidine-2,4-dione **I** to the tricyclic ring compounds **II**. The reaction of **I** with an excess of methyl acrylate in chloroform containing 0.5 to 1 equivalent of benzyltrimethylammonium hydroxide (40% in methanol, Triton B) produced **IIIa** (n = 2) in 37 to 94 precent yield (Method A). When a longer alkyl chain was required, the anion of **I** (sodium hydride/DMF) was treated with a haloalkyl ester, *e.g.* ethyl 4-bromobutyrate, to produce **IIIa** (n = 3, Method B) [5]. The esters **IIIa** were then hydrolyzed to their corresponding carboxylic acids **IIIb** using sodium hydroxide in aqueous methanol (Method C). A summary of the carboxylic esters and acids prepared by Methods A, B and C is shown in Table I. In a few cases (**13, 15, 17, 23** and **37**) the carboxylic acid sodium salt was isolated. The phenyl ring R_2-substituent was either hydrogen (**16, 17**), methoxy (**10, 11, 18, 19, 22, 23**), methyl (**12, 13**), chlorine (**14, 15, 20, 21**) or fluorine (**24, 25**) and the thiophene substituent was either hydrogen or methyl (**36, 37**). The $(CH_2)_m$-spacer was also varied from m = 3-5 (**26-31**) and Method B was used to prepare the ethyl pentanoate derivative **34** (n = 4).

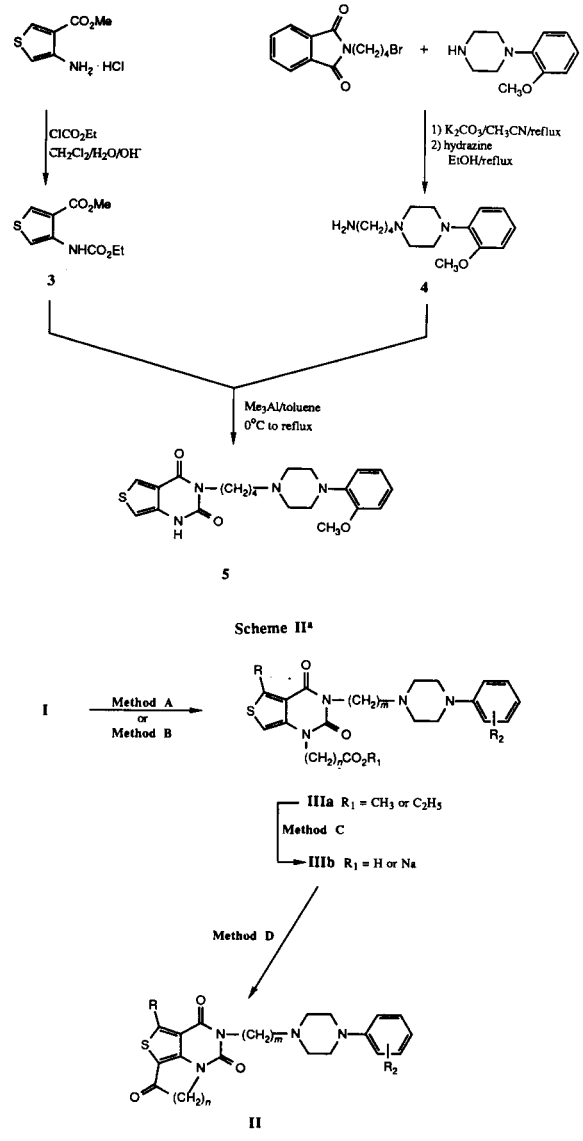
The intramolecular Friedel-Crafts cyclization of **IIIb** to **II** was accomplished with phosphorus pentoxide/methanesulfonic acid (1:10) [6] (Scheme II). Table II shows the tricyclic ketones prepared by this procedure (Method D). In general, the intramolecular Friedel-Crafts cyclization onto the activated α-position of the [3,4-*d*]thiophene ring proceeded smoothly at ambient temperature in 2-16 hours [7,8]. The crude products were isolated and purified using silica gel chromatography. The data in Table II shows that the yield (44-83%) of ketone **II** (n = 2) was not greatly affected by the R-substituent on the thiophene ring (R = H or CH_3, compound **38** or **51**) or by the R_2-substituent on the phenyl ring (R_2 = OCH_3, CH_3, Cl, H, or F, compounds **38-45**). Surprisingly, when the methylene chain length (n) was varied from 2 to 3 or 4, the yield of **II** was *not* affected, even though seven- and eight-membered rings were formed (**49** and **50**, respectively).

