POTENTIAL ANXIOLYTICS AND HYPNOTICS: 1-(ALKANESULFONAMIDOALKYL)-6-ARYL-8-HALOGENO--*s*-TRIAZOLO[4,3-*a*]-1,4-BENZODIAZEPINES AND RELATED COMPOUNDS

Zdeněk VEJDĚLEK[a], Jan METYŠ[a], Jiří HOLUBEK[a], Miloš BUDĚŠÍNSKÝ[b], Emil SVÁTEK[a], Oluše MATOUŠOVÁ[a] and Miroslav PROTIVA[a]

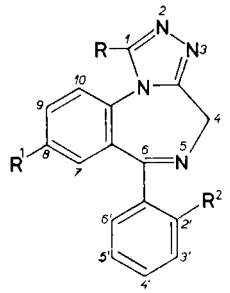
[a] *Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3 and*
[b] *Institute of Organic Chemistry and Biochemistry Czechoslovak Academy of Sciences, 166 10 Prague 6*

Received April 27th, 1987

7-Chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-thione and its 5-(2-chlorophenyl) and 7-bromo-5-(2-chlorophenyl) analogues were reacted with N-(methanesulfonyl)- and N-(ethanesulfonyl)glycine and -alanine hydrazides (*X*—*XIII*) in boiling butanol to give the title compounds *Iabc*—*IVabc*. The alanine-derived substances *IIIabc* and *IVabc* were characterized by ^{1}H NMR spectra as mixtures of two diastereoisomers. Similar reactions of 5-methylimidazole-4-carboxylic acid hydrazide (*XIV*) gave the *s*-triazolo[4,3-*a*]-1,4-benzodiazepines *Vabc* together with their ring-opened precursors *XVI* and *XVII*. The compounds prepared showed the activity profile of the anxiolytic and hypnotic 4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine derivatives.

The nature of the substituent in position 1 in molecules of 6-aryl-8-halogeno-4*H*-*s*--triazolo[4,3-*a*]-1,4-benzodiazepines has an important influence on the central (anxiolytic, sedative, hypnotic, anticonvulsant) activity of the corresponding members of the series[1]. Our previous contributions[2,3] to this topic dealt especially with alkylthiomethyls as 1-substituents. Now, we wanted to contribute to the knowledge of the influence of alkanesulfonamidoalkyl groups in position 1 of the mentioned series on the activity. The present paper describes in the first line the synthesis of twelve such compounds (*Iabc*—*IVabc*) and includes also results of their pharmacological screening.

For preparing the title compounds, we selected the method using the reaction of the corresponding 5-aryl-7-halogeno-1,3-dihydro-1,4-benzodiazepin-2-thiones with acid hydrazides in boiling butanol[4,5]. The syntheses of the hydrazides started from the hydrochlorides of glycine ethyl ester and α-alanine methyl ester[6]. The free ester bases, released by treatment with a solution of ammonia in chloroform, were used in 100% excess and were reacted with methanesulfonyl chloride and ethanesulfonyl chloride[7] in ether like described for the preparation of ethyl methanesulfonamidoacetate (*VI*) (ref.[8]). The esters *VII*—*IX*, obtained by this method were characterized



I, R = $CH_2NHSO_2CH_3$
II, R = $CH_2NHSO_2CH_2CH_3$
III, R = $CHNHSO_2CH_3$ (CH_3)
IV, R = $CHNHSO_2CH_2CH_3$ (CH_3)
V, R = 4-methyl-5-imidazolyl

In formulae *I–V*: *a*, R^1 = Cl; R^2 = H *b*, R^1 = R^2 = Cl
c, R^1 = Br; R^2 = Cl

by the IR and ^{1}H NMR spectra. Reactions of the esters *VI–IX* with concentrated hydrazine hydrate afforded the acid hydrazides *X–XIII* in good yields which, likewise, were characterized by spectra. These hydrazides were reacted with 7-chloro-5--phenyl-1,3-dihydro-1,4-benzodiazepin-2-thione[2] (series *a*), 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[2] (series *b*), and 7-bromo-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[3] (series *c*) in boiling butanol. The products *Iabc–IVabc* are assembled in Table I with the usual experimental data. Only the preparation of *IIb* is described in detail in the Experimental; differences from this example, relating especially to the isolation procedures, are mentioned in the notes to Table I.

$R^1SO_2NHCHCOOR$ (R^2)

VI, R = C_2H_5; R^1 = CH_3; R^2 = H
VII, R = R^1 = C_2H_5; R^2 = H
VIII, R = R^1 = R^2 = CH_3
IX, R = R^2 = CH_3; R^1 = C_2H_5

$R^1SO_2NHCHCONHNH_2$ (R^2)

X, R^1 = CH_3; R^2 = H
XI, R^1 = C_2H_5; R^2 = H
XII, R^1 = R^2 = CH_3
XIII, R^1 = C_2H_5; R^2 = CH_3

UV, IR, and NMR spectra of compounds *Iabc–IVabc* are assembled in Table II. Whereas the ^{1}H NMR spectra of *Iabc* and *IIabc* (the glycine series) were in agreement with the expectation, the ^{1}H NMR spectra of *IIIabc* and *IVabc* (the alanine

TABLE I

1-(Alkanesulfonamidoalkyl)-6-aryl-8-halogeno-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines

Compound[a] (yield, %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/found					
			% C	% H	% Br	% Cl	% N	% S
Ia	192–193	$C_{18}H_{16}ClN_5O_2S$	53·79	4·02	—	8·82	17·43	7·98
(57)[b]	(chloroform–ethyl acetate)	(401·9)	53·69	4·01	—	8·89	17·44	7·98
Ib	271–272[d]	$C_{18}H_{15}Cl_2N_5O_2S$	49·55	3·47	—	16·25	16·05	7·35
(60)[c]	(2-propanol)	(436·3)	49·63	3·84	—	15·98	15·93	7·09
Ic	273–274	$C_{18}H_{15}BrClN_5O_2S$	44·96	3·15	16·62	7·37	14·57	6·67
(57)[e]	(butanol)	(480·8)	45·49	3·50	16·19	7·08	14·46	6·52
IIa	201	$C_{19}H_{18}ClN_5O_2S$	54·87	4·36	—	8·53	16·84	7·71
(61)[f]	(chloroform–ethyl acetate)	(415·9)	54·28	4·45	—	8·84	16·77	7·82
IIb[g]	145–146	$C_{19}H_{17}Cl_2N_5O_2S$	50·67	3·81	—	15·75	15·55	7·12
(68)	(chloroform–ethyl acetate)	(450·3)	50·67	3·87	—	15·63	15·60	7·34
IIc	187–188	$C_{19}H_{17}BrClN_5O_2S$	46·12	3·46	16·15	7·16	14·16	6·48
(53)	(chloroform–ethyl acetate)	(494·8)	45·73	3·62	16·36	7·05	14·27	6·67

