REACTIONS OF $PO(NCS)_3$ WITH 4-HYDROXY-1,3-DIOXANES. CRYSTAL STRUCTURE OF *rel*-(2*S*,4*R*,5*S*,6*S*)-2,6-DIETHYL-5-METHYL-4-(N'-BENZYLTHIOUREIDO)-1,3-DIOXANE

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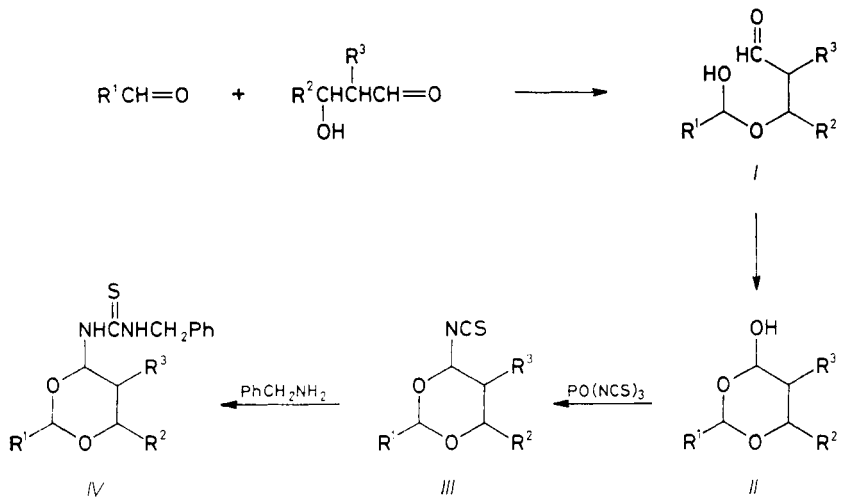
Substituted 4-hydroxy-1,3-dioxanes *II* react rapidly with $PO(NCS)_3$ to give 4-isothiocyanato-1,3-dioxanes *III*. The ^1H NMR spectra showed that in the isothiocyanate *IIIa* the predominant stereoisomer has its NCS group in axial position. The addition of benzylamine to the isothiocyanates *IIIa* and *IIIb* gave uniform thioureas *IVa* and *IVb* with equatorial alkyl groups at 2 and 6 positions and axial thioureido group at the 4 position. On the other hand, the isothiocyanate *IIIc* reacts with benzylamine to give a mixture of three stereoisomeric thioureas *V*, *VI*, