Synthesis of 5*H*-Triazolo[1,5-*d*]- and 5*H*-Tetrazolo-[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones

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5*H*-Triazolo[1,5-*d*]- and 5*H*-tetrazolo[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones have been obtained by the base catalysed ring expansion reaction of 5-chloromethyl-1,2,4-triazolo[1,5-*c*]- and 5-chloromethyltetrazolo-[1,5-*c*]thieno[3,2-*e*]pyrimidines. The required thienopyrimidine derivatives were synthesized from 2-amino-3-triazolyl- and 2-amino-3-tetrazolylthiophenes by acylation, followed by dehydrative cyclization.

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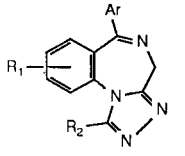
The synthesis of tricyclic 1,4-diazepines with a triazole ring fused to the *a* face of the benzodiazepines **1** and thienodiazepines **2** is an area of current interest in the search for compounds with CNS activities [1-11]. Our earlier investigations [12,13] on the synthesis, isomerization and ring cleavage reactions of triazolothienopyrimidines **3a** and **3b** presented us with an opportunity to explore the synthesis of novel thienodiazepines **4a-c** with triazole and tetrazole rings fused to the *d* face of thienodiazepine ring system.



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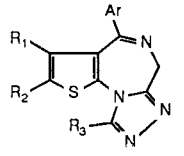

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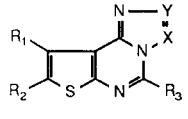
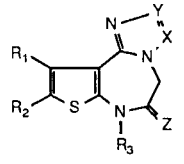
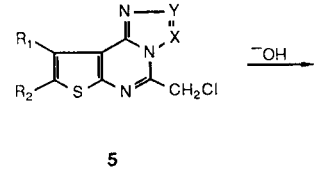


3a, X = N, Y = CH
3b, X = CH, Y = N



4a, X = N, Y = CH
4b, X = CH, Y = N
4c, X = Y = N

Based on the literature precedent with triazoloquinazolines [14] and our own observations on the nucleophilic ring opening and recyclization reactions of triazolothienopyrimidines [13], it appeared that the hydroxide ion induced ring opening of chloromethyltriazolothienopyrimidines **5** could set the stage for their eventual cyclization to the desired ring expanded products, diazepinones **6**. Detailed in this paper are the results of our investigation on such an approach.



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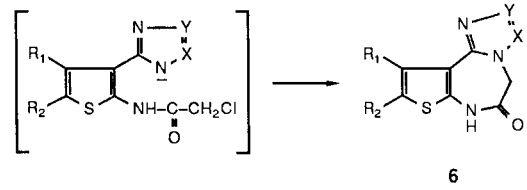
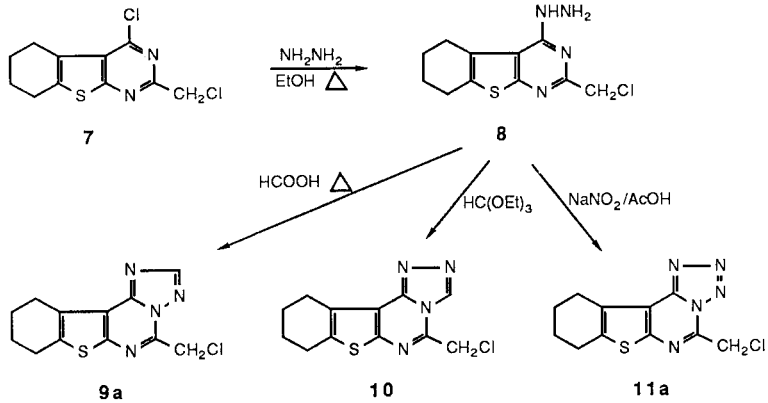


6

An initial approach that was investigated for the preparation of the desired starting materials, *viz.*, chloromethyltriazolo and tetrazolothienopyrimidines is depicted in Scheme I. Thus, treatment of 2-chloromethyl-4-hydrazino-

