S-SUBSTITUTED DERIVATIVES OF 8-CHLORO-6-(2-CHLOROPHENYL)-1-MERCAPTOMETHYL--4*H*-*s*-TRIAZOLO[4,3-*a*]-1,4-BENZODIAZEPINE; SYNTHESIS AND PHARMACOLOGY*

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Reactions of 7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-thione (*XVIII*) and its 5-(2-chlorophenyl) analogue *XIX* with hydrazides of methylthio-, ethylthio-, cyclohexylthio-, phenylthio-, 4-tolylthio-, 4-chlorophenylthio-, benzylthio-, S-(2-dimethylaminoethyl)thio-, 2-furfurylthio- and 3-pyridylmethylthioacetic acid in boiling butanol gave substance *VII* and the title compounds *VIII*—*XVII*. The synthesis of hydrazides *XXVIII*—*XXXII* is described. The compounds prepared are very little toxic, have strong discoordinating activity and are very potent as anticonvulsant agents. In this line they are substantially more active than alprazolam (*II*) and are not far behind triazolam (*III*).

In the preceding communication[1] we described the synthesis of several derivatives of 4*H*-s-triazolo[4,3-*a*]-1-benzazepine which revealed central depressant and anticonvulsant effects only in relatively high doses. From this point of view they are evidently much less interesting than the suitably substituted 4*H*-*s*-triazolo[4,3-*a*]--1,4-benzodiazepine derivatives whose discovery was announced almost simultaneously by the research teams of the companies Takeda[2,3] and Upjohn[4,5], which were successively joined by Ciba-Geigy[6], Hoffmann-La Roche[7] and further laboratories[8–10]. The practical results of the first phase of research in this area are represented by the introduced anxiolytic agents estazolam (*I*) (refs[11–14]) and alprazolam (*II*) (ref.[15,16]) and further by the sovereign hypnotic agent triazolam (*III*) (refs[15,17–20]); two review articles[21,22] summarize the work done by the Upjohn team. The next phase is characterized by systematic manipulation with the structures of the basic compounds *I*—*III* and by studies of the structure–activity relationships; much effort was devoted to variation of substituents in positions 1 (refs[23–26]), 4 (refs[27,28]) and 6 (ref.[28]). The results are the experimental agents "GP 55129" (*IV*) (refs[29–31]) as an anxiolytic, adinazolam (*V*) (refs[29,32]) as and antidepressant and anxiolytic, and "U-37.576" (*VI*) (refs[29,33,34]) as an orexigenic agent.

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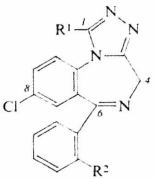
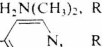
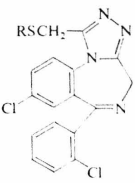


I, $R^1 = R^2 = H$
II, $R^1 = CH_3$, $R^2 = H$
III, $R^1 = CH_3$, $R^2 = Cl$
IV, $R^1 = CH_2OH$, $R^2 = H$

V, $R^1 = CH_2N(CH_3)_2$, $R^2 = H$
VI, $R^1 =$  , $R^2 = H$
VII, $R^1 = CH_2SCH_3$, $R^2 = H$

The structure–activity relations led to the recognition of the following conclusions: (*a*) For attaining a high degree of the central depressant and anticonvulsant activity, the presence of a suitable substituent in position 8 of the skeleton is indispensable (atom of chlorine or bromine, nitro or trifluoromethyl group), (*b*) The presence of a specific substituent (atom of chlorine or fluorine) in the *ortho*-position of the benzene nucleus in position 6 of the skeleton is very useful; compounds unsubstituted in this position are considerably less active than the *o*-chloro derivatives. (*c*) Any substitution in position 4 leads to a reduction of activity. (*d*) The high degree of activity is preserved with various substitution in position 1 of the skeleton. In connection with our systematic studies of the sulfur-containing neurotropic and psychotropic agents we considered useful to contribute to the knowledge of the influence of sulfur-containing substituents in position 1 in the series under discussion on the activity. The literature[23] described in this line the 1-mercapto, 1-methylthio and 1-(2-dimethylaminoethyl)thio derivatives, lacking, however, the very important *ortho*-substituent on the benzene nucleus in position 6. In molecules of these compounds, the sulfur atom is bound directly to the carbon atom $C_{(1)}$ of the skeleton. The object of our investigation were compounds in whose molecules the sulfur atom is connected to the carbon $C_{(1)}$ of the skeleton through a methylene group. We are thus dealing with S-substituted 8-chloro-6-(2-chlorophenyl or phenyl)-1-mercaptomethyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines of formulae *VII*–*XVII* whose synthesis and pharmacological properties are being described in the present communication. Only after termination of our experimental work there have been published reports on patent applications[10] describing compounds corresponding to our general formula but having R = hydrogen atom, alkoxycarbonyl, acyl, alkylthio, aralkylthio, arylthio or aminothio residues. Only in the table of pharmacological activities of these compounds in a preliminary communication[35] there was also mentioned compound *VIII* without any data on the synthetic method and without the usual chemical characterization.