Further elaboration of this novel tricyclic ring system is shown in Scheme III. The ketone **38** was readily reduced with sodium borohydride in ethanol to give alcohol **52** (Method E). This material could be either acetylated with alkyl/aryl acid chlorides in the presence of 4-dimethylaminopyridine to produce compounds **56-62** (Table II) or dehydrated with methanesulfonyl chloride-triethylamine to produce **55**. The reaction of ketone **38** with either hydroxylamine hydrochloride or *O*-methylhydroxylamine hydrochloride in ethanol (Method H) produced the oximes **IV**. The hydroxylamine hydrochloride reaction produced the sand-like material **63** (**IV**, R'' = H) which was stirred in 1:10 phosphorus pentoxide/methanesulfonic acid [6] to afford lactam **68** in 18% yield. The isolation of this lactam and not its isomer **9** was evident by the ^{1}H nmr (deuteriochloroform) wherein the N*H* proton was a broad triplet (J = 4.5 Hz) at δ 7.77. Similar alkyl *vs* aryl migration results in the Beckmann rearrangement has also been observed by others [6,9] and may suggest that the oxime **63** exists with the OH-group *anti* to the alkyl chain [10]. Oximes **64-67** (Table II) were also prepared. Compound **IV** (R'' = CH_3) was then reacted with diborane-THF in refluxing THF to produce the amine **69** which was converted to the amides **70** and **71**.



9

Scheme I



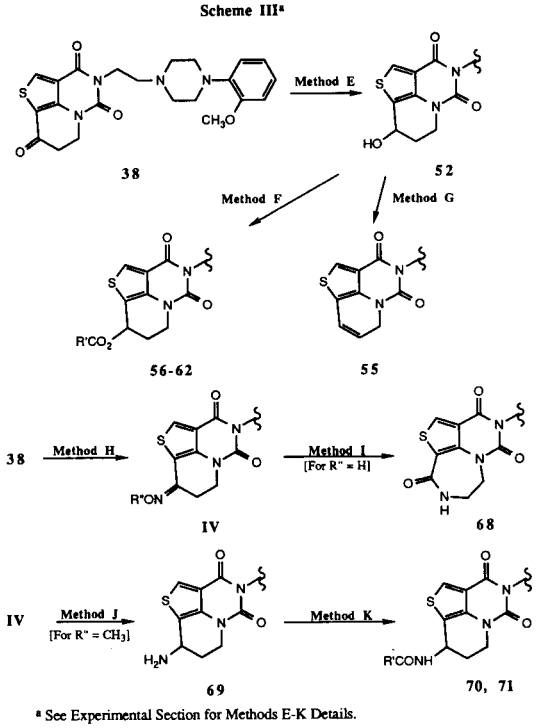
Scheme II[a]

[a] See Experimental Section for Methods A-D Details.

Many of the compounds in Table II (*e.g.* **38, 39, 45, 49, 52, 54, 55, 56, 58, 59, 68** and **69**) were evaluated for blood pressure lowering activity in the conscious spontaneously hypertensive rat (SHR) and were found to reduce blood pressure similar to that reported for **I** [1].

In summary, we have described a new synthesis of the thieno[3,4-*d*]pyrimidine-2,4-dione ring system and the conversion of these pyrimidinediones to the novel thieno[4,3,-2-*de*] tricyclic ring system **II**. The key step in this transformation was the intramolecular Friedel-Crafts cyclization using 1:10 phosphorus pentoxide-methanesulfonic acid. The ketone moiety of the new ring system was used to prepared the alcohol **52**, olefin **55**, amine **69** and the Beckmann ring-expanded product **68**.

Scheme III[a]



[a] See Experimental Section for Methods E-K Details.

EXPERIMENTAL

Materials.

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 or 1430 instrument. Proton nmr spectra were recorded on an EM 390 instrument with the chemical shifts reported in δ downfield from tetramethylsilane as internal standard. The signals are described as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). All spectra were in agreement with the structures cited. The elemental analyses were run on a Perkin-Elmer 240C or 2400 instruments. Standard flash column techniques [12] were employed to purify crude reaction mixtures using 230-400 mesh E. Merck silica gel under positive nitrogen pressure.

The preparation of the thieno[3,4-*d*]pyrimidine-2,4-diones used in this study has been described earlier [1]. The new compounds (**1,3,5** and **8**) and the synthetic Methods A-K (Schemes II and III) are described below.

N-(4-Bromobutyl)-*N'*-(4-methoxycarbonylthien-3-yl)urea (**1**).