Scheme I

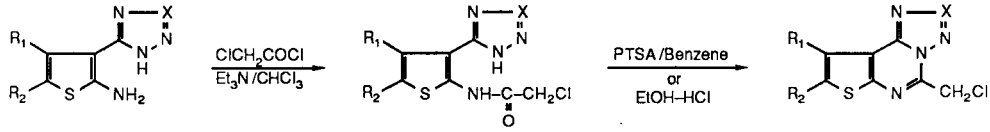


7 **8** **9a** **10** **11a**

thienopyrimidine **8** with sodium nitrite in acetic acid yielded the tetrazolothienopyrimidine **11a**. The isomeric triazolothienopyrimidines **9a** and **10** were obtained by the cyclization of the hydrazine **8** with formic acid and triethyl orthoformate, respectively. The structure assignments to the isomers obtained are based on their method of preparation and on the ^{1}H-nmr spectral characteristics [12]. Despite the fact that the chloromethyl-hydrazinothienopyrimidine **8** could be cyclized to yield triazolo- and tetrazolothienopyrimidines **9a**, **10** and **11a**, this approach to the preparation of starting materials was abandoned in favor of an alternative method mainly because of the difficulties encountered in obtaining clean conversions of 2-chloromethyl-4-chlorothienopyrimidine **7** to the 2-chloromethyl-4-hydrazinothienopyrimidine **8**. The method also suffers from poor overall yields.

The alternative approach envisaged the cyclization of triazolyl- and tetrazolylaminothiophenes to the desired chloromethyltriazolo- and tetrazolothienopyrimidines (Scheme II). Chloroacetylation of 2-amino-3-triazolyl- and tetrazolylthiophenes **12** and **14** with chloroacetyl chloride in the presence of triethylamine yielded the amides **13** and **15** (Table I). Acid catalysed cyclization of **13** with *p*-toluenesulphonic acid in benzene or ethanolic hydrogen chloride afforded exclusively a single product characterized as triazolo[1,5-*c*]thienopyrimidine isomer **9** (Table II).

Scheme II

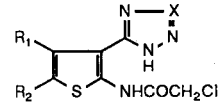


12, 14 **13, 15** **9, 11**

12a, 13a, 9a: R_1R_2 = –$(CH_2)_4$–, X = CH
12b, 13b, 9b: R_1 = R_2 = CH_3, X = CH
12c, 13c, 9c: R_1 = C_6H_5, R_2 = H, X = CH
12d, 13d, 9d: R_1R_2 = –$(CH_2)_4$–, X = C–CH_3
14a, 15a, 11a: R_1R_2 = –$(CH_2)_4$–, X = N
14b, 15b, 11b: R_1 = R_2 = CH_3, X = N
14c, 15c, 11c: R_1 = C_6H_5, R_2 = H, X = N

Table I

Physical Data of 2-(Chloroacetamido)-3-(1*H*-1,2,4-triazol-3-yl)- and 2-(Chloroacetamido)-3-(1*H*-tetrazol-5-yl)thiophenes **13** and **15**

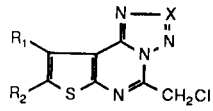


Compound No.	R_1	R_2	X	MP °C	Yield %	Recrystallization Solvent [a]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
13a	–$(CH_2)_4$–		CH	233-235	57	D	$C_{12}H_{13}ClN_4OS·H_2O$	314.79	45.78 45.80	4.80 4.42
13b	CH_3	CH_3	CH	194-195	63	E	$C_{10}H_{11}ClN_4OS$	270.74	44.36 44.61	4.10 4.48
13c	C_6H_5	H	CH	208-210	75	Bz-C	$C_{14}H_{11}ClN_4OS$	318.78	52.74 53.06	3.48 3.81
13d	–$(CH_2)_4$–		CCH_3	203-205	42	E-C	$C_{13}H_{15}ClN_4OS$	310.8	50.23 50.17	4.86 4.55
15a	–$(CH_2)_4$–		N	223-225	60	E	$C_{11}H_{12}ClN_5OS$	297 [b]	44.37 44.77	4.06 4.52
15b	CH_3	CH_3	N	225-227	40	E	$C_9H_{10}ClN_5OS$	271.7	39.78 40.10	3.71 3.62
15c	C_6H_5	H	N	223-225	81	E	$C_{13}H_{10}ClN_5OS$	319.77	48.83 48.73	3.15 3.50

[a] Bz = Benzene, C = Chloroform, D = Dioxane, E = Ethanol. [b] Molecular weight determined by mass spectrum.