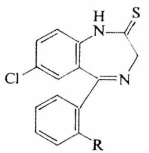


VIII, R = CH_3
IX, R = C_2H_5
X, R = 
XI, R = C_6H_5
XII, R = 

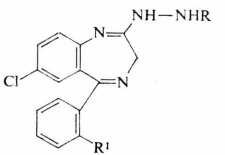
XIII, R = 
XIV, R = $CH_2C_6H_5$
XV, R = $CH_2CH_2N(CH_3)_2$
XVI, R = CH_2 
XVII, R = CH_2 

Our synthesis of compounds *VII*–*XVII* was preceded by the preparation of compound *III* considered a suitable model experiment, using the most accessible method[4,15] consisting in a reaction of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*XIX*) (ref.[15,36]) with acethydrazide[37]. When carrying out the reaction in boiling butanol[4,15], compound *III* was obtained in a yield of 67% and in the course of purifying the crude product there were separated 13% of a more polar impurity on the basis of its insolubility in boiling dichloromethane. This compound was identified as the acetylhydrazine derivative *XXII*, which was designated in the literature[4,15] as being an intermediate of the transformation of the thione *XIX* to compound *III* but it never was prepared in a pure state. For comparison it has now been synthesized by a reaction of the hydrazine derivative *XX* (ref.[13]) with acetic anhydride in chloroform, *i.e.* similarly like described for compound *XXI* (ref.[13]). Using boiling pyridine as the medium for the reaction of the thione *XIX* with acethydrazide. compound *III* was obtained in a yield of 63% and the purification procedure of the crude product led to separation of 8% of a less polar impurity which was insoluble in boiling 2-propanol. This compound was identified as the symmetrically disubstituted hydrazine *XXIV*. For confirming this structure, the compound was also prepared by a thermic reaction from the hydrazine derivative *XX* (ref.[13]) which takes place already during his recrystallization from a boiling mixture of chloroform and ethanol. In a similar manner the preparation of its dechloro analogue *XXIII* (ref.[12]) has been described. The preparation of the starting thione *XIX* was modified by decreasing the quantity of phosphorus pentasulfide used in the reaction with 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-

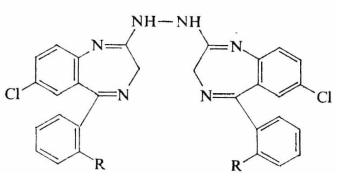
-2-one[38]; this change proved that more than one sulfur atom in the molecule of phosphorus pentasulfide participates in the reaction and this modification led to a substantial increase of the yield. On the other hand, the use of an excess of phosphorus pentasulfide decreased the yield. A similar modification has now been used also in the preparation of thione *XVIII* (ref.[15,36]) from 7-chloro-5-phenyl-1,3-dihydro--1,4-benzodiazepin-2-one[39].



XVIII, R = H
XIX, R = Cl



XX, R = H, R¹ = Cl
XXI, R = $COCH_3$, R¹ = H
XXII, R = $COCH_3$, R¹ = Cl



XXIII, R = H
XXIV, R = Cl

Compounds *VII* and *VIII* were obtained by reactions of the thiones *XVIII* and *XIX* with methylthioacethydrazide[40] in boiling butanol. Compounds *IX*–*XVII* were prepared similarly by reactions of the thione *XIX* with hydrazides of ethylthioacetic[40,41], cyclohexylthioacetic (*XXIX*), phenylthioacetic[40,42], 4-tolylthioacetic[40], 4-chlorophenylthioacetic[40], benzylthioacetic[40], S-(2-dimethylaminoethyl)-thioacetic (*XXX*), 2-furfurylthioacetic (*XXXI*) and 3-pyridylmethylthioacetic acid (*XXXII*). The hydrazides *XXIX*–*XXXII* together with butylthioacethydrazide (*XXVIII*) (its reaction with the thione *XIX* did not lead to a crystalline product) were obtained by reactions of hydrazine hydrate with ethyl esters of butylthioacetic[43], cyclohexylthioacetic[44], S-(2-dimethylaminoethyl)thioacetic (*XXV*), 2-furfurylthioacetic (*XXVI*) and 3-pyridylmethylthioacetic acid (*XXVII*) at 100°C. In an attempt at crystallizing the hydrazide *XXXI* from acetone there was obtained N,N′-bis-(2-furfurylthioacetyl)hydrazine (*XXXIII*) formed under the cleavage of hydrazine –

evidently in the form of acetone hydrazone. The new esters *XXV–XXVII* resulted from reactions of the sodium salts of 2-dimethylaminoethanethiol[45], 2-furylmethanethiol[46] and 3-pyridylmethanethiol[47] with ethyl chloroacetate in boiling ethanol. Compounds *VII–XVII* are assembled in Table I with the usual experimental data. The Experimental brings as an example the description of preparation of compound *XVI*.