IIIa	206–207	$C_{19}H_{18}ClN_5O_2S$	54·87	4·36	—	8·53	16·84	7·71
(84)[h]	(ethanol)	(415·9)	54·46	4·67	—	8·55	16·51	7·80
IIIb	237–238	$C_{19}H_{17}Cl_2N_5O_2S$	50·67	3·81	—	15·75	15·55	7·12
(64)[i]	(chloroform–ethyl acetate)	(450·3)	50·77	3·91	—	15·64	15·50	7·31
IIIc	240–241	$C_{19}H_{17}BrClN_5O_2S$	46·12	3·46	16·15	7·16	14·16	6·48
(64)[f]	(chloroform–ethyl acetate)	(494·8)	46·40	3·64	15·92	7·34	14·00	6·71
IVa	236–237	$C_{20}H_{20}ClN_5O_2S$	55·87	4·69	—	8·25	16·29	7·46
(63)[h]	(ethanol)	(429·9)	55·85	4·75	—	8·46	16·31	7·73
IVb	221–222	$C_{20}H_{19}Cl_2N_5O_2S$	51·73	4·12	—	15·27	15·08	6·91
(66)	(chloroform–ethyl acetate)	(464·4)	51·66	4·32	—	15·29	14·72	7·20
IVc	219–220	$C_{20}H_{19}BrClN_5O_2S$	47·21	3·76	15·70	6·97	13·77	6·30
(51)	(chloroform–ethyl acetate)	(508·8)	47·15	3·91	15·30	6·78	13·79	6·40

[a] The compounds were prepared similarly like described for *IIb* in the Experimental; for UV, IR, and NMR spectra, cf. Table II. [b] The crude product was chromatographed on Al_2O_3 and the fraction obtained by elution with chloroform, containing 10% ethanol, was crystallized from ethyl acetate. [c] The crude product was crystallized from acetic acid, filtered, and washed with ethyl acetate and ether. [d] Mass spectrum: 435 (M^+, $C_{18}H_{15}Cl_2N_5O_2S$, 1·3), 420 ($C_{17}H_{12}Cl_2N_5O_2S$, 1·2), 356 ($C_{17}H_{12}Cl_2N_5$, 45), 293 (13), 239 ($C_{14}H_8ClN_2$, 11), 137 (C_7H_4ClN, 22), 111 (29), 102 (29), 88 (39), 75 (C_6H_3, 56), 45 (100). [e] It was not necessary to use extraction with dichloromethane; the product precipitated after the first evaporation by dilution of the residue with water. [f] The general method was used and chromatography of the mother liquor on Al_2O_3 afforded a second crop of product. [g] See Experimental. [h] The crude product was crystallized from ethanol. [i] The crude product was crystallized from acetic acid, the mother liquor was evaporated in vacuo, and the residue was processed by chromatography on Al_2O_3.

TABLE II

UV, IR and NMR spectra of compounds *Iabc—IVabc*

Compound	Spectra
Ia	UV: infl. 246 (4·17). IR: 696, 770, 790, 799, 808, 837, 888 (5 and 2 adjacent, and solitary Ar—H); 1 154, 1 328 (SO_2NH); 1 488, 1 538, 1 568, 1 580, 1 594, 3 010, 3 080 (Ar); 1 608 (Ar—C=N); 3 120 (NH). ^{1}H NMR (C^2HCl_3): 2·98 s, 3 H (SO_2CH_3); 4·48 s, 2 H (CH_2N in the side chain); 3·95 d, 1 H and 5·31 d, 1 H (ABq, 2 H-4, J = 13·0); 7·00—7·80 bm, 9 H (8 ArH and NH).
Ib	UV: infl. 251 (3·98). IR (KBr): 750, 760, 800, 822, 862, 890 (4 and 2 adjacent, and solitary Ar—H); 1 152, 1 323 (SO_2NH); 1 490, 1 530, 1 570, 1 590, 3 000 (Ar); 1 615 (Ar—C=N); 3 100 (NH). ^{1}H NMR (200 MHz): 2·92 s, 3 H (CH_3SO_2); 4·29 d, 1 H and 5·29 d, 1 H (2 H-4, J(4, 4) = 13·0); 4·60 bs, 2 H (NCH_2, J(CH_2, NH) = c. 2, proved by decoupling as narrowing of the half-width of CH_2-signal at irradiation of NH); 7·11 d, 1 H (H-7, J(7, 9) = 2·4); 7·41—7·64 m, 4 H (H-3′, 4′, 5′, 6′); 7·69 bs, 1 H (NH, J(NH, CH_2) = c. 2); 7·79 dd, 1 H (H-9, J(9, 7) = 2·4; J(9, 10) = 8·8); 7·96 d, 1 H (H-10, J(10, 9) = 8·8). ^{13}C NMR: 38·07 (C-4); 39·91 (CH_3SO_2); 45·79 ($NHCH_2$); 126·44, 127·44, 128·64, 129·89, 131·37, 131·60, 131·89 (7—CH=); 130·96, 131·50, 131·80, 132·23, 138·14, 151·05, 155·23, 167·23 (8>C=).
Ic	UV: 225 (4·52), infl. 250 (4·06). IR: 750, 770, 790, 808, 825, 864, 890 (4 and 2 adjacent, and solitary Ar—H); 1 155, 1 328 (SO_2NH); 1 490, 1 515, 1 532, 1 569, 1 590, 3 015, 3 070 (Ar); 1 615 (Ar—C=N); 3 100 (NH). ^{1}H NMR: 2·93 s, 3 H (SO_2CH_3); 4·60 s, 2 H (NCH_2 in the side chain); 4·29 d, 1 H and 5·29 d, 1 H (ABq, 2 H-4, J = 13·0); 7·20—8·00 m, 7 H (7 ArH).
IIa	UV: infl. 244 (4·22). IR: 745, 759, 774, 805, 835, 884 (5 and 2 adjacent, and solitary Ar—H); 1 140, 1 320 (SO_2NH); 1 530, 1 561, 1 575 (Ar); 1 602 (Ar—C=N); 3 105 (NH). ^{1}H NMR (C^2HCl_3): 1·29 t, 3 H (CH_3, J = 7·0); 3·00 q, 2 H (CH_2SO_2, J = 7·0); 4·48 bd, 2 H (CH_2N in the side chain); 3·92 d, 1 H and 5·31 d, 1 H (ABq, 2 H-4, J = 13·0); c. 7·30 bs, 1 H (NH); 7·00—7·80 m, 8 H (8 ArH).
IIb	IR: 745, 760, 826, 870, 879 (4 and 2 adjacent, and solitary Ar—H); 1 150, 1 331 (SO_2NH); 1 530, 1 568 (Ar); 1 615 (Ar—C=N); 3 100 (NH). ^{1}H NMR (C^2HCl_3): 1·35 t, 3 H (CH_3, J = 7·0); 3·12 q, 2 H (CH_2SO_2, J = 7·0); 4·65 bs, 2 H (CH_2N in the side chain); 4·15 d, 1 H and 5·48 d, 1 H (ABq, 2 H-4, J = 13·0); 6·98 bs, 1 H (NH); 7·10—7·80 m, 7 H (7 ArH).
IIc	UV: infl. 250 (4·12). IR: 743, 765, 780, 800, 825, 872 (4 and 2 adjacent, and solitary Ar—H); 1 152, 1 330 (SO_2NH); 1 511, 1 534, 1 562 (Ar); 1 611 (Ar—C=N); 3 070 (NH). ^{1}H NMR (C^2HCl_3): 1·35 t, 3 H (CH_3, J = 7·0); 3·10 q, 2 H (CH_2SO_2, J = 7·0); 4·60 s, 2 H (CH_2N in the side chain); 4·11 bd, 1 H and 5·48 bd, 1 H (ABq, 2 H-4, J = 13·0); 6·38 bs, 1 H (NH); 7·20—7·90 m, 7 H (7 ArH).

TABLE II
(*Continued*)

Compound	Spectra
IIIa	UV: 244 (4·20). IR: 700, 750, 780, 820, 892 (5 and 2 adjacent, and solitary Ar—H); 1 165, 1 295, 1 314 (SO_2NH); 1 485, 1 536, 1 566 (Ar); 1 610 (Ar—C=N); 3 080 (NH). ^{1}H NMR (80 MHz): 1·44 d and 1·75 d, $\sum$3 H (CH_3 of the alanine fragment, J = 7·0); 2·55 s and 3·10 s, $\sum$3 H (CH_3SO_2); 5·10 bm, 1 H (CH of the alanine fragment); 4·20 bd, 1 H and 5·30 d, 1 H (ABq, 2 H-4, J = 13·0); 7·10—8·10 m, 8 H (8 ArH) (ratio of diastereoisomers A : B = 73 : 27). ^{1}H NMR (200 MHz): 1·39 d (CH_3—C(B), J(CH_3, CH) = 6·9); 1·71 d (CH_3—C(A), J(CH_3, CH) = 6·9); 2·52 s (CH_3SO_2(A)); 3·03 s (CH_3SO_2(B)); 4·16 d and 5·22 d (2 H-4(A), J(4, 4) = 13·0); 4·18 d and 5·22 d (2 H-4(B), J(4, 4) = 13·0); 5·01 p (CH(B), J(CH, CH_3) = c. J(CH, NH) = 6·9); 5·07 p (CH(A), J(CH, CH_3) = c. J(CH, NH) = 6·9); 7·32 d (H-7(A), J(7, 9) = = 2·3); 7·37 d (H-7(B), J(7, 9) = 2·1); 7·36—7·55 m (H-2′, 3′, 4′, 5′, 6′ (A + B), NH(B)); 7·64 bd (NH(A), J(NH, CH) = 6·9); 7·80 dd (H-9(A), J(9, 7) = 2·3; J(9, 8) = 8·7); 7·87 dd (H-9(B), J(9, 7) = 2·1; J(9, 10) = 8·7); 7·88 d (H-10(A), J(10, 9) = 8·5); 7·93 d (H-10(B), J(10, 9) = 8·7) (ratio of diastereoisomers A : B = 73 : 27).
IIIb	UV: 245 (4·13). IR: 732, 751, 769, 817, 896 (4 and 2 adjacent, and solitary Ar—H); 1 120, 1 146, 1 161, 1 310 (SO_2NH); 1 500, 1 530, 1 566, 1 590, 3 020, 3 065, 3 093 (Ar); 1 610 (Ar—C=N); 3 310 (NH). ^{1}H NMR spectrum: 1·35 d and 1·78 d, $\sum$3 H (CH_3 of the alanine fragment, J = 7·0); 2·68 s and 3·10 s, $\sum$ 3 H (CH_3SO_2); 4·28 and 4·31 2 d, $\sum$1 H and 5·32 d, 1 H (ABq, 2 H-4, J = 13·0); c. 5·10 bm, 1 H (CH of the alanine fragment); 7·10 d and 7·15 d, $\sum$1 H (H-7, J = 2·0); 7·20—8·20 m, 6 H (remaining ArH) (A : B = 57 : 43).
IIIc	UV: infl. 248 (4·16). IR: 754, 770, 900 (4 and 2 adjacent, and solitary Ar—H); 1 123, 1 150, 1 165, 1 310 (SO_2NH); 1 485, 1 544, 1 565, 1 595, 3 086, 3 095 (Ar); 1 614 (Ar—C=N); 3 320 (NH). ^{1}H NMR: 1·35 d and 1·80 d, $\sum$3 H (CH_3 of the alanine fragment, J = 7·0); 2·65 s and 3·10 s, $\sum$3 H (CH_3SO_2); 4·28 and 4·30 2 d, $\sum$1 H and 5·30 d, 1 H (ABq, 2 H-4, J = 13·0); c. 5·10 bm, 1 H (CH of the alanine fragment); 7·20—8·10 m, 7 H (7 ArH) (A : B = 58 : 42).
IVa	UV: 244 (4·22). IR: 700, 750, 785, 820, 880 (5 and 2 adjacent, and solitary Ar—H); 1 124, 1 140, 1 315 (SO_2NH); 1 485, 1 536, 1 564, 1 576 (Ar), 1 605 (Ar—C=N), 3 340 (NH). ^{1}H NMR: 0·95 t and 1·30 t, $\sum$3 H (CH_3 of ethylsulfonyl, J = 7·0); 1·42 d and 1·75 d, $\sum$3 H (CH_3 of the alanine fragment, J = 7·0); 2·50 q and 3·15 q, $\sum$2 H (CH_2SO_2, J = 7·0); 4·20 bd, 1 H and 5·30 d, 1 H (ABq, 2 H-4, J = 13·0); 5·10 bm, 1 H (CH of the alanine fragment); 7·20—8·00 m, 8 H (8 ArH) (A : B = 78 : 22).
IVb	UV: infl. 246 (4·10). IR: 740, 754, 775, 817, 875 (4 and 2 adjacent, and solitary Ar—H); 1 120, 1 140, 1 315 (SO_2NH); 1 488, 1 540, 1 566, 1 590, 3 050, 3 095 (Ar); 1 610 (Ar—C=N); 3 270 (NH). ^{1}H NMR: 1·09 t and 1·32 t, $\sum$3 H (CH_3 of ethylsulfonyl, J = 7·0); 1·35 d and 1·79 d, $\sum$3 H (CH_3 of the alanine