Methyl 4-aminothiophene-3-carboxylate [13] (4.2 g, 26.8 mmoles) in 50 ml of toluene at room temperature was treated with 4-bromobutylisocyanate (5.3 g, 29.4 mmoles). After the reaction had stirred at room temperature for 16 hours, the mixture was cooled in an ice bath and the solid was isolated to yield 5.43 g (16.2 mmoles, 60%) of **1**. A portion of this material was filtered through silica gel and then recrystallized from dichloromethane/-ether/hexane to afford **1** as a tan solid, mp 108-109°; ^{1}H nmr (deuteriochloroform): δ 1.53-2.17 (m, 4H, methylene), 3.17-3.4 (m, 2H, NHC*H*$_2$), 3.4 (t, J = 6 Hz, 2H, CH_2Br), 3.87 (s, 3H, OCH_3), 4.6-4.93 (m, 1H, N*H*CH_2), 7.7 (d, J = 3 Hz, 1H, thiophene), 8.0 (d, J = 3 Hz, 1H, thiophene), 9.13 (s, 1H, NHCO); ir (potassium bromide): 3330, 1710, 1650, 1565, 1540, 1445, 1260, 1230, 1075, 780 cm^{-1}.

Anal. Calcd. for $C_{11}H_{15}BrN_2O_3S$: C, 39.41; H, 4.51; N, 8.36; S, 9.56. Found: C, 39.73; H, 4.52; N, 8.40; S, 9.64.

Ethyl (4-Methoxycarbonyl)thiophene-3-carbamate (**3**).

Methyl 4-aminothiophene-3-carboxylate hydrochloride [13] (10 g, 51.8 mmoles) in 100 ml of dichloromethane containing 5.6 ml (57 mmoles) of ethyl chloroformate at 0° was slowly treated with 57 ml of 2 *N* sodium hydroxide. After the addition had been completed, the mixture was allowed to warm to room temperature and rapidly stirred for two hours. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over magnesium sulfate. Solvent removal produced an oily material. This material was purified by filtration through silica gel using 1-5% ethyl acetate in hexane to afford 10 g (84%) of **3** as a light yellow oil which slowly crystallized. A portion of this material was recrystallized from hexane to produce **3** as a white solid, mp 51.5-53°; ^{1}H nmr (deuteriochloroform): δ 1.3 (t, J = 6 Hz, 3H, OCH_2CH_3), 3.87 (s, 3H, OCH_3), 4.17 (q, J = 6 Hz, 2H, OCH_2CH_3), 7.6 (d, J = 3 Hz, 1H, thiophene), 8.0 (d, J = 3 Hz, 1H, thiophene), 9.23 (br s, 1H, NH); ir (potassium bromide): 3370, 1735, 1705, 1550, 1270, 1055, 785 cm^{-1}.

Anal. Calcd. for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84; N, 6.11; S, 13.99. Found: C, 47.20; H, 4.73; N, 5.96; S, 13.98.

3-[4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]thieno[3,4-*d*]pyrimidine-2,4-dione (**5**).

Procedure A.

To ice-cold toluene (120 ml) under nitrogen was added 12 ml (24 mmoles) of a 2 *M* trimethylaluminum/toluene solution followed by 4.35 g (24 mmoles) of 4-[(2-methoxyphenyl)piperazin-1-yl]-butanamine (**4**) [2]. After stirring for 10 minutes, a toluene solution of **3** (4.61 g, 20 mmoles) was added and the solution was warmed to reflux for 8 hours. The solution was then quenched with glacial acetic acid and enough concentrated ammonium hydroxide was added to produce two phases. After the aqueous phase had been extracted with dichloromethane the combined organic layers were washed with brine and dried (magnesium sulfate). Solvent removal produced a residue which was purified by flash silica gel chromatography using 2-4% methanol in dichloromethane and finally 0.5% ammonium hydroxide/4.5% methanol in dichloromethane. The thienopyrimidine-2,4-dione **5**

was obtained as a creamed-colored solid in 20% yield (1.63 g) after recrystallization from chloroform/hexane, mp 162-163.5°; ^{1}H nmr (deuteriochloroform/DMSO-d_6): δ 1.6 (m, 4H, methylene), 2.3-2.65 (br m, 6H, methylene), 3.03 (m, 4H, methylene), 3.83 (s, 3H, OCH_3), 3.93 (br t, J = 6 Hz, 2H, methylene), 6.67 (d, J = 3 Hz, 1H, thiophene), 6.9 (s, 4H, phenyl), 8.13 (d, J = 3 Hz, 1H, thiophene), 11.0 (s, 1H, NH); ir (potassium bromide): 2940, 1705, 1665, 1495, 1240, 755, 745 cm^{-1}.

Anal. Calcd. for $C_{21}H_{26}N_4O_3S$: C, 60.84; H, 6.32; N, 13.52. Found: C, 60.99; H, 6.29; N, 13.40.

Procedure B.