$RSCH_2COOC_2H_5$

XXV, $R = CH_2CH_2N(CH_3)_2$

XXVI, $R = CH_2$–(2-furyl)

XXVII, $R = CH_2$–(3-pyridyl)

$RSCH_2CONHNH_2$

XXVIII, $R = (CH_2)_3CH_3$

XXIX, $R =$ –(cyclohexyl)

XXX, $R = CH_2CH_2N(CH_3)_2$

XXXI, $R = CH_2$–(2-furyl)

XXXII, $R = CH_2$–(3-pyridyl)

XXXIII

Compounds *VII–XVII* were pharmacologically evaluated by a series of tests in mice oriented to the central depressant and anticonvulsant activity; they were administered orally. The results are assembled in Table II which includes alprazolam (*II*) (refs[15,16]) and triazolam (*III*) (ref.[20]) as standards. With regard to the fact that compounds *XIX*, *XXII* and *XXIV* have to be considered as probable impurities of triazolam (*III*) their pharmacological properties are also of interest and therefore they also were included in Table II. All compounds tested are characterized by a very low toxicity; none of them was lethal in the maximum administered dose of 1 g/kg; toxic effects appeared already in doses of 100–200 mg/kg in the form of central depression, ataxia and exceptionally loss of the righting reflex. The discoordinating activity was evaluated in the rotarod test; the Table gives the medium effective doses (ED_{50}) at the time of maximum effect which brought about ataxia in 50% animals. As a nonspecific criterion of the central depressant activity, the potentiation of the thiopental sleeping time was examined; the threshold doses (ED) which prolong with statistical significance the duration of sleep elicited by thiopental are given. The inhibition of the spontaneous locomotor activity was used as a further criterion of the central depressant activity and it was evaluated by the photo-cell method of Dews; the medium effective doses (D_{50}) decreasing the motility to 50% of the

TABLE I

S-Substituted 8-Chloro-6-(2-chlorophenyl and phenyl)-1-mercaptomethyl-4*H*-*s*-triazolo[4,3-*a*]--1,4-benzodiazepines *VII*—*XVII*

Compound (yield %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found				
			% C	% H	% Cl	% N	% S
VII	172—173[a]	$C_{18}H_{15}ClN_4S$	60·92	4·27	9·99	15·79	9·03
(65)	(ethyl acetate)	(354·9)	61·14	4·35	9·83	15·38	9·20
VIII	204—205[b]	$C_{18}H_{14}Cl_2N_4S$	55·53	3·62	18·22	14·39	8·24
(74)	(ethyl acetate)	(389·3)	55·72	3·61	18·01	14·54	8·07
IX	129—130[c]	$C_{19}H_{16}Cl_2N_4S$	56·58	4·00	17·58	13·89	7·95
(79)	(benzene–hexane)	(403·3)	56·02	4·05	17·43	13·76	7·88
X	150—151[d]	$C_{23}H_{22}Cl_2N_4S$	60·39	4·85	15·50	12·25	7·01
(59)	(benzene–hexane)	(457·4)	60·75	4·90	15·52	12·41	6·93
XI	138—140[e]	$C_{23}H_{16}Cl_2N_4S$	61·20	3·58	15·71	12·41	7·10
(67)	(benzene–ethyl acetate–hexane)	(451·4)	61·34	3·53	15·45	12·18	6·98
XII	199—200[f]	$C_{24}H_{18}Cl_2N_4S$	61·93	3·90	15·24	12·04	6·89
(71)	(benzene–hexane)	(465·4)	61·82	3·83	15·50	12·16	6·98
XIII	198—199[g]	$C_{23}H_{15}Cl_3N_4S$	56·86	3·11	21·90	11·53	6·60
(62)	(benzene–hexane)	(485·8)	56·68	3·15	21·72	11·66	6·84
XIV	168—169[h]	$C_{24}H_{18}Cl_2N_4S$	61·93	3·90	15·24	12·04	6·89
(80)	(ethyl acetate–hexane	(465·4)	61·63	4·03	15·55	12·10	6·62
XV[i]	85—86[j]	$C_{21}H_{21}Cl_2N_5S$	59·40	4·97	14·61	14·42	6·60
(84)	(benzene–hexane)	$+ 0·5\ C_6H_6$	60·02	5·11	14·58	14·37	6·40
		(485·4)					
XVI[k]	154—155	$C_{22}H_{16}Cl_2N_4OS$	58·03	3·54	15·57	12·31	7·04
(77)	(benzene–hexane)	(455·4)	57·92	3·98	15·54	12·23	7·22
XVII	149—150[l]	$C_{23}H_{17}Cl_2N_5S$	59·23	3·67	15·21	15·02	6·87
(77)	(benzene–hexane)	(466·4)	59·49	3·78	15·26	14·66	7·09
XVII·2 HCl[m]	197—199	$C_{23}H_{19}Cl_4N_5S$	50·38	3·68	25·86	12·77	5·85
	(ethanol–ether)	$+ 0·5\ H_2O$	50·45	3·62	25·83	12·93	6·43
		(548·3)					

[a] UV spectrum: λ_{max} 249 nm (log ε 4·19); IR spectrum: 700, 748, 780, 815, 831, 891 (5 and 2 adjacent and solitary Ar—H), 1 488, 1 549, 1 569, 1 599, 3 015, 3 038 (Ar), 1 611 cm^{-1} (C=N); ^1H NMR spectrum: δ 7·80 (d, J = 8·0 Hz, 1 H, 10-H), 7·20—7·70 (m, 7 H, remaining ArH), 5·44 and 4·05 (ABq. J = 12·0 Hz, 2 H, CH_2 in position 4), 4·44 and 3·84 (ABq, J = 15·0 Hz, 2 H, 1-CH_2S), 2·04 (s, 3 H, SCH_3). [b] UV spectrum: inflexes at 250 nm (log ε 4·11) and 295 nm (3·19); IR spectrum: 749, 821, 848, 864 (4 and 2 adjacent and solitary Ar—H), 1 489, 1 530, 1 568,

control value are given. The anticonvulsant activity was evaluated by two tests: (*a*) Antagonization of the convulsant and lethal effects of pentetrazole and (*b*) antagonization of the convulsant effect of the electroshock. In the latter case the medium protective doses (PD_{50}) are given which decrease the appearance of convulsions to 50% in comparison with the control group.