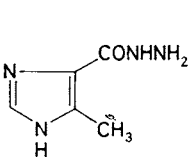
TABLE II
(*Continued*)

Compound	Spectra
	fragment, $J = 7{\cdot}0$); 2·75 q and 3·18 q, $\sum$2 H (CH_2SO_2, $J = 7{\cdot}0$); 4·28 and 4·30 2 d, $\sum$1 H and 5·30 d, 1 H (ABq, 2 H-4, $J = 13{\cdot}0$); 5·10 bm, 1 H (CH of the alanine fragment); 7·10 d and 7·15 d, $\sum$1 H (H-7, $J = 2{\cdot}0$); 7·30–8·20 m, 6 H (6 ArH) (A : B = 60 : 40).
IVc	UV: 248 (4·15). IR: 754, 775, 810, 875 (4 and 2 adjacent, and solitary Ar—H); 1 120, 1 140, 1 310 (SO_2NH); 1 485, 1 538, 1 565, 1 590, 3 060, 3 095 (Ar); 1 610 (Ar—C=N); 3 260 (NH). ^{1}H NMR: 1·08 t and 1·32 t, $\sum$3 H (CH_3 of ethylsulfonyl, $J = 7{\cdot}0$); 1·35 d and 1·80 d, $\sum$3 H (CH_3 of the alanine fragment, $J = 7{\cdot}0$); 2·75 q and 3·18 q, $\sum$ 2 H (CH_2SO_2, $J = 7{\cdot}0$); 4·28 and 4·30 2 d, $\sum$1 H and 5·30 d, 1 H (ABq, 2 H-4, $J = 13{\cdot}0$); 5·10 bm, 1 H (CH of the alanine fragment); 7·10–8·20 m, 7 H (7 ArH) (A : B = 60 : 40).

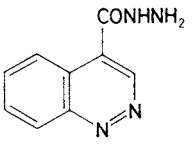
series) showed doubled signals. They thus behaved like mixtures of two similar substances in which one component (*A*) predominated, the other (B) was the minor one, and it was possible to determine the ratio of both components in every case. The first assumption was that this phenomenon is due to the presence of two rather stable conformers. For testing the correctness of this hypothesis, one compound (*IIIa*) was subjected to a detailed investigation of the ^{1}H NMR spectrum at 200 MHz at room temperature and at 60°C. The difference in temperature practically did not change the ratio of components A and B which, in fact, eliminated the conformer hypothesis. It appears thus more likely that we are dealing here with mixtures of two diastereoisomers. The asymmetric carbon in α-position to the skeleton represents one element of chirality. The other one is the chiral axis of the quasi diaryl system, formed by the benzene and triazole nuclei.

In a similar context, two heterocyclic acid hydrazides were prepared and used. 5-Methylimidazole-4-carboxylic acid hydrazide (*XIV*) was obtained by the procedure described[9] and cinnoline-4-carboxylic acid hydrazide (*XV*) was prepared from ethyl cinnoline-4-carboxylate[10] by treatment with hydrazine hydrate at 110–120°C. The former was subjected to reactions with all the three mentioned thiones in boiling butanol. In series *a*, *Va* was obtained in moderate yield as the only product isolated. In series *b* and *c*, the higher melting products *Vb* and *Vc* were accompanied by lower melting by-products which were separated on the basis of their insolubility. These by-products were identified as the noncyclized primary products *XVI* and *XVII* (cf. ref.[2]). In the case of *XV* which was reacted with 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[2] in boiling butanol, the reaction stopped com-

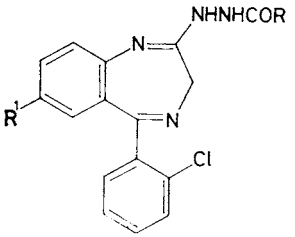
pletely in the stage of the noncyclized product *XVIII* which was obtained in a high yield. Attempts to cyclize *XVIII* by heating were not successful.