A mixture of **1** (1.66 g, 5 mmoles), 1-(2-methoxyphenyl)piperazine hydrochloride (3.43 g, 15 mmoles), sodium bicarbonate (1.85 g, 22 mmoles) and sodium iodide (0.466 g, 3 mmoles) in 10 ml of 2-propanol was heated at reflux for 16 hours. Water was added to the cooled brown mixture and the 2-propanol was removed by distillation under vacuum. The aqueous mixture was extracted with chloroform (3x) and the combined chloroform extracts were washed with brine and dried (magnesium sulfate). After solvent removal, the residue was dissolved in 10 ml of methanol and treated with 0.37 ml of 50% sodium hydroxide. This solution was refluxed for 45 minutes, cooled and then acidified to *p*H 6 with 2 *N* hydrochloric acid. The methanol was removed by distillation under vacuum and the aqueous mixture was extracted with chloroform. These combined chloroform extracts were washed with brine and dried (magnesium sulfate). Solvent removal produced an oily residue which was purified by flash silica gel chromatography using dichloromethane/methanol/ammonium hydroxide (95/4.5/0.5). There was obtained 1.84 g (84%) of **5** as a yellow-brown solid which was identical with that obtained in Procedure A.

3-[4-[5-(2-Methoxyphenyl)piperazin-1-yl]pentyl]thieno[3,4-*d*]-pyrimidine-2,4-dione (**8**).

The starting *N*-(5-bromopentyl)-*N'*-(4-methoxycarbonylthien-3-yl)urea was prepared in a similar fashion as **1** in 98% yield. A portion of this material was recrystallized from dichloromethane/ether/hexane to afford the urea as a white solid, mp 92-93.5°; ^{1}H nmr (deuteriochloroform): δ 1.4-2.1 (m, 6H, methylene), 3.15-3.5 (m, 4H, methylene), 3.8 (s, 3H, OCH_3), 4.6-4.8 (m, 1H, CH_2NH), 7.68 (d, J = 3.5 Hz, 1H, thiophene), 7.98 (d, J = 3.5 Hz, 1H, thiophene), 9.13 (s, 1H, NHCO); ir (potassium bromide): 3320, 1700, 1540, 1450, 1230, 1080, 780 cm^{-1}.

Anal. Calcd. for $C_{12}H_{17}BrN_2O_3S$: C, 41.26; H, 4.91; N, 8.02. Found: C, 41.52; H, 4.94; N, 7.98.

The thienopyrimidine-2,4-dione **8** was prepared in 91% (10.8 g) yield by Procedure B starting with 8.0 g (23 mmoles) of *N*-(5-bromopentyl)-*N'*-(4-methoxycarbonylthien-3-yl)urea. A portion of this material was recrystallized from dichloromethane/ether to afford **8** as a tan solid, mp 148-153°; ^{1}H nmr (deuteriochloroform): δ 1.3-1.8 (m, 6H, methylene), 2.5-2.7 (m, 6H, methylene), 2.9-3.2 (m, 4H, methylene), 3.8 (s, 3H, OCH_3), 3.97 (t, J = 6 Hz, 2H, $CONCH_2$), 6.6 (d, J = 3 Hz, 1H, thiophene), 6.7-6.9 (m, 4H, phenyl), 8.2 (d, J = 3 Hz, thiophene), 9.3-9.8 (br s, 1H, NH); ir (potassium bromide): 2950, 1720, 1650, 1510, 1250, 760 cm^{-1}.

Anal. Calcd. for $C_{22}H_{28}N_4O_3S$: C, 61.66; H, 6.59; N, 13.08. Found: C, 61.41; H, 6.61; N, 13.21.

Method A. General Procedure for the Preparation of Propanoates **IIIa** (Table I, *n* = 2).

A chloroform solution of 3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[3,4-*d*]pyrimidine-2,4-dione (**7**) [1] (20 g, 51.6 mmoles) was mixed with 0.5 equivalent of benzyltrimethylammonium hydroxide (40% in methanol, Triton B) and methyl acrylate (44.56 g, 0.516 mole) at reflux for one hour. Another 0.5 equivalent of Triton B was added and the solution was refluxed for an additional hour. After the solvents had been carefully removed by vacuum distillation, the dark residue was purified by flash silica gel chromatography using dichloromethane and then 1% methanol in dichloromethane. There was obtained 18.43 g (75%) of methyl 3-[3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxothieno[3,4-*d*]pyrimdin-1-yl]propanoate (**10**) which was recrystallized from ether to afford a white solid, mp 140-140.5°; ^{1}H nmr (deuteriochloroform): δ 2.6-2.93 (m, 6H, methylene), 3.0-3.2 (m, 4H, methylene), 3.67 (s, 3H, OCH_3), 3.83 (s, 3H, CO_2CH_3), 4.03-4.33 (m, 4H, $CONCH_2$), 6.73 (d, J = 3 Hz, 1H, thiophene), 6.83-7.0 (m, 4H, phenyl), 8.25 (d, J = 3 Hz, 1H, thiophene); ir (potassium bromide): 2820, 1725, 1700, 1655, 1580, 1500, 1435, 1310, 1235, 1215, 760 cm^{-1}.

Method B. General Procedure for the Preparation of Alkanoates **IIIa** (Table I, *n* > 2).

An ice-cold DMF (20 ml) solution of **7** (1.0 g, 2.6 mmoles) was treated with 60% sodium hydride (0.155 g, 3.9 mmoles) under nitrogen. After stirring at room temperature for 30 minutes, the solution was quenched with ethyl 4-bromobutyrate (95%) (0.757 g, 3.6 mmoles) and stirred at room temperature for 16 hours. The reaction was poured into ice water and extracted with dichloromethane. The extracts were washed with brine and dried over magnesium sulfate. Solvent removal produced the crude product which was crystallized from ether to give ethyl 4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-2,4-dioxothieno[3,4-*d*]pyrimidin-1-yl]-butanoate (**32**) as a white solid (0.85 g, 65%), mp 108-109.5°; ^{1}H nmr (deuteriochloroform): δ 1.25 (t, J = 7.5 Hz, 3H, OCH_2CH_3), 1.93-2.23 (m, 2H, methylene), 2.45 (t, J = 7.5 Hz, 2H, CH_2CO_2Et), 2.57-2.9 (m, 6H, methylene), 2.97-3.2 (m, 4H, methylene), 3.8 (s, 3H, OCH_3), 3.9-4.25 (m, 6H, $CONCH_2$ and OCH_2CH_3), 6.83-7.0 (m, 5H, thiophene and phenyl), 8.23 (d, J = 3 Hz, 1H, thiophene); ir (potassium bromide): 2820, 1730, 1700, 1660, 1585, 1500, 1245, 750 cm^{-1}.

Method C. General Procedure for the Preparation of Alkanoic Acids **IIIb** (Table I, *n* = 2, 3 or 4).

The ester **10** (3.08 g, 6.52 mmoles) was suspended in methanol (5 ml) and water (5 ml) and treated with 0.568 g (7.1 mmoles) of 50% sodium hydroxide. The mixture was heated to dissolve the ester and after two hours the hydrolysis was complete. Water was added and the *p*H of the solution was adjusted to 6-7 with 2 *N* hydrochloric acid. This aqueous solution was extracted with dichloromethane and the combined extracts were washed with brine and dried (sodium sulfate). Solvent removal produced a light yellow foam which was crystallized from hot ethanol to produce 0.857 g (28%) of 3-[3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-ethyl]-2,4-dioxothieno[3,4-*d*]pyrimidin-1-yl]propanoic acid (**11**) as a white solid, mp 186-187.5°; ^{1}H nmr (deuteriochloroform): δ 2.5-2.87 (m, 6H, methylene), 2.93-3.2 (m, 4H, methylene), 3.83 (s, 3H, OCH_3), 4.03-4.33 (m, 4H, $CONCH_2$), 6.77-7.0 (m, 5H, thiophene and phenyl), 8.23 (d, J = 3 Hz, 1H, thiopene), 8.3 (br s, 1H,

CO_2H); ir (potassium bromide): 3070, 2830, 1700, 1660, 1580, 1495, 1320, 1235, 1020, 770, 745 cm^{-1}.

Method D. General Procedure for the Preparation of Ketones **II** (Table II, X = CO).

The acid **11** (7.76 g, 17 mmoles) was vigorously stirred in 330 g of 1:10 phosphorus pentoxide-methanesulfonic acid [6] at room temperature under nitrogen for 2 hours. After this red solution had been carefully poured into ice water, the *p*H of the solution was then carefully adjusted to 8 with concentrated ammonium hydroxide at 40-45°. The solid was isolated and purified by flash silica gel chromatography using 1% methanol in dichloromethane. The material obtained from the column was triturated with ether to produce 4.58 g (61%) of 3,4,5,7,8,9-hexahydro-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[4,3,2-*de*]pyrido-[1,2-*c*]pyrimidine-3,5,9-trione (**38**) as a yellow crystalline solid, mp 158-160°; ^1H nmr (deuteriochloroform): δ 2.53-2.9 (m, 8H, methylene), 2.9-3.2 (m, 4H, methylene), 3.83 (s, 3H, OCH_3), 4.07-4.43 (m, 4H, $CONCH_2$), 6.93 (s, 4H, phenyl), 8.55 (s, 1H, thiophene); ir (potassium bromide): 2820, 1710, 1670, 1580, 1495, 1380, 1300, 1235, 1180, 750 cm^{-1}.

Method E. General Procedure for the Preparation of Alcohols **52-54** (Table II, X = HOCH).

The ketone **38** (2.71 g, 6.15 mmoles) in absolute ethanol was treated with sodium borohydride (0.233 g, 6.15 mmoles) under nitrogen. After stirring at room temperature for 3 days, water was added and the ethanol was removed by distillation. The *p*H of aqueous solution was adjusted to 12 with 2 *N* sodium hydroxide and then the aqueous solution was extracted with dichloromethane. The combined extracts were washed with brine and dried (magnesium sulfate). Solvent removal produced a residue which was crystallized from chloroform/ethanol/ether to afford 1.58 g (58%) of 3,4,5,7,8,9-hexahydro-9-hydroxy-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[4,3,2-*de*]pyrido[1,2-*c*]-pyrimidine-3,5-dione (**52**) as a light yellow solid, mp 210-211.5°; ^1H nmr (DMSO-d_6): δ 1.97-2.27 (m, 2H, methylene), 2.4-2.8 (m, 6H, methylene), 2.8-3.1 (m, 4H, methylene), 3.8 (s, 3H, OCH_3), 3.85-4.2 (m, 4H, $CONCH_2$), 4.8-5.0 (m, 1H, C*H*OH), 5.6 (d, J = 6 Hz, 1H, OH), 6.9 (s, 4H, phenyl), 8.23 (s, 1H, thiophene); ir (potassium bromide): 3070, 2800, 1695, 1645, 1595, 1490, 1230, 745 cm^{-1}.

Method F. General Procedure for the Preparation of Esters **56-62**.

The alcohol **52** (2.0 g, 4.5 mmoles) was suspended in ice-cold dichloromethane and treated with 1.5 equivalents of 4-dimethylaminopyridine (DMAP) and acetyl chloride (0.390 g, 4.97 mmoles). After this mixture had been stirred at reflux for 16 hours, the golden-brown solution was washed with water and brine and dried (magnesium sulfate). Solvent removal produced a residue which was purified by flash silica gel chromatography using 2% methanol in dichloromethane. There was obtained 1.13 g (52%) of 9-acetyloxy-3,4,5,7,8,9-hexahydro-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[4,3,2-*de*]pyrido[1,2-*c*]pyrimidine-3,5-dione (**56**) as a yellow solid after recrystallization from ether, mp 120-122°; ^1H nmr (deuteriochloroform): δ 1.87-2.17 (m, 1H, methylene), 2.07 (s, 3H, $COCH_3$), 2.23-2.43 (m, 1H, methylene), 2.57-2.9 (m, 6H, methylene), 2.9-3.2 (m, 4H, methylene), 3.5-3.83 (m, 1H, methylene), 3.85 (s, 3H, OCH_3), 4.2 (t, J = 7.5 Hz, 2H, $CONCH_2$), 4.5 (t d, J = 13.5, 3 Hz, 1H, methylene), 5.87 (t, J = 3 Hz, 1H, CHOAc), 6.93 (s, 4H, phenyl), 8.2 (s, 1H, thiophene); ir (potassium bromide): 3070, 2810, 1725, 1700, 1645, 1590, 1235, 1200, 1015, 745 cm^{-1}.

Method G. Procedure for the Preparation of 3,4,5,7-Tetrahydro-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno[4,3,2-*de*]-pyrido[1,2-*c*]pyrimidine-3,5-dione (**55**).

The alcohol **52** (2.72 g, 6.1 mmoles) was suspended in ice-cold dichloromethane and was treated with methanesulfonyl chloride (0.774 g, 6.8 mmoles) followed by one equivalent of triethylamine. After refluxing for 16 hours, the reaction was quenched with water and the organic layer was washed with saturated sodium bicarbonate solution and brine and dried (magnesium sulfate). Solvent removal produced a residue which was purified by flash silica gel chromatography using 2% methanol in dichloromethane. There was obtained 1.3 g (50%) of **55** as a yellow solid after recrystallization from dichloromethane/ether, mp 180-181°; ^1H nmr (deuteriochloroform): δ 2.53-2.9 (m, 6H, methylene), 2.9-3.17 (m, 4H, methylene), 3.83 (s, 3H, OCH_3), 4.17 (t, J = 7.5 Hz, 2H, $CONCH_2$), 5.67 (t d, J = 10.5, 4 Hz, 1H, olefin), 6.37 (t d, J = 10.5, 1.5 Hz, 1H, olefin), 6.77-7.0 (m, 4H, phenyl), 7.83 (s, 1H, thiophene); ir (potassium bromide): 3080, 2810, 1705, 1655, 1580, 1495, 1235, 755 cm^{-1}.

Method H. General Procedure for the Preparation of Oximes **IV**.

The ketone **38** (7.0 g, 15.9 mmoles), was mixed with *O*-methylhydroxylamine hydrochloride (2.66 g, 31.8 mmoles) and sodium acetate (2.6 g, 31.8 mmoles) in absolute ethanol (160 ml). After this mixture has been refluxed for 16 hours under nitrogen, the solvent was removed by distillation and aqueous sodium bicarbonate was added. The aqueous solution was extracted with dichloromethane and the combined extracts were washed with brine and dried (sodium sulfate). Solvent removal produced 8.4 g of yellow solid which was crystallized from dichloromethane/-ether/hexane to give 5.5 g (74%) of 3,4,5,7,8,9-hexahydro-9-methoxyimino-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-thieno[4,3,2-*de*]pyrido[1,2-*c*]pyrimidine-3,5-dione (**64**) as a yellow solid, mp 165-168°; ^1H nmr (deuteriochloroform): δ 2.6-2.93 (m, 6H, methylene), 2.93-3.17 (m, 4H, methylene), 3.83 (s, 3H, OCH_3), 3.93-4.17 (m, 4H, $CONCH_2$), 4.03 (s, 3H, $NOCH_3$), 6.8-6.97 (m, 4H, phenyl), 8.27 (s, 1H, thiophene); ir (potassium bromide): 3090, 2820, 1700, 1665, 1580, 1500, 1310, 1240, 1030, 750, 740 cm^{-1}.

Method I. Procedure for the Preparation of 3,4,5,7,9,10-Hexahydro-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-9*H*-thieno-[4,3,2-*de*]pyrimido[1,2-*a*][1,4]diazepine-3,5,10-trione (**68**).

The ketone **38** (2.5 g, 5.7 mmoles) was mixed with hydroxylamine hydrochloride (0.79 g, 11.35 mmoles) and sodium acetate (0.93 g, 11.35 mmoles) in absolute ethanol. After this mixture had been refluxed for 16 hours under nitrogen, water was added and the ethanol was removed by distillation. The crude oxime **63** (2.21 g, 86%) was isolated as an off-white solid. This crude material was dissolved in 66 g of 1:10 phosphorus pentoxide-methanesulfonic acid and warmed to 100° for 2 hours. After this red solution had been carefully poured into ice-water, the *p*H of the solution was adjusted to 8 with concentrated ammonium hydroxide at 40-45°. The solid was isolated and purified by flash silica gel chromatography using 1-4% methanol in dichloromethane. The material obtained from the column was recrystallized from dichloromethane/ether to produce **68** (0.472 g,

18%) as a yellow solid, mp 197-199°; ^{1}H nmr (deuteriochloroform): δ 2.57-2.9 (m, 6H, methylene), 2.9-3.2 (m, 4H, methylene), 3.5-3.77 (m, 2H, CONHC*H*$_2$), 3.87 (s, 3H, OCH_3), 4.2 (t, J = 7.5 Hz, 4H, $CONCH_2$), 6.8-7.0 (m, 4H, phenyl), 7.77 (br t, J = 4.5 Hz, 1H, CONH), 8.5 (s, 1H, thiophene); ir (potassium bromide): 3260, 3170, 3060, 1700, 1655, 1630, 1565, 1490, 1315, 1230, 765 cm^{-1}.

Method J. Procedure for the Preparation of 9-Amino-3,4,5,7,8,9-hexahydro-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]thieno-[4,3,2-*de*]pyrido[1,2-*c*]pyrimidine-3,5-dione (**69**).

The oxime **64** (1.4 g, 2.99 mmoles) was slurried in ice-cold THF (20 ml) under nitrogen and treated with 1*M* diborane-THF (12 ml). After refluxing the solution for two hours, the reaction was carefully quenched with 2 *N* hydrochloric acid and the THF was removed by distillation. The resulting acidic residue was warmed on a steambath for 15-20 minutes, cooled and then treated with 2 *N* sodium hydroxide until a *p*H of 10 was obtained. The aqueous solution was extracted with dichloromethane and the combined extracts were washed with brine and dried (sodium sulfate). Solvent removal produced 1.3 g (98%) of **69** which was crystallized from dichloromethane/ether to afford a beige solid, mp 152-155°; ^{1}H nmr (deuteriochloroform): δ 1.68 (s, 2H, NH_2), 1.8-2.5 (m, 2H, methylene), 2.55-2.9 (m, 6H, methylene), 2.93-3.17 (m, 4H, methylene), 3.87 (s, 3H, OCH_3), 3.87-4.3 (m, 5H, $CONCH_2$ and NH_2CH), 6.77-7.0 (m, 4H, phenyl), 8.03 (s, 1H, thiophene); ir (potassium bromide) 2820, 1700, 1643, 1600, 1495, 1240, 755, 745 cm^{-1}.

Method K. General Procedure for the Preparation of Amides **70** and **71**.