The compounds *VII*–*XVII* have very high anticonvulsant and considerable central depressant activity. The are substantially more active than alprazolam (*II*) but they do not attain the extremely high activity of triazolam (*III*) in the tests of anticonvulsant

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1 572, 2 990, 3 020, 3 035 (Ar), 1 610, 1 618 cm^{-1} (C=N in conjugation); ^{1}H NMR spectrum: δ 7·80 (d, J = 8·5 Hz, 1 H, 10-H), 7·58 (q, J = 8·5; 2·0 Hz, 1 H, 9-H), 7·20–7·60 (m, 4 H, 4 ArH of 2-chlorophenyl), 7·12 (d, J = 2·0 Hz, 1 H, 7-H), 5·50 and 4·10 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·05 and 3·75 (ABq, J = 15,0 Hz, 2 H, 1-CH_2S), 2·12 (s, 3 H, SCH_3). [c] IR spectrum (KBr): 750, 824, 885, 891 (4 and 2 adjacent and solitary Ar–H), 1 488, 1 530, 1 568, 1 590, 3 030 (Ar), 1 612 cm^{-1} (C=N in conjugation). [d] UV spectrum: λ_{max} 225 nm (log ε 4·54), infl. at 251 nm (4·07); IR spectrum: 730, 746, 760, 818, 836, 892 (4 and 2 adjacent and solitary Ar–H), 1 488, 1 533, 1 570, 1 592, 3 030, 3 050, 3 065 (Ar), 1 620 cm^{-1} (C=N in conjugation); ^{1}H NMR spectrum: δ 7·96 (d, J = 8·5 Hz, 1 H, 10-H), 7·30–7·80 (m, 5 H, 4 ArH of 2-chlorophenyl and 9-H), 7·21 (d, J = 2·5 Hz, 1 H, 7-H), 5·59 and 4·22 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·22 and 3·86 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S), 2·90 (m, 1 H, S–CH of cyclohexyl), 1·00–2·20 (m, 10 H, 5 CH_2 of cyclohexyl). [e] IR spectrum (KBr): 690, 740, 750, 824, 883, 890 (5, 4 and 2 adjacent and solitary Ar–H), 1 484, 1 533, 1 568, 1 580, 1 590, 3 030 (Ar), 1 611 cm^{-1} (C=N in conjugation); ^{1}H NMR spectrum: δ 7·00–7·80 (m, 12 H, ArH), 5·48 and 4·12 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·50 and 4·28 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S). [f] IR spectrum: 750, 756, 770, 780, 810, 883 (4 and 2 adjacent and solitary Ar–H), 1 483, 1 530, 1 568, 1 590, 3 035 (Ar), 1 617 cm^{-1} (C=N in conjugation); ^{1}H NMR spectrum: δ 6·90–7·80 (m, 11 H, ArH), 5·48 and 4·12 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·45 and 4·18 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S), 2·21 (s, 3 H, $ArCH_3$). [g] IR spectrum: 757, 770, 780, 820, 844, 850, 890 (4 and 2 adjacent and solitary ArH), 1 475, 1 489, 1 530, 1 569, 1 598, 3 038, 3 065 (Ar), 1 618 cm^{-1} (C=N in conjugation); ^{1}H NMR spectrum: δ 7·00–7·80 (m, 11 H, ArH), 5·50 and 4·12 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·48 and 4·22 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S). [h] ^{1}H NMR spectrum: δ 7·00–7·80 (m, 11 H, ArH), 5·50 and 4·10 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 3·95 and 3·62 (ABq, J = 15·0 Hz, 2 H, $ArCH_2$S), 3·82 and 3·65 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S). [i] Solvate with 0·5 C_6H_6. [j] UV spectrum: λ_{max} 220·5 nm (log ε 4·55), infl. 252 nm (4·02); IR spectrum: 750, 825, 855, 882 (4 and 2 adjacent and solitary Ar–H), 1 482, 1 530, 1 566, 1 588, 3 030 (Ar), 1 600 cm^{-1} (C=N); ^{1}H NMR spectrum: δ 7·82 (d, J = = 8·5 Hz, 1 H, 10-H), 7·20–7·70 (m, 8 H, 9-H, 4 ArH of 2-chlorophenyl and 3 ArH of 0·5 C_6H_6), 7·12 (d, J = 2·5 Hz, 1 H, 7-H), 5·50 and 4·12 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·12 and 3·75 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S), 2·60 (m, 4 H, NCH_2CH_2S), 2·19 (s, 6 H, CH_3NCH_3). [k] See Experimental. [l] UV spectrum: inflexes at 217 nm (log ε 4·57), 252 nm (4·07); IR spectrum: 720, 750, 767, 820, 828, 891 (4 and 2 adjacent and solitary Ar–H and pyridine C–H), 1 491, 1 537, 1 570, 1 590, 3 036 (Ar), 1 610 cm^{-1} (C=N in conjugation); ^{1}H NMR spectrum: δ 8·62 (d, J = 2·0 Hz, 1 H, 2-H in pyridyl), 8·48 (q, J = 5·0; 2·0 Hz, 1 H, 6-H in pyridyl), 7·10 to 7·90 (m, 9 H, remaining ArH), 5·50 and 4·12 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 3·95 and 3·61 (ABq, J = 15·0 Hz, 2 H, pyridyl-CH_2S), 3·88 and 3·62 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S). [m] Hemihydrate.