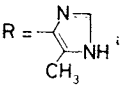


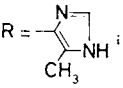
XIV

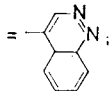


XV



XVI, R =  ; R^1 = Cl

XVII, R =  ; R^1 = Br

XVIII, R =  ; R^1 = Cl

Compounds *Iabc*–*Vabc*, *XVI*, and *XVII* were subjected to a preliminary pharmacological screening using oral adminstration. In acute toxicity tests, all compounds were administered in doses of 0·5 and 1·0 g/kg which caused sedation, ataxia, and myorelaxation lasting for about 24 h; in all cases the LD_{50} were higher than 1·0 g/kg. The discoordinating activity was evaluated in the rotarod test in mice, ED_{50} in mg/kg (or doses used and their effects): *Ia*, c. 10; *Ib*, 2·7; *Ic*, 2·0; *IIa*, 5·5; *IIb*, 0·4; *IIc*, 1·8; *IIIa*, c. 50; *IIIb*, 2·3; *IIIc*, 2·7; *IVa*, 50 (ataxia with 10–20% animals); *IVb*, 2·9; *IVc*, 3·5; *Va*, 50 (ataxia with 10–20% animals); *Vb*, c. 50; *Vc*, >50; *XVI*, c. 10; *XVII*, c. 10. In the last two cases (*XVI* and *XVII*), the full effect appears only in 45–90 min after the administration; this latentiation of effects could be explained by the metabolic cyclization of *XVI* and *XVII* to *Vb* and *Vc*. On the other hand, compounds *Vb*, *Vc*, per se, are less active. The anticonvulsant effect in mice was evaluated on the basis of antagonization of the convulsant effect of electroshock (the medium protective doses decrease the appearance of convulsions to 50% in comparison with the control group), PD_{50} in mg/kg (or doses used and their effect): *Ia*, >10; *Ib*, 2·1; *Ic*, 3·1; *IIa*, >10; *IIb*, 3·4; *IIc*, 5·9; *IIIa*, >10; *IIIb*, 8–16 (significant

effect but no dose effect relation); *IIIc*, 7·1; *IVa*, >10; *IVb*, 10 (effect with 40% animals); *IVc*, 10 (effect with 30% animals); *Va*, >10; *Vb*, >10; *Vc*, >10 (this dose gave full protection against the lethal effect of the electroshock); *XVI*, 10 (effect with 70% animals; the dose of 3 mg/kg protected fully from the lethality); *XVII*, >10. Anticonvulsant effect against pentetrazole (ED in mg/kg): *Ib*, 1–10 (in doses of 0·1–1·0 mg/kg protection from the lethal effect of pentetrazole); *IIIa*, 5–10. Inhibition of the spontaneous motor activity of mice by the photo-cell method (Dews): *Ia*, 1 mg/kg inhibited to 66% of the control value; *Ib*, 2 mg/kg inhibited to 33%. Thiopental potentiation in mice (ED in mg/kg prolonging the sleeping time to 200% in comparison with the control): *Ib*, 1·0; *IIIa*, 50. In conclusion, the compounds prepared show the activity profile of the anxiolytic and hypnotic 1,4-benzodiazepine and 4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine derivatives; members of series *b* are the most active but even these are relatively weak in comparison with some similar compounds (*cf.* with data in ref.[2]).

EXPERIMENTAL

The melting points were determined in Kofler block and were 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, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, NMR spectra (in $C^2H_3SOC^2H_3$ unless stated otherwise, δ, J in Hz) with the Tesla BS 487 C (^1H at 80 MHz) and Varian XL-200 (^1H at 200 MHz; ^{13}C at 50·3 MHz) spectrometers, and finally the mass spectra with MCH 1 320 and Varian MAT 44S spectrometers (m/z and % given). The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral Al_2O_3 (activity II).

Ethyl (Ethanesulfonamido)acetate (*VII*)

Glycine ethyl ester hydrochloride (100 g) in 500 ml chloroform was treated with 265 ml solution of NH_3 in chloroform, containing 53·8 mg NH_3 in 1 ml. The mixture was shaken for 30 min, the precipitated NH_4Cl was filtered off, washed with chloroform, and the filtrate was evaporated in vacuo at 40°C. The residue was dissolved in 1 000 ml ether, the solution was cooled to 5°C, and treated over 1 h under stirring and cooling with a solution of 48·5 g ethanesulfonyl chloride[7] in 220 ml ether. The mixture was stirred for 2·5 h at room temperature and allowed to stand overnight. The precipitated glycine ethyl ester hydrochloride (48·3 g) was filtered off, washed with ether, and the filtrate was distilled; 67·0 g (96%), b.p. 145–150°C/30–70 Pa, n_D^{23} 1·4598. The distillate crystallized on standing in the refrigerator, m.p. 26–28°C (ether–hexane). IR spectrum (film): 1 140, 1 320 (SO_2NH); 1 210, 1 288, 1 740 (RCOOR'); 3 290 (NH). ^1H NMR spectrum (C^2HCl_3): 1·30 t, 3 H (CH_3 of ethylsulfonyl, J = 7·0); 1·40 t, 3 H (CH_3 in ethoxyl, J = 7·0); 3·10 q, 2 H (CH_2SO_2, J = 7·0); 3·90 bs, 2 H (NCH_2COO), 4·21 q, 2 H (OCH_2, J = 7·0); c. 5·10 flat band, 1 H (NH). For $C_6H_{13}NO_4S$ (195·2) calculated: 36·91% C, 6·71% H, 7·18% N, 16·42% S; found: 36·75% C, 6·78% H, 7·03% N, 16·21% S.

Methyl 2-(Methanesulfonamido)propionate (*VIII*)

(±)-Alanine methyl ester hydrochloride[6] (115 g) in 560 ml chloroform was similarly decomposed by shaking with a solution of 16 g NH_3 in 280 ml chloroform, NH_4Cl was filtered off, and the filtrate was evaporated in vacuo at 42°C. The residue was dissolved in 1 200 ml ether and the solution was reacted similarly like in the preceding case with a solution of 46 g methanesulfonyl chloride in 250 ml ether. Similar processing gave 70·2 g (94%) crude product which crystallized by standing; m.p. 56–57°C (ether–hexane). IR spectrum: 1 125, 1 305, 1 332 (SO_2NH); 1 220, 1 740 (RCOOR'); 3 280 (NH). ^1H NMR spectrum (C^2HCl_3): 1·50 d, 3 H (CH_3 of propionate, J = 7·0); 3·04 s, 3 H (SO_2CH_3); 3·80 s, 3 H (OCH_3); 4·22 m, 1 H (N—CH—CO); 5·50 bd, 1 H (NH, J = 7·5). For $C_5H_{11}NO_4S$ (181·2) calculated: 33·14% C, 6·12% H, 7·73% N, 17·69% S; found: 33·21% C, 6·03% H, 7·44% N; 17·62% S.