Table II

Physical Data of 5-Chloromethyl-l,2,4-triazolo[1,5-*c*]- and 5-Chloromethyltetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **9** and **11**

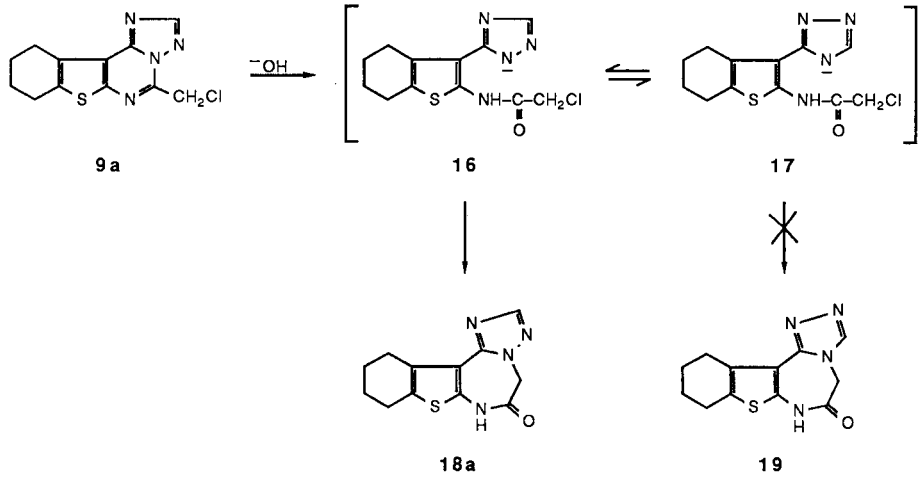


Compound No.	R_1	R_2	X	MP °C	Yield %	Recrystallization Solvent [a]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
9a	-$(CH_2)_4$-		CH	161-163 [c]	72	E-C	$C_{12}H_{11}ClN_4S$	278 [b]	51.70 52.00	3.98 4.22
9b	CH_3	CH_3	CH	175-176	60	E	$C_{10}H_9ClN_4S$	252.72	47.52 47.90	3.59 3.41
9c	C_6H_5	H	CH	184-185 [d]	27	H-B	$C_{14}H_9ClN_4S$	300.77	--	--
9d	-$(CH_2)_4$-		C-CH_3	180-182	41	H	$C_{13}H_{13}ClN_4S$	292.79	53.33 53.64	4.48 4.51
11a	-$(CH_2)_4$-		N	140-142 [e]	43	E	$C_{11}H_{10}ClN_5S$	279.75	47.22 47.62	3.60 3.98
11b	CH_3	CH_3	N	186-188	75	B	$C_9H_8ClN_5S$	253.72	42.60 43.00	3.18 3.18
11c	C_6H_5	H	N	171-173	53	H-B	$C_{13}H_8ClN_5S$	301.76	51.74 52.10	2.67 3.08

[a] B = Benzene, C = Chloroform, E = Ethanol, H = *n*-Hexane. [b] Molecular weight determined by mass spectrum. [c] Also obtained by the cyclization of 2-chloromethyl-4-hydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-*d*]pyrimidine with formic acid at reflux and 2-amino-3-(1*H*-1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene with chloroacetyl chloride in chloroform at reflux. [d] Reported mp 184-185 [13]. [e] Also obtained by the cyclization of 2-chloromethyl-4-hydrazino-5,6,7,8-tetrahydrobenzo[b]thieno[2,3-*d*]pyrimidine with sodium nitrite in acetic acid.

A solution of 5-chloromethyltriazolothienopyrimidine **9a** in dimethylformamide when treated with aqueous sodium hydroxide solution and stirred at room temperature for 12 hours yielded a product devoid of chlorine. The ir spectrum of the compound exhibited characteristic amide NH and C=O absorptions at 3200, 3100 cm^{-1} and 1690 cm^{-1}, respectively [15]. In the ^{1}H-nmr spectrum the amide NH proton appears as broad singlet at δ 11.0. Intense molecular ion peak at m/e 260 characterized the mass spectrum and the loss of CO, CHO$^{\cdot}$, and $CH_2=C=O$ from the parent and daughter ions were the important modes of fragmentation. These spectral characteristics indicate that the product obtained is, indeed, the triazolothienodiazepine **18a**.

This ring expansion reaction of chloromethyltriazolothienopyrimidines is assumed to proceed *via* the pyrimidine ring opened triazole anion intermediates **16** or **17** which, in principle, can cyclize to yield the isomeric tri-

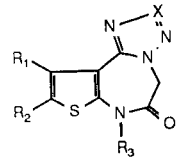


azolo[1,5-*d*]- and triazolo[4,3-*d*]thienodiazepinones **18a** and **19**. However, only one isomer of triazolothienodiazepiones could be obtained from the ring expansion reaction. The appearance of the triazole proton as a singlet at δ 8.0, a comparatively more shielded proton [12], indicates that the product obtained is thermodynamically stable 5*H*-1,2,4-triazolo[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-one **18a**, formed by the preferential intramolecular alkylation of the vicinal nitrogen (N_2) of triazole, rather than triazolo[4,3-*d*] isomer.