action towards electroshock, inhibition of locomotor activity, thiopental sleep potentiation and the rotarod test. Out of the possible impurities of the triazolam substance the acetylhydrazine derivative *XXII* is considerably active, especially in the tests of the anticonvulsant effects towards pentetrazole, inhibition of locomotor activity and thiopental potentiation. The thione *XIX* has some central depressant and anticonvulsant activity but a rather low one in comparison with the other compounds. The N,N'-disubstituted hydrazine *XXIV* is practically devoid of activity.

The compounds *II*, *VII*, *VIII*, *X*, *XIV*—*XVII*, *XXII*, *XXIV* and *XXXIII* were also tested for antimicrobial activity *in vitro*. The used microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Staphylococcus pyogenes aureus*, *X* 50; *Mycobacterium tuberculosis* H37Rv, *XIV* 100, *XV* 100, *XVII* 100; *Trichophyton mentagrophytes*, *X* 50, *XIV* 50, *XVI* 50, *XVII* 50. All compounds were inactive towards *Streptococcus* β-*haemolyticus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Saccharomyces pasterianus*, *Candida albicans* and *Aspergillus niger*.

TABLE II

Discoordinating, central depressant and anticonvulsant effects of substances *VII*—*XVII* and of some related compounds (all doses in mg/kg orally)

Compound	Rotarod ED_{50}	Thiopental potentiation ED	Inhibition of locomotor activity D_{50}	Anticonvulsant activity	
				pentetrazole ED	electroshock PD_{50}
II	1·0	0·5 —1·0	0·1—0·5	0·5—1·0	—
III	0·13	0·01—0·1	0·009	0·03	0·032
VII	5·3	0·3	10	3	0·14
VIII	1·0	0·03—0·1	<0·3	0·1	0·12
IX	1·9	—	—	—	0·09
X	> 1·0	—	—	>0·1	0·19
XI	0·8	—	0·23	0·1	0·07
XII	0·35	—	—	0·01—0·1	0·19
XIII	0·27	—	—	0·01—0·1	0·23
XIV	0·40	—	>0·1	0·017	0·31
XV	1·1	—	—	>0·1	0·26
XVI	0·34	—	—	0·01—0·1	0·23
XVII	0·56	—	—	0·1	0·15
XIX	100	10—50	1—10	5—10	300
XXII	5·0	1·0—5·0	0·1—1·0	0·05	—
XXIV	>300	>300	10	100—300	>300

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (mostly in C^2H_3Cl) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with the MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel. The column chromatography was carried out on neutral Al_2O_3 (activity II).

7-Chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-thione (*XVIII*)

A mixture of 55·3 g (0·2 mol) 7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-one[39], 22·2 g (0·1 mol) P_2S_5 and 400 ml pyridine was stirred and refluxed for 30 min under nitrogen and stirred for another 1 h without heating. After cooling the solution was poured into a stirred solution of 630 g NaCl in 2·1 l water, the mixture was cooled to 5°C and the separated oil crystallized after 10 min stirring. After 1 h it was filtered, washed with water and dried *in vacuo*. This crude product was dissolved in 3 l dichloromethane, the solution was filtered and the filtrate chromatographed through a column of 200 g Al_2O_3. Elution with dichloromethane gave 43·8 g product which was boiled with 200 ml ethanol and filtered after standing overnight at room temperature; 38·1 g (67%), m.p. 233–238°C. Lit.[15,36], yield 41 and 40%, m.p. 236° and 244 to 246°C, respectively.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione (*XIX*)

A mixture of 152·2 g (0·5 mol) 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepi-2-one[38], 88·8 g ((0·4 mol) P_2S_5 and 880 ml pyridine was processed similarly like in the preceding case. The crude product was dissolved in 150 ml dimethylformamide, the solution was filtered and the filtrate poured into 550 ml boiling ethanol. It was allowed to stand overnight at 0°C, filtered, washed with ethanol and hexane, and dried; 104 g (65%), m.p. 240–242°C. UV spectrum: λ_{max} 303 nm (log ε 4·40). IR spectrum: 751, 783, 839, 880 (4 and 2 adjacent and solitary Ar—H), 1 380 (CS—NH), 1 477, 1 530, 1 584, 3 068, 3 116 (Ar), 1 615 (C=N), 2 660 cm^{-1} (NH···S). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 12·65 (s, 1 H, NH), 7·65 (q, J = 8·5; 2·0 Hz, 1 H, 8-H), 7·50 (m, 4 H, 4 ArH of 2-chlorophenyl), 7·39 (d, J = 8·5 Hz, 1 H, 9-H), 6·95 (d, J = 2·0 Hz, 1 H, 6-H), 4·63 (s, 2 H, CH_2 in position 3), Lit[15,36], yield 35 and 40%, m.p. 240–241°C and 251–253°C, respectively.