Methyl 2-(Ethanesulfonamido)propionate (*IX*)

(±)-Alanine methyl ester hydrochloride[6] (50 g) was transformed similarly to the free base which was reacted with 24·0 g ethanesulfonyl chloride[7] in 550 ml ether. Similar processing gave 32·0 g (92%) product, b.p. 146°C/0·13 kPa, n_D^{24} 1·4589. IR spectrum (film): 1 130, 1 320 (SO_2NH); 1 215, 1 735 (RCOOR'); 3 270, 3 560 (NH). ^1H NMR spectrum (C^2HCl_3): 1·32 t, 3 H (CH_3 of ethylsulfonyl, J = 7·0); 1·43 d, 3 H (CH_3 of propionate, J = 7·0); 3·02 q, 2 H (CH_2SO_2, J = 7·0); 3·72 s, 3 H (OCH_3); 4·12 m, 1 H (N—CH—CO); 5·30 bd, 1 H (NH, J = 8·0). For $C_{16}H_{13}NO_4S$ (195·2) calculated: 36·91% C, 6·71% H, 7·18% N, 16·42% S; found: 37·45% C, 6·80% H, 7·40% N, 16·29% S.

(Methanesulfonamido)acethydrazide (*X*)

A mixture of 69 g *VI* (ref.[8]) and 23·9 g 97·5% $N_2H_4.H_2O$ was stirred for 20 min and then heated under stirring for 1 h in vacuo to 80–90°C. The oily product was dissolved in 65 ml boiling ethanol, the solution was cooled under stirring, and crystallization was finished by standing in the refrigerator; 62·5 g (98%), m.p. 103–105°C. Analytical sample, m.p. 105–106°C (aqueous 2-propanol). IR spectrum: 1 142, 1 302 (SO_2NH); 1 550, 1 658 (CONH); 2 700 (N—H···O=C); 3 200, 3 255, 3 325 (NH, NH_2). ^1H NMR spectrum: 2·95 s, 3 H (CH_3SO_2); 3·59 s, 2 H (CH_2CO); 4·30 bs, 2 H (NH_2); 7·30 bs, 1 H and 9·10 bs, 1 H (SO_2NH and CONH). For $C_3H_9N_3O_3S$ (167·2) calculated: 21·55% C, 5·43% H, 25·14% N, 19·17% S; found: 21·57% C, 5·52% H, 25·48% N, 18·90% S.

(Ethanesulfonamido)acethydrazide (*XI*)

Similar reaction of 66 g *VII* with 25·0 g 97·5% $N_2H_4.H_2O$ gave 56 g (91%) *XI*, m.p. 64–65°C (ethanol). IR spectrum: 1 148, 1 312 (SO_2NH); 1 537, 1 595, 1 655 (CONH); 2 690, 2 780, 2 820 (N—H···O=C); 3 055, 3 270, 3 290, 3 330 (NH, NH_2). ^1H NMR spectrum: 1·21 t, 3 H (CH_3, J = 7·0); 3·02 q, 2 H (CH_2SO_2, J = 7·0); 3·55 bs, 2 H (N—CH_2—CO); 4·28 bs, 2 H (NH_2); 7·30 bs, 1 H (SO_2NH); 9·08 bs, 1 H (CONH). For $C_4H_{11}N_3O_3S$ (181·2) calculated: 26·51% C, 6·12% H, 23·19% N, 17·69% S; found: 26·20% C, 6·26% H, 23·74% N, 17·56% S.

2-(Methanesulfonamido)propionhydrazide (*XII*)

Similar reaction of 54·2 g *VIII* with 18·8 g 97·5% $N_2H_4.H_2O$ gave 52·6 g (97%) *XII*, m.p. 133 to 134°C (aqueous 2-propanol). IR spectrum: 1 127, 1 150, 1 310 (SO_2NH); 1 519, 1 644, 1 665 (CONH); 2 990, 3 000, 3 010, 3 070, 3 200, 3 300, 3 360 (NH_2, NH). ^1H NMR spectrum: 1·29 d,

3 H (CH_3 of propionyl, J = 7·0); 2·91 s, 3 H (SO_2CH_3); 3·90 bm, 1 H (CHCO); 7·36 bd, 1 H ($NHSO_2$, J = 8·0); 6·00—8·00 flat band, 3 H ($NHNH_2$). For $C_4H_{11}N_3O_3S$ (181·2) calculated: 26·51% C, 6·12% H, 23·19% N, 17·69% S; found: 26·63% C, 6·27% H, 23·62% N, 17·71% S:

2-(Ethanesulfonamido)propionhydrazide (*XIII*)

Similar reaction of 31·3 g *IX* with 9·75 g 97·5% $N_2H_4.H_2O$ gave 31·8 g (theoretical)crude *XIII* which crystallized after longer standing; m.p. 90—91°C (ethanol). IR spectrum: 1 127, 1 325 (SO_2NH); 1 515, 1 640 (CONH); 2 790, 3 065, 3 200, 3 310, 3 400 (NH_2, NH). ^{1}H NMR spectrum: 1·10 t, 3 H (CH_3 of ethylsulfonyl, J = 7·0); 1·15 d, 3 H (CH_3 of propionyl, J = 7·0); 2·85 q, 2 H (SO_2CH_2, J = 7·0); 3·75 bm, 1 H (CHCO); 6·20—8·00 flat band. 3 H ($NHNH_2$); 7·30 bd, 1 H (SO_2NH). For $C_5H_{13}N_3O_3S$ (195·2) calculated: 30·76% C, 6·71% H, 21·52% N, 16·42% S; found: 30·93% C, 6·91% H, 21·64% N, 16·14% S.

Cinnoline-4-carboxylic Acid Hydrazide (*XV*)

A mixture of 7·4 g ethyl cinnoline-4-carboxylate[10] and 20 ml 97·5% $N_2H_4.H_2O$ was stirred for several minutes and then heated for 90 min to 110—120°C. The cooled mixture was diluted with 40 ml ethanol which led to crystallization of 5·0 g product. Processing of the mother liquor gave further 1·8 g *XV*, the total yield being 6·8 g (99%), m.p. 172—174°C. Analytical sample, m.p. 177—178°C (yellow needles from ethanol). UV spectrum: 229 (4·58), 296 (3·60), 326 (3·57). IR spectrum: 764 (4 adjacent Ar—H); 1 532, 1 564, 1 605 (Ar); 1 645 (ArCONH); 3 180, 3 290 (NH). ^{1}H NMR spectrum: 7·40 bs, 3 H ($CONHNH_2$); 8·00 m, 2 H (H-6 and H-7); 8·40 m, 1 H (H-8); 8·60 m, 1 H (H-5); 9·46 s, 1 H (H-3). For $C_9H_8N_4O$ (188·2) calculated: 57·43% C, 4·29% H, 29·78% N; found: 57·51% C, 4·40% H, 30·07% N.