This ring expansion procedure was successfully employed for the preparation of a number of triazolo[1,5-*d*]- and tetrazolo[1,5-*d*]thienodiazepinones **18b-d** and **20a-c** from the corresponding chloromethyltriazolo- and tetrazolothienopyrimidines **9b-d** and **11a-c** (Table III). A one-step base catalysed cyclization of chloroacetamide derivatives **13, 15** to yield directly the triazolo-and tetrazolothienodiazepinones **18, 20** could be an attractive alternative to the above described two-step procedure involving first the cyclization to the thienopyrimidines, followed by ring

Table III

Physical Data of 5*H*-1,2,4-Triazolo[1,5-*d*]- and 5*H*-Tetrazolo[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones **18** and **20-22**



Compound No.	R_1	R_2	R_3	X	MP °C	Yield %	Recrystallization Solvent [a]	Molecular Formula	Mol Wt	Microanalysis Calcd./Found %C	%H
18a	-$(CH_2)_4$-		H	CH	242-244	73	E	$C_{12}H_{12}N_4OS$	260 [b]	55.36 55.63	4.65 4.92
18b	CH_3	CH_3	H	CH	246-248	72	E	$C_{10}H_{10}N_4OS$	234.28	51.26 51.57	4.30 4.50
18c	C_6H_5	H	H	CH	286-288	78	M-C	$C_{14}H_{10}N_4OS$	**282 [b]**	59.56 59.83	3.57 3.74
18d	-$(CH_2)_4$-		H	C-CH_3	285-287	80	E	$C_{13}H_{14}N_4OS$	274 [b]	56.91 56.60	5.14 5.46
20a	-$(CH_2)_4$-		H	N	235-236	54	B-C	$C_{11}H_{11}N_5OS$ ½ C_6H_6	261 [b]	55.97 55.77	4.70 4.94
20b	CH_3	CH_3	H	N	266-268	85 [c]	B-E	$C_9H_9N_5OS$	235.27	45.94 46.19	3.86 4.14
20c	C_6H_5	H	H	N	>330	57	E-DM	$C_{13}H_9N_5OS$	283.31	55.11 55.28	3.20 3.47
21a	-$(CH_2)_4$-		CH_3	CH	213-215	80	E	$C_{13}H_{14}N_4OS$	274 [b]	56.93 56.84	5.15 5.24
21b	CH_3	CH_3	CH_3	CH	161-163	48	H-B	$C_{11}H_{12}N_4OS$	248.3	53.20 53.60	4.87 5.22
21c	C_6H_5	H	CH_3	CH	234-235	74	E	$C_{15}H_{12}N_4OS$	296 [b]	60.79 60.71	4.08 4.25
21d	-$(CH_2)_4$-		CH_3	C-CH_3	196-198	90	CH	$C_{14}H_{16}N_4OS$	288.37	58.31 58.37	5.59 5.84
22a	-$(CH_2)_4$-		CH_3	N	230-232	44	E	$C_{12}H_{13}N_5OS$	275.33	52.34 52.42	4.76 5.00
22b	CH_3	CH_3	CH_3	N	231-233	88	B	$C_{10}H_{11}N_5OS$	249.29	48.18 48.39	4.45 4.50
22c	C_6H_5	H	CH_3	N	210-211	61	H-B	$C_{14}H_{11}N_5OS$	297.33	56.55 56.47	3.73 3.83

[a] B = Benzene, C = Chloroform, CH = Cyclohexane, DM = Dimethylformamide, E = Ethanol, H = *n*-Hexane, M = Methanol. [b] Molecular weight determined by mass spectra. [c] Obtained in 76% yield by the treatment of 5-chloromethyl-8,9-dimethyltetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine in dioxane with aqueous sodium hydroxide.

expansion. However, the direct approach was successful only in the conversion of 2-(chloroacetamido)-3-tetrazolylthiophenes **15a-c** to the diazepinones **20a-c**.