8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*III*)

A) A mixture of 10·8 g *XIX*, 6·6 g acethydrazide[37] and 300 ml 1-butanol was refluxed for 5 h under nitrogen and evaporated *in vacuo*. The residue was suspended in 150 ml water, the suspension allowed to stand overnight, the solid was filtered, washed with water and dried *in vacuo*. The crude product was dissolved in 900 ml boiling dichloromethane and 1·6 g undissolved by-product A were filtered off. The filtrate was evaporated and the residue was dissolved in 300 ml boiling 2-propanol. It was filtered again and from the filtrate 190 ml 2-propanol were distilled off. The residue was allowed to crystallize for 24 h in a refrigerator; 7·72 g (67%), m.p. 223 to 225°C. According to thin-layer chromatography of this substance with densitometric evaluation

it still contains 0·13% of the more polar by-product A. Mass spectrum m/z (%): 342·0455 (M^+ corresponding to $C_{17}H_{12}Cl_2N_4$, 100%), 313 (80), 278 (40), 238 (60), 202 (40). UV spectrum: λ_{max} 290 nm (log ε 3·20), inflex at 275 nm (3·93). IR spectrum (KBr): 760, 826, 849, 882 (4 and 2 adjacent and solitary Ar—H), 1 489, 1 550, 1 569, 1 594, 3 060, 3 108 (Ar), 1 620 cm^{-1} (C=N). ^1H NMR spectrum: δ 7·00—7·70 (m, 7 H, ArH), 5·48 and 4·15 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 2·60 (s, 3 H, 1-CH_3). Lit.[15], m.p. 223—225°C.

Crystallization from dioxane proved a suitable purification procedure leading, however, to a new crystal modification, m.p. 237—239°C. By crystallization from a mixture of chloroform and ethanol, a product melting at 241·5—243°C was obtained. This modification crystallizes in little needles which — when heated — change at 210—220°C the form and become thick prisms, melting then at the temperatures given. For $C_{17}H_{12}Cl_2N_4$ (343·2) calculated: 59·48% C, 3·53% H, 20·66% Cl, 16·33% N; found: 59·53% C, 3·54% H, 20·50% Cl, 16·84% N.

B) A stirred mixture of 10·8 g *XIX*, 6·6 g acethydrazide[37] and 70 ml pyridine was refluxed for 5 h under nitrogen. After cooling to 25°C it was poured into 1 l water, the suspension was stirred for 15 min and the crude product (10·6 g) was filtered and dried *in vacuo*. A sample was completely soluble in dichloromethane. It was dissolved in 360 ml boiling 2-propanol and 0·8 g of the less polar by-product B were filtered off. From the filtrate 270 ml 2-propanol were distilled off and the residue was allowed to crystallize for 24 h at 5°C; 7·3 g (63%), m.p. 223—225°C. This melting point is precisely identical with that of the product obtained under *A*) and with the literature[15] value but according to thin-layer chromatography and densitometry it contains 0·21% by-product A and 6·8% by-product B.

N-Acetyl-N′-[7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]hydrazine (*XXII*)

A) A solution of 6·70 g *XX* (ref.[13]) in 160 ml chloroform was stirred and treated over 10 min at 20°C with 2·6 g acetic anhydride and the stirring was continued for 1 h. After cooling with ice and water the product was filtered, washed with a mixture of chloroform and hexane and dried; 7·3 g (96%), m.p. 194—196°C. Crystallization from ethyl acetate gave the analytical sample melting at 195—196°C which proved to be the hemihydrate of *XXII*. Mass spectrum (m/z): 360 (M^+ corresponding to $C_{17}H_{14}Cl_2N_4O$). UV spectrum: inflexes at 280 nm (log ε 4·21), 315 nm (3·68) and 340 nm (3·35). IR spectrum: 745, 764, 781, 838, 898 (4 and 2 adjacent and solitary Ar—H), 1 495, 3 070 (Ar), 1 580, 1 640 (CONH), 3 220 cm^{-1} (NH, H_2O). For $C_{17}H_{14}$. Cl_2N_4O + 0·5 H_2O (370·2) calculated: 55·13% C, 4·09% H, 19·14% Cl, 15·12% N; found: 54·82% C, 4·00% H, 19·53% Cl, 15·20% N. This compound was mentioned in a paper[48] describing the synthesis of [1-^{14}C]-*III* and for the labeled substance a m.p. of 198—200°C with decomposition was given.

B) The by-product A obtained in the preparation of *III* under *A*) (1·6 g, 13%) was crystallized from ethyl acetate, m.p. 193—194°C. It proved identical with the compound described under *A*) (mixed melting point, analysis, spectra, TLC).

N,N′-Bis[7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]hydrazine (*XXIV*)

A) *XX* (ref.[13]) (8·3 g) was heated for a short time with a boiling mixture of 70 ml chloroform and 20 ml ethanol. The solution obtained was diluted with 120 ml hexane and allowed to crystallize overnight in a refrigerator; 3·20 g, m.p. 257—258°C. Mass spectrum (m/z): 604·0505 (M^+ corresponding to $C_{30}H_{20}Cl_4N_6$). UV spectrum: λ_{max} 305 nm (log ε 4·53). IR spectrum (KBr): 763, 831, 874 (4 and 2 adjacent and solitary Ar—H), 1 362 (=C—N), 1 494, 1 606, 3 065 (Ar),

1 640 (C=N), 3 345 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·42 (bs, 2 H, NH—NH), 7·40 (bs, 12 H, 8,9,8′,9′-H_4 and 8 ArH of two 2-chlorophenyls), 6·75 (d, 2 H, 6,6′-H_2), 4·45 (bs, 4 H, 3,3,3′,3′-H_4). For $C_{30}H_{20}Cl_4N_6$ (606·3) calculated: 59·44% C, 3·32% H, 23·38% Cl, 13·86% N; found: 58·78% C, 3·27% H, 23·58% Cl, 13·62% N.

B) The by-product B obtained in the preparation of *III* under *B*) (0·8 g, 8%) was crystallized from a mixture of chloroform and hexane, m.p. 256—258°C. It proved identical with *XXIV* obtained under *A*) (analysis, spectra, TLC).

Ethyl S-(2-Dimethylaminoethyl)thioacetate (*XXV*)

2-Dimethylaminoethanethiol[47] (15·1 g) was added to a solution of sodium ethoxide (from 3·3 g Na and 70 ml ethanol). The stirred solution was treated under cooling with 17·5 g ethyl chloroacetate, refluxed for 1 h and after cooling, filtered. The filtrate was evaporated, the residue was dissolved in benzene and the solution was washed with water. After drying with $MgSO_4$ it was distilled; 16·8 g (61%), b.p. 122°C/2 kPa, n_D^{22} 1·4711. ^1H NMR spectrum: δ 4·19 (q, 2 H, OCH_2), 3·21 (s, 2 H, SCH_2CO), 2·40—2·80 (m, 4 H, NCH_2CH_2S), 2·21 (s, 6 H, CH_3NCH_3), 1·30 (t, J = 7·0 Hz, 3 H, CH_3 of ethyl). For $C_8H_{17}NO_2S$ (191·3) calculated: 50·23% C, 8·96% H, 7·32% N, 16·76% S; found: 50·12% C, 9·11% H, 7·64% N, 16·98% S.

Hydrochloride, m.p. 85—86°C (ethanol–ether). For $C_8H_{18}ClNO_2S$ (227·8) calculated: 42·19% C, 7·97% H, 15·57% Cl, 6·15% N, 14·07% S; found: 42·07% C, 7·89% H, 15·52% Cl, 6·14% N, 14·79% S.

Ethyl 2-Furfurylthioacetate (*XXVI*)

Was prepared similarly from 6·3 g 2-furylmethanethiol[46], sodium ethoxide (3·3 g Na and 70 ml ethanol) and 17·5 g ethyl chloroacetate; 24·6 g (86%), b.p. 145—146°C/2·4 kPa, n_D^{25} 1·5093. For $C_9H_{12}O_3S$ (200·2) calculated: 53·98% C, 6·04% H, 16·01% S; found: 53·67% C, 6·07% H, 15·94% S.

Ethyl 3-Pyridylmethylthioacetate (*XXVII*)

Was prepared similarly from 18·0 g 3-pyridylmethanethiol[47], sodium ethoxide (3·3 g Na and 70 ml ethanol) and 17·5 g ethyl chloroacetate; 27·0 g (89%), b.p. 145—148°C/0·2 kPa, n_D^{22} 1·5390. For $C_{10}H_{13}NO_2S$ (211·3) calculated: 56·85% C, 6·20% H, 6·63% N, 15·17% S; found: 56·80% C, 6·13% H, 6·88% N, 14·87% S.

Picrate, m.p. 86—87°C (ethanol–acetone). For $C_{16}H_{16}N_4O_9S$ (440·4) calculated: 43·64% C, 3·66% H, 12·72% N, 7·28% S; found: 43·78% C, 3·57% H, 13·04% N, 7·20% S.

Butylthioacethydrazide (*XXVIII*)

A homogeneous mixture of 22·0 g ethyl butylthioacetate[43] and 8·5 ml 100% hydrazine hydrate was heated for 2 h to 100°C and for further 2 h to 100°C *in vacuo*. The melt crystallized after cooling and was filtered after treatment with 50ml hexane; 18·0 g (86%), m.p. 37—38°C (benzene–hexane). IR spectrum: 1 485, 1 585, **1 660** (CONH), 3 120, 3 250 cm^{-1} (NH, NH_2). For $C_6H_{14}N_2OS$ (162·3) calculated: 44·41% C, 8·70% H, 17·27% N, 19·76% S; found: 44·65% C, 8·67% H, 17·30% N, 19·41% S.

Cyclohexylthioacethydrazide (*XXIX*)

Was prepared similarly from 26·0 g ethyl cyclohexylthioacetate[44] and 8·5 ml $N_2H_4.H_2O$; 24·0 g (almost theoretical yield) of viscous oil. For characterization it was transformed by neutralization with HCl in ethanol to the hydrochloride which crystallized from a mixture of ethanol and ether and melted at 122—123°C. For $C_8H_{17}ClN_2OS$ (224·8) calculated: 42·75% C, 7·62% H, 15·78% Cl, 12·46% N, 14·26% S; found: 42·48% C, 7·57% H, 16·02% Cl, 12·47% N, 14·26% S.