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

A mixture of 6·42 g 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[2], 9·78 g *XI*, and 150 ml butanol was refluxed for 8 h under nitrogen. After standing overnight the solution was filtered with charcoal and the filtrate was evaporated in vacuo. The residue was distributed between water (the hydrazide *XI*, used in excess, is water-soluble) and dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in 12 ml boiling ethyl acetate and the solution was allowed to crystallize by standing in the refrigerator; 6·10 g (68%), m.p. 145—146°C (chloroform–ethyl acetate). For analysis and spectra, cf. Tables I and II.

8-Chloro-1-(5-methyl-4-imidazolyl)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*Va*)

A mixture of 5·73 g 7-chloro-5-phenyl-1,3-dihydro-1,4-benzodiazepin-2-thione[2], 6·0 g *XIV* (ref.[9]), and 150 ml butanol was refluxed for 8 h under nitrogen. After filtration with carbon, the filtrate was evaporated in vacuo. The residue was extracted with 200 ml warm water, the insoluble so id was filtered, and dissolved in 90 ml dichloromethane. The solution was filtered and evaporated. The residue was chromatographed on 180 g Al_2O_3. Elution with dichloromethane removed the less polar components and a mixture of dichloromethane with 3% ethanol eluted crude *Va* which crystallized from 12 ml ethyl acetate; 2·80 g (38%), m.p. 300—301°C (ethanol), UV spectrum: infl. 245 (4·33), infl. 264 (4·15). IR spectrum: 745, 787, 824, 888 (5 and 2 adjacent. and solitary Ar—H); 1 484, 1 540, 1 566 (Ar); 1 610 (Ar—C=N); 3 060, 3 100, 3 150 (NH).

For $C_{20}H_{15}ClN_6$ (374·8) calculated: 64·08% C, 4·03% H, 9·47% Cl, 22·42% N; found: 63·94% C 4·33% H, 9·52% Cl, 22·28% N.

8-Chloro-6-(2-chlorophenyl)-1-(5-methyl-4-imidazolyl)-
-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*Vb*)

A mixture of 6·4 g 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[2], 6·5 g *XIV* (ref.[9]), and 150 ml butanol was refluxed under nitrogen for 8 h. The solution was filtered with 2 g carbon and evaporated in vacuo. The residue was diluted with 250 ml warm water and the mixture was extracted with 50 ml dichloromethane. The extract was allowed to stand overnight at room temperature which led to precipitation of 2·5 g solid melting at 194—197°C. Its crystallization from ethanol gave 2·1 g homogeneous substance which was identified as N^1-(7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl)-N^2-(5-methyl-4-imidazolylcarbonyl) -hydrazine (*XVI*) hemihydrate, m.p. 214—215°C. Mass spectrum (EI): 428 (2), 426 (M^+, $C_{20}H_{16}Cl_2N_6O$, 3), 410 (2), 408 (3), 385 (0·5), 383 (0·8), 320 (1·3), 318 (2), 307 (2), 306 (6), 305 (6·5), 304 (12), 303 (8), 109 (52), 91 (38), 43 (100). UV spectrum: infl. 233 (4·45), 285 (4·28). IR spectrum: 750, 820, 880 (4 and 2 adjacent, and solitary Ar—H); 1 500, 1 520, 1 590 (Ar); 1 620 (Ar—C=N); 1 650 (CONH); 3 060, 3 120, 3 190, 3 350 (H_2O and NH). ^{1}H NMR spectrum: 2·40 s, 3 H (CH_3); 4·25 bs, 2 H (2 H-3); 6·75 d, 1 H (H-6, J = 2·0); 7·00—7·80 m, 6 H (remaining ArH); 7·59 s, 1 H (H-2 of imidazole). For $C_{20}H_{16}Cl_2N_6O + 0{\cdot}5\ H_2O$ (436·3) calculated: 55·06% C, 3·93% H, 16·25% Cl, 19·26% N; found: 55·59% C, 4·10% H, 16·00% Cl, 19·14% N.

The filtrate was evaporated and the residue was induced to crystallize by heating with 17 ml ethyl acetate; 5·50 g (68%) *Vb*, m.p. 295—296°C (ethanol). UV spectrum: 246 (4·22). IR spectrum: 750, 828, 880 (4 and 2 adjacent, and solitary Ar—H); 1 540, 1 570, 1 595, 1 605 (Ar); 1 619 (Ar—C=N); 3 125, 3 200 (NH). ^{1}H NMR spectrum: 2·48 s, 3 H (CH_3); 5·30 d, 1 H and 4·30 d, 1 H (ABq, 2 H-4, J = 13·0); 7·08 d, 1 H (H-7, J = 2·0); 7·20—7·80 m, 7 H (remaining ArH and H-2 of imidazole). For $C_{20}H_{16}Cl_2N_6$ (409·3) calculated: 58·68% C, 3·45% H, 17·33% Cl, 20·54% N; found: 58·60% C, 3·63% H, 17·10% Cl, 20·52% N.

8-Bromo-6-(2-chlorophenyl)-1-(5-methyl-4-imidazolyl)-
-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*Vc*)

A mixture of 5·48 g 7-bromo-5-(2-chlorophenyl)-1,2-dihydro-1,4-benzodiazepin-2-thione[3], 4·80 g *XIV* (ref.[9]), and 140 ml butanol was processed similarly like in the preceding case. After the distribution of the crude product between 250 ml warm water and 70 ml dichloromethane, there crystallized 2·2 g N^1-(7-bromo-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl)-N^2-(5-methyl -4-imidazolylcarbonyl)hydrazine (*XVII*), 2 : 1 solvate with ethanol, m.p. 209—210°C (ethanol). Mass spectrum (EI): 472 (1), 470 (M^+, $C_{20}H_{16}BrClN_6O$, 0·8), 454 (6), 452 (4), 439 (1·2), 437 (1), 316 (14), 314 (14), 109 (100). UV spectrum: infl. 234 (4·47), 288 (4·45). IR spectrum: 750, 768, 825, 880 (4 and 2 adjacent, and solitary Ar—H); 1 048 (CH_2OH of ethanol); 1 500, 1 520, 1 570, 1 593 (Ar); 1 620 (Ar—C=N); 1 660 (CONH); 3 120, 3 180, 3 360 (OH and NH). ^{1}H NMR spectrum: 1·02 t, 1·5 H (CH_3 of ethanol, J = 7·0); 2·40 s, 3 H (CH_3 of methylimidazolyl); 3·40 q, 1 H (CH_2O of ethanol, J = 7·0); 4·25 bs, 2 H (2 H-3); 6·88 d, 1 H (H-6, J = 2·0); 7·00 to 7·50 m, 6 H (remaining ArH); 7·60 s, 1 H (H-2 of imidazole). For $C_{20}H_{16}BrClN_6O + 0{\cdot}5\ C_2H_5OH$ (517·8) calculated: 51·03% C, 4·28% H, 15·42% Br, 6·85% Cl, 16·24% N; found: 50·93% C, 4·26% H, 15·00% Br, 6·79% Cl, 16·61% N.