The *N*-methyl derivatives **21a-d** and **22a-c** and the thione analogue **18e**, needed for biological testing and for further chemical transformations, were prepared from the diazepinones **18a-d** and **20a-c** by methylation with iodomethane in the presence sodium hydride in benzene-dimethylformamide or dioxane and thionation with phosphorous pentasulphide in pyridine under standard reaction conditions.

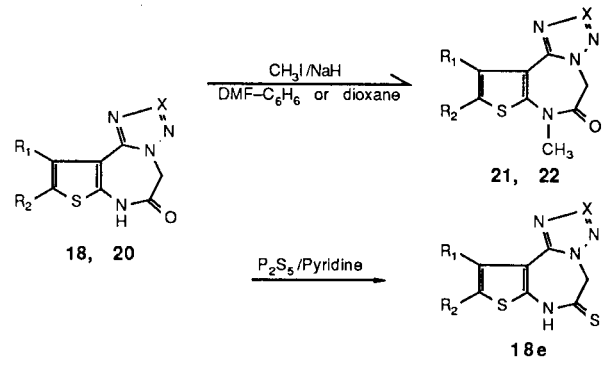


Table IV

Spectral Data of Compounds **9**, **11**, **13**, **15**, **18**, and **20-22**

Compound No.	UV λ max(log ε) [a]	IR (cm^{-1}) [b]	^{1}H-NMR (δ ppm) [c]	MS: m/z
13a	– –	3120 (NH), 1660 (C=O) [B]	– –	– –
13b	– –	3200 (NH), 1660 (C=O) [A]	– –	– –
13c	– –	3240, 3120 (NH), 1640 (C=O) [B]	– –	– –
13d	– –	3200 (NH), 1640 (C=O) [B]	– –	– –
15a	225 (4.13), 302 (3.94)	3200, 3180 (NH), 1660 (C=O) [A]	– –	299, 297 (M^+), 269, 261, 241, 220, 205, 204, 192, 177, 164
15b	– –	3200 (NH), 1650 (C=O) [B]	– –	– –
15c	– –	3200 (NH), 1660 (C=O) [B]	– –	– –
9a	– –	1620 [A]	2.0 (4H, m, CH_2 at C-10 and C-11), 3.05 (4H, m, CH_2 at C-9 and C-12), 5.2 (2H, s, CH_2Cl), 8.5 (1H, s, CH at C-2) [C]	280, 278 (M^+), 277, 263, 252, 250, 244, 243, 229, 215, 202, 188, 175, 174, 148
9b	– –	1610 [B]	– –	– –
9d	– –	1610 [B]	– –	– –
11a	– –	1610 [B]	2.05 (4H, m, CH_2 at C-9 and C-10), 3.15 (4H, m, CH_2 at C-8 and C-11), 5.34 (2H, s, CH_2Cl) [C]	– –
11b	– –	1605 [B]	– –	– –
11c	– –	1610 [A]	– –	– –
18a	235 (4.43), 292 (3.95)	3200, 3100 (NH), 1690 (C=O) [A]	2.33 (4H, m, CH_2 at C-10 and C-11), 3.33 (4H, m, CH_2 at C-9 and C-12), 4.83 (2H, s, CH_2 at C-5), 8.0 (1H, s, CH at C-2), 11.0 (1H, broad s, NHCO) [D]	260 (M^+), 259, 245, 232, 231, 217, 204, 203, 190, 177, 176
18b	233 (4.32), 288 (3.92)	3180, 3070 (NH), 1690 (C=O) [B]	– –	– –
18c	240 (4.45)	3220, 3140 (NH), 1700 (C=O) [B]	– –	282 (M^+), 281, 254, 253, 239, 227, 226, 221
18d	235 (4.41), 290 (3.92)	3210, 3100 (NH), 1700 (C=O) [A]	1.83 (4H, m, CH_2 at C-10 and C-11), 2.36 (3H, s, CH_3 at C-2), 2.66 (4H, m, CH_2 at C-9 and C-12), 4.71 (2H, s, CH_2 at C-5), 10.86 (1H, broad s, NHCO) [D]	274 (M^+), 273, 259, 246, 245, 231, 218, 217, 204, 203, 190, 177, 176
20a	– –	3200, 3100 (NH), 1700 (C=O) [A]	– –	261 (M^+), 260, 233, 232, 205, 204, 191, 190, 177, 162
20b	– –	3200 (NH), 1670 (C=O) [A]	2.33 (6H, m, CH_3 at C-9 and C-10), 5.11 (2H, s, CH_2 at C-5), 11.18 (1H, broad s, NHCO) [D]	– –

Table IV (continued)

Spectral Data of Compounds **9**, **11**, **13**, **15**, **18**, and **20-22**

Compound No.	UV λ max(log ε) [a]	IR (cm^{-1}) [b]	^{1}H-NMR (δ ppm) [c]	MS: m/z
20c	– –	3200 (NH), 1680 (C=O) [A]	– –	– –
21a	– –	1670 (C=O) [A]	2.0 (4H, m, CH_2 at C-10 and C-11), 2.83 (4H, m, CH_2 at C-9 and C-12), 3.47 (3H, s, CH_3 at N-7), 4.87 (2H, s, CH_2 at C-5), 8.0 (1H, s, CH at C-2) [C]	274 (M^+), 273, 259, 246, 245, 231, 218, 217, 204, 191, 190, 176
21b	– –	1675 (C=O) [B]	– –	– –
21c	– –	1680 (C=O) [A]	3.47 (3H, s, CH_3 at N-7), 4.97 (2H, s, CH_2 at C-5), 7.32 (6H, s, C_6H_5 and CH at C-9), 7.83 (1H, s, CH at C-2) [C]	296 (M^+), 295, 269, 268, 254, 241, 240, 239, 212, 211
21d	– –	1670 (C=O) [B]	– –	– –
22a	– –	1690 (C=O) [A]	– –	– –
22b	– –	1670 (C=O) [B]	–	– –
22c	– –	1685 (C=O) [B]	3.6 (3H, s, CH_3 at N-7), 5.27 (2H, s, CH_2 at C-5), 7.27-7.57 (6H, m, C_6H_5 and H at C-9) [C]	– –

[a] Measured solvent: Methanol. [b] Measured in: [A] Nujol Mull; [B] Potassium bromide. [c] Measured solvents: [C] Deuteriochloroform; [D] Deuteriochloroform-DMSO-d_6.

The triazolothienodiazepinones **18a-d**, and **21a-d** and tetrazolo[1,5-*d*]thienodiazepinones **20a-c** and **22a-c** are colorless crystalline compounds sparingly soluble in ethanol, chloroform and benzene. Triazolothienodiazepine-6-thione **18e** is a pale yellow colored solid, soluble in dilute sodium hydroxide solution. Triazolo[1,5-*d*]thienodiazepinones **18a-d** exhibit two characteristic absorptions around 230-240 nm and 288-292 nm in uv. The ir spectra of these diazepinones exhibit N-H stretching absorptions around 3220-3180 cm^{-1}. The C=O stretching absorption is found in the region 1700-1670 cm^{-1}.

The mass spectra of triazolo- and tetrazolothienodiazepinones **18a**, **18c**, **18d**, **20a**, **21a**, and **21c** exhibit intense molecular ion peak. A broad one proton singlet corresponding to the amide N-H in the ^{1}H-nmr spectra of triazolo-and tetrazolothienodiazepinones **18a**, **18d**, and **20b** is found around δ 10.86-11.8. Additionally, these compounds exhibit a sharp, highly deshielded methylene proton signal around δ 4.71-5.20. The triazole proton singlet (HC_2) appears around δ 7.8-8.0. *N*-Methyltriazolo[1,5-*d*]- and tetrazolo[1,5-*d*]thienodiazepinones **21a**, **21c**, and **22c** exhibit a three proton singlet due to the methyl group at N-7 at δ 3.4-3.7 (Table IV).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The uv spectra were recorded on a Beckman model 25 spectrophotometer in methanol. The ir spectra were recorded in nujol mulls or potassium bromide on a Perkin-Elmer Grating spectrophotometer. The ^{1}H-nmr spectra were taken on a Varian A-60 spectrometer using TMS as the internal standard. The mass spectra were obtained on a Varian Atlas CH-7 spectrometer at 70 ev ionizing beam, using direct insertion probe. The starting materials **7** [16], **12a-c** [13] were prepared according to the literature methods. The compound **12d** was prepared essentially according to the procedure described for **12c** [13] and was used in further reactions without purification.

2-Amino-4-phenyl-3-(tetrazol-5-yl)thiophene **14c**.

To a suspension of 9-phenyltetrazolo[1,5-c]thieno[3,2-*e*]pyrimidine (2.53 g, 0.01 mole) in ethanol (25 ml) was added an aqueous solution of sodium hydroxide (15 ml, 2*N*). The reaction mixture was refluxed for 2 hours, cooled and poured into ice-water. The resulting solution was clarified by filtration and acidified with dilute acetic acid. The solid obtained was filtered, washed with water and dried. Crystallization from *n*-hexane afforded 1.5 g (62%) of **14c**, mp 192-193°; ir (potassium bromide): cm^{-1} 3380, 3340, 3280 (NH_2, NH), 1600, 1540, 1500, 1440, 1240, 1200, 1050, 905, 765; nmr (deuteriochloroform): δ 6.3 (s, 2H, NH_2 at C-2), 7.3 (s, 1H, tetrazole NH), 7.5 (m, 6H, Ar-H and H at C-5).

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.30; H, 3.72. Found: C, 54.18; H, 3.85.

Similarly, the 2-amino-3-(tetrazol-5-yl)thiophenes **14a** and **14b** were obtained through the base catalysed hydrolysis of the corresponding tetrazolo[1,5-c]thieno[3,2-*e*]pyrimidines and were used in further reactions without purification.

General Procedure for the Preparation of 2-(Chloroacetamido)-3-(1*H*-1,2,4-triazol-3-yl)thiophenes **13a-13d** and 2-(Chloroacetamido)-3-(tetrazol-5-yl)thiophenes **15a-15c**.

To an ice-cold mixture of 2-amino-3-(1*H*-1,2,4-triazol-3-yl)thiophene or 2-amino-3-(tetrazol-5-yl)thiophene (0.01 mole) and triethylamine (1.1 g, 0.01 mole) in chloroform (25 ml) was added, dropwise, chloroacetyl chloride (1.4 g, 0.012 mole). The reaction mixture was allowed to stand at room temperature for 12 hours. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

5-(Chloromethyl)-1,2,4-triazolo[1,5-c]-8,9,10,11-tetrahydrobenzo[*b*]thieno-[3,2-*e*]pyrimidine **9a**.

Method A.

To a warm solution of 4-chloro-2-(chloromethyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (2.73 g, 0.01 mole) in ethanol (20 ml) was added, dropwise, a solution of hydrazine hydrate (98%, 5 ml) in ethanol (10 ml). The reaction mixture was refluxed for 3 hours and cooled. The solid obtained was filtered, washed with cold ethanol, dried and used in further reactions without purification.

A mixture of crude 2-(chloromethyl)-4-hydrazino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (2.7 g) and formic acid (25 ml) was refluxed for 3 hours. The reaction mixture was cooled and poured into ice-water. The solid obtained was filtered and crystallized from ethanol-chloroform to yield 0.9 g of **9a**, mp 161-162°.

Method B.

A mixture of 2-amino-3-(1*H*-1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo-[*b*]thiophene (2.2 g) and chloroacetyl chloride (1.7 g, 0.015 mole) in chloroform (25 ml) was refluxed for 6 hours. The reaction mixture was concentrated under vacuum and the solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform yielded 0.4 g of **9a**, mp 161-162°, identical (mmp, tlc, ir) with the product obtained by Method A.

Method C.

A mixture of 2-(chloroacetamido)-3-(1*H*-1,2,4-triazol-3-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene **13a** (2.97 g, 0.01 mole) and concentrated hydrochloric acid (0.2 ml) in absolute ethanol (25 ml) was refluxed for 4 hours. The reaction mixture was cooled and the solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform afforded 2.0 g (72%) of **9a**, mp 161-162°, identical (mmp, tlc, ir) with the product obtained by Method A.

Similarly, 5-(chloromethyl)-8,9-dimethyl-1,2,4-triazolo-[1,5-*c*]thieno[3,2-*e*]pyrimidine **9b** was obtained by the cyclization of the corresponding 2-(chloroacetamido)-3-(1*H*-1,2,4-triazol-3-yl)-4,5-dimethylthiophene **13b** in refluxing ethanol in the presence of a catalytic quantity of hydrochloric acid.

Alternatively, 5-(chloromethyl)triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **9c** and **9d**, and 5-(chloromethyl)tetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **11a-c** were prepared by the cyclization of the corresponding 2-(chloroacetamido)-3-triazolyl- or 2-(chloroacetamido)-3-tetrazolylthiophenes in refluxing benzene in the presence of an equimolar quantity of *p*-toluenesulphonic acid.

5-(Chloromethyl)-1,2,4-triazolo[4,3-*c*]-8,9,10,11-tetrahydrobenzo[*b*]-thieno[3,2-*e*]pyrimidine **10**.

A mixture of crude 2-(chloromethyl)-4-hydrazino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (2.7 g) and triethyl orthoformate (25 ml) was warmed on a water bath at 50-60° for 10 minutes and allowed to stand at room temperature for 12 hours. The solid obtained was filtered, and dried. Crystallization from ethanol-chloroform afforded 1.5 g of **10** as crystalline product, mp 204-205°, ir (nujol): cm^{-1} 1600, 1480, 1280, 1185, 1170, 970, 890, 820; nmr (DMSO): δ 2.1 (m, 4H, CH_2 at C-9 and C-10), 3.3 (m, 4H, CH_2 at C-8 and C-11), 5.65 (s, 2H, CH_2 at C-5), 9.8 (s, 1H, H at C-3).

Anal. Calcd. for $C_{12}H_{11}ClN_4S$: C, 51.70; H, 3.98. Found: C, 51.57; H, 4.20.

5-(Chloromethyl)tetrazolo[1,5-*c*]-8,9,10,11-tetrahydrobenzo[*b*]thieno-[3,2-*e*]pyrimidine **11a**.

To an ice-cold solution of crude 2-(chloromethyl)-4-hydrazino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (2.7 g) in acetic acid (100 ml, 50% w/v) was added a solution of sodium nitrite (0.76 g, 0.011 mole) in water (10 ml), dropwise, with stirring. The reaction mixture was allowed to stand for 2 hours, and the solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform afforded 1.3 g of **11a** as a crystalline solid, mp 140-142°, identical (mmp, tlc, ir) with the product obtained by the cyclization of 2-(chloroacetamido)-3-(tetrazol-5-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene in refluxing benzene in the presence of an equimolar quantity of *p*-toluenesulphonic acid.

General Procedure for the Preparation of 5*H*-1,2,4-Triazolo[1,5-*d*]-thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones **18a-18d** and 5*H*-tetrazolo[1,5-*d*]-thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones **20a-20c**.

a) To a well stirred suspension of an appropriate 5-(chloromethyl)-tetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine (0.01 mole) in dioxane or dimethylformamide (25 ml) was added an aqueous solution of sodium hydroxide (25 ml, 1 *N*). The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and acidified with dilute acetic acid. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

b) To a well stirred suspension of an appropriate 2-(chloroacetamido)-3-(tetrazol-5-yl)thiophene (0.01 mole) in dioxane (30 ml) was added, dropwise, an aqueous solution of sodium hydroxide (25 ml, 1 *N*). The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and acidified with dilute acetic acid. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

General Procedure for the Preparation of 5*H*-7-Methyl-1,2,4-triazolo-[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones **21a-21d** and 5*H*-7-Methyltetrazolo[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-ones **22a-22c**.

To a suspension of sodium hydride (50%) (0.5 g, 0.01 mole) in dioxane (50 ml) was added, portionwise, with stirring, an appropriate 1,2,4-triazolo- or tetrazolo[1,5-*d*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-one (0.01 mole). The reaction mixture was stirred at 10-15° for 15 minutes, treated dropwise with an excess of methyl iodide (3 g, 0.02 mole) and stirred for an additional two hours. After allowing to stand at room temperature for 12 hours, the reaction mixture was poured into ice-water. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

5*H*-1,2,4-Triazolo[1,5-*d*]-9,10,11,12-tetrahydrobenzo[*b*]thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-thione **18e**.

To a solution of 5*H*-1,2,4-triazolo[1,5-*d*]-9,10,11,12-tetrahydrobenzo[*b*]-thieno[3,2-*f*]-1,4-diazepin-6(7*H*)-one (1.3 g, 0.005 mole) in dry pyridine (15 ml) was added phosphorus pentasulphide (1.1 g, 0.005 mole). The reaction mixture was refluxed for 3 hours, cooled and poured into ice water. The solid obtained was filtered, washed with water and dried. Crystallization from ethanol-chloroform afforded 1.0 g (72%) of **18e** as crystalline product, mp 287-289°, ir (nujol): cm^{-1} 3100 (NH), 1570, 1520, 1260, 1200, 1170, 1125, 995; ms: m/z 276 (M^+), 275, 261, 248, 247, 231, 221, 220, 218, 203, 189, 176, 175, 162, 161.

Anal. Calcd. for $C_{12}H_{12}N_4S_2$: C, 52.15; H, 4.38. Found: C, 51.83; H, 4.65.

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