S-(2-Dimethylaminoethyl)thioacethydrazide (*XXX*)

Was prepared similarly from 15·8 g *XXV* and 5·5 ml $N_2H_4.H_2O$; 14·7 g (100%) oil, b.p. 144°C/40 Pa, n_D^{22} 1·5345. IR spectrum (film): 1 535, **1 655** (CONH), 2 775, 2 820 (dimethylamino), 3 030, 3 300 cm^{-1} (NH, NH_2). ^1H NMR spectrum: δ 9·40 (bs, 1 H, CONH), 4·00 (bs, 2 H, NH_2), 3·30 (s, 2 H, SCH_2CO), 2·65 (m, 4 H, NCH_2CH_2S), 2·30 (s, 6 H, CH_3NCH_3). For $C_6H_{15}N_3OS$ (177·3) calculated: 40·65% C, 8·52% H, 23·71% N; found: 40·52% C, 8·62% H, 24·04% N.

2-Furfurylthioacethydrazide (*XXXI*)

Similarly like in the preceding cases from 25·0 g *XXVI* and 8·7 ml $N_2H_4.H_2O$; 23·3 g (100%) oil. Neutralization with HCl in ethanol gave the hydrochloride, m.p. 101—102°C (ethanol–ether). For $C_7H_{11}ClN_2O_2S$ (222·7) calculated: 37·75% C, 4·98% H, 15·92% Cl, 12·58% N, 14·40% S; found: 37·87% C, 5·23% H, 15·56% Cl, 12·86% N, 14·10% S.

In an attempt at crystallizing oily *XXXI* from boiling acetone, conversion to N,N′-bis(2-furfurylthioacetyl) hydrazine (*XXXIII*) took place; m.p. 107—108°C (aqueous ethanol). IR spectrum: 730, 800 (C—H of furan), 1 480, 1 502 (furan), 1 601 (RCONHNHCOR), 3 205 cm^{-1} (NH). ^1H NMR spectrum: δ 9·40 (bs, 2 H, NH—NH), 7·31 (m, 2 H, 5,5′-H_2 of the two furyls), 6·25 (m, 4 H, remaining 4 C—H of furyls), 3·84 (s, 4 H, 2 2-furyl-CH_2S), 3·25 (s, 4 H, 2 SCH_2CO). For $C_{14}H_{16}N_2O_4S_2$ (340·3) calculated: 49·41% C, 4·74% H, 8·23% N, 18·82% S; found: 49·74% C, 4·86% H, 8·43% N, 18·98% S.

3-Pyridylmethylthioacethydrazide (*XXXII*)

Similarly like in the preceding cases from 25·0 g *XXVII* and 7·7 ml $N_2H_4.H_2O$; 23·0 g (100%) oil. Neutralization with HCl in ethanol gave the dihydrochloride, m.p. 177—178°C (aqueous ethanol). For $C_8H_{13}Cl_2N_3OS$ (270·2) calculated: 35·56% C, 4·85% H, 26·25% Cl, 15·55% N, 11·87% S; found: 35·86% C, 4·95% H, 26·15% Cl, 15·53% N, 11·60% S.

8-Chloro-6-(2-chlorophenyl)-1-(2-furfurylthiomethyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XVI*)

A mixture of 3·21 g *XIX*, 5·1 g *XXXI* and 80 ml 1-butanol was refluxed for 8 h under nitrogen and evaporated *in vacuo*. The residue was diluted with 100 ml water and extracted with 100 ml benzene. The extract was washed with water, dried with Na_2SO_4 and evaporated. The residue was chromatographed on a column of 120 g Al_2O_3 with elution starting with benzene. The first benzene fractions containing less polar impurities were discarded. Further benzene fractions and the following chloroform eluates were combined, evaporated *in vacuo*, the residue was dissolved in 10 ml warm benzene and the solution treated with 3 ml hexane. Standing overnight in a refrigerator led to crystallization of the product; 3·5 g (77%), m.p. 153—155°C. Analytical

sample, m.p. 154—155°C (benzene–hexane). UV spectrum: λ_{max} 222 nm ($\log \varepsilon$ 4·63), inflex at 252 nm (4·06). IR spectrum: 744, 838, 880 (4 and 2 adjacent, solitary Ar—H and the furan C—H), 1 490, 1 530, 1 567, 1 591, 3 020, 3 060, 3 090 (Ar), 2 610 cm^{-1} (C≡N). ^{1}H NMR spectrum: δ 7·00—7·80 (m, 8 H, ArH and the furan 5-H), 6·30 (m, 2 H, furan 3,4-H_2), 5·50 and 4·12 (ABq, J = 13·0 Hz, 2 H, CH_2 in position 4), 4·10 and 3·70 (ABq, J = 15·0 Hz, 2 H, 2-furyl-CH_2S), 3·90 and 3·68 (ABq, J = 13·0 Hz, 2 H, 1-CH_2S). Analysis, *cf.* Table I.

The other compounds described in Table I were prepared similarly. In some cases the chromatography was not necessary because the product crystallized directly after mixing with water. On the other hand it was indispensable in all cases where the starting acid hydrazides were insoluble in water. In some cases chloroform was used instead of benzene for extracting the products.

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