An ice-cold dichloromethane (20 ml) solution of **69** (0.883 g, 2 mmoles) was sequentially treated with triethylamine (0.31 ml, 2.2 mmoles), DMAP (61 mg, 0.5 mmoles), and a 3 ml dichloromethane solution of acetyl chloride (0.16 ml, 2.2 mmoles) under nitrogen. The resulting solution was allowed to warm to room temperature and then quenched with water. The organic layer was removed and dried (magnesium sulfate). Solvent removal produced 1.1 g of light yellow foam which was crystallized from dichloromethane/ether to give 0.65 g (67%) of 9-acetylamino-3,4,5,-7,8,9-hexahydro-4-[2-[4-(2-methoxyphenyl)piperazin-1-yl]-ethyl)thieno[4,3,2-*de*]pyrido[1,2-*c*]pyrimidine-3,5-dione (**70**), mp 193.5-196.5°; ^{1}H nmr (deuteriochloroform): δ 2.03 (s, 3H, CH_3CON), 2.1-2.45 (m, 2H, methylene), 2.53-2.87 (m, 6H, methylene), 2.9-3.15 (m, 4H, methylene), 3.83 (s, 3H, OCH_3), 4.0-4.23 (m, 4H, $CONCH_2$), 5.13-5.33 (m, 1H, AcNHC*H*), 6.07 (d, J = 7.5 Hz, 1H, AcNH), 6.77-7.0 (m, 4H, phenyl), 7.97 (s, 1H, thiophene); ir (potassium bromide): 3280, 2820, 1700, 1650, 1600, 1599, 1285, 1240, 750 cm^{-1}.

Acknowledgment.

We thank Dr. M. L. Cotter and staff for spectral measurements and elemental analyses. The authors would also like to thank Dr. J. Press for his assistance with the manuscript.

REFERENCES AND NOTES

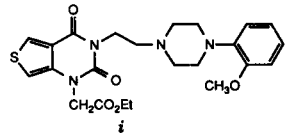
[1] R. K. Russell, J. B. Press, R. A. Rampulla, J. J. McNally, R. Falotico, J. A. Keiser, D. A. Bright and A. Tobia, *J. Med. Chem.*, **31**, 1786 (1988).

[2] Y.-H. Wu, K. R. Smith, J. W. Rayburn and J. W. Kissel, *J. Med. Chem.*, **12**, 876 (1969).

[3] A. Basha, M. Lipton and S. M. Weinreb, *Tetrahedron Letters*, 4171 (1977).

[4] R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Chem.*, **5**, 1944 (1962).

[5] Compound **i** was prepared by Method B in 91% crude yield and hydrolyzed to its corresponding carboxylic acid. This acid failed to afford **V** (*n* = 1).

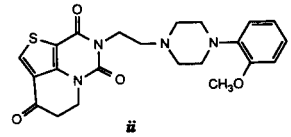


i

[6] P. E. Eaton, G. R. Carlson and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).

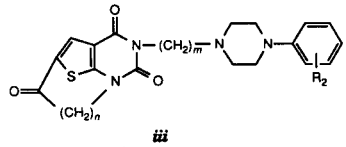
[7] R. Taylor, Electrophilic Substitution of Thiophene and Its Derivatives, in Thiophene and its Derivatives, Vol **44**, Part **2**, S. Gronowitz, ed, John Wiley and Sons, New York, 1985, pp 1-117.

[8] Starting with 3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-thieno[3,2-*d*]pyrimidine-2,4-dione [1], the thieno[2,3,4-*de*] tricyclic compound **ii** was prepared by the methods described in Scheme II in 26% overall yield. Since this intramolecular Friedel-Crafts cyclization occurred on the less activated β-position of the thiophene ring, [7] a higher reaction temperature (100°) was necessary.



ii

The thieno[2,3-*d*]pyrimidine-2,4-diones were not used as starting materials since the position of the thiophene sulfur atom would have caused the formation of compound **iii**. The preparation of these tricyclics and the problems expected in their formation was beyond the scope of this investigation.



iii

[9] P. Dallemagne, S. Rault, M. C. de Sévricourt and M. Robba, *Heterocycles*, **27**, 1637 (1988).

[10] It is also possible the oxime OH-group of **65** is *syn* to the alkyl group and then rearranges in the 1:10 phosphorus pentoxide-methanesulfonic acid [11]; however, to what extent, if any, this rearrangement is possible in 1:10 phosphorus pentoxide-methanesulfonic acid is not known.

[11] R. E. Gawley, *Organic Reactions*, **35**, 1988, pp 1-420.

[12] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

[13a] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy and J. H. Williams, *J. Org. Chem.*, **18**, 138 (1953); [b] O. Hromatka, D. Binder and K. Eichinger, *Monatsh. Chem.*, **104**, 1520 (1973).