The organic layer of the filtrate was evaporated and the residue was crystallized from 12 ml ethyl acetate; 4·1 g (60%) 1 : 1 solvate of *Vc* with ethanol, m.p. 280—281°C (ethanol). Mass

spectrum (EI): 456 (8), 455 (9), 454 (33), 453 (13), 452 (M^+, $C_{20}H_{14}BrClN_6$, 24), 317 (40); 316 (100), 315 (48), 314 (88), 236 (20), 209 (16), 208 (11), 203 (14), 106 (10), 102 (12), 75 (21). UV spectrum: infl. 246 (4·26). IR spectrum: 750, 843, 882 (4 and 2 adjacent, and solitary Ar—H), 1 054, 1 095 (CH_2OH of ethanol); 1 525, 1 535, 1 560, 1 589, 1 593 (Ar); 1 614 (Ar—C=N), 3 090, 3 120, 3 160 (OH and NH). ^{1}H NMR spectrum: 1·00 t, 3 H (CH_3 of ethanol); 2·38 s, 3 H (CH_3 of methylimidazolyl); 3·35 q, 2 H (CH_2O of ethanol, J = 7·0); 5·20 d, 1 H and 4·20 d, 1 H (ABq, 2 H-4, J = 13·0); 7·10 d, 1 H (H-7, J = 2·0); 7·20 d, 1 H (H-10, J = 8·5); 7·25 to 7·60 m, 5 H (4 ArH of chlorophenyl and H-2 of imidazole); 7·60 dd, 1 H (H-9, J = 8·5; 2·0). For $C_{20}H_{14}BrClN_6 + C_2H_5OH$ (499·8) calculated: 52·88% C, 4·03% H, 15·99% Br, 7·09% Cl, 16·81% N; found: 52·88% C, 4·07% H, 15·39% Br, 7·09% Cl, 17·07% N.

N^1-(7-Chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl)-
-N^2-(4-cinnolylcarbonyl)hydrazine (*XVIII*)

A mixture of 6·0 g 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[2], 5·3 g *XV*, and 150 ml butanol was refluxed for 6 h in nitrogen atmosphere. After standing overnight, the yellow solid was filtered, washed with 40 ml ethanol, and dried in vacuo; 7·3 g (82%) *XVIII*, m.p. 267—269°C. Crystallization from pyridine did not change the melting point. Mass spectrum (EI): 476 (0·5), 474 (M^+, $C_{24}H_{16}Cl_2N_6O$, 0·7), 459 (4), 458 (9), 457 (9), 456 (13), 455 (8), 321 (24), 320 (48). 319 (72), 318 (100), 284 (32), 102 (9), 101 (13), 75 (16). UV spectrum: 229 (4·71), infl. 254 (4·38), infl. 278 (4·27), 330 (3·95). IR spectrum: 745, 770, 835, 863, 880, 889 (4 and 2 adjacent, and solitary Ar—H); 1 562, 1 640 (CONH); 1 584 (Ar); 1 612 (C=N); 3 075, 3 145, 3 200 (NH). ^{1}H NMR spectrum: 4·40 bs, 2 H (2 H-3); 6·81 d, 1 H (H-6, J = 2·5); 7·25 d, 1 H (H-9, J = 8·5); 7·30—8·70 m, 10 H (remaining 10 ArH). For $C_{24}H_{16}Cl_2N_6O$ (475·3) calculated: 60·64% C, 3·39% H, 14·92% Cl, 17·68% N; found: 60·80% C, 3·39% H, 15·04% Cl, 17·81% N.

The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the investigation presented: Drs M. Ryska, I. Koruna, and J. Schlanger (mass spectra), Mrs A. Hrádková and Mrs Z. Janová (recording of the UV *and* IR *spectra), and finally Mrs J. Komancová and Mrs V. Šmídová (elemental analyses).*

REFERENCES

1. Hester J. B. jr, Von Voigtlander P.: J. Med. Chem. *22*, 1390 (1979).
2. Vejdělek Z., Metyš J., Protiva M.: Collect. Czech. Chem. Commun. *48*, 123 (1983).
3. Vejdělek Z., Protiva M.: Collect. Czech. Chem. Commun. *48*, 1477 (1983).
4. Hester J. B. jr (Upjohn Co.): Ger. Offen. 2,012,190 (U.S. Appl. 17. 03. 69 and 29. 10. 69); Ger. Offen. 2,065,893; Australian 462,769; Belg. 747, 493; Chem. Abstr. *73*, 109801 (1970); *85*, 192782 (1976).
5. Hester J. B. jr, Rudzik A. D., Kamdar B. V.: J. Med. Chem. *14*, 1078 (1971).
6. Brenner M., Huber W.: Helv. Chim. Acta *36*, 1109 (1953).
7. Sprague J. M., Johnson T. B.: J. Am. Chem. Soc. *59*, 1837 (1937); Chem. Zentralbl. 1938, I, 2158.
8. Helferich B., Mittag R.: Ber. Dtsch. Chem. Ges. *71* 1480 (1938); Chem. Zentralbl. 1938, II, 1579.
9. Tamamusi Y.: J. Pharm. Soc. Jpn. *60*, 184 (1940); Chem. Abstr. *34*, 5447 (1940).
10. Jacobs T. L., Winstein S., Henderson R. B., Spaeth E. C.: J. Am. Chem. Soc. *68*, 1310 (1946).

Translated by the author (M.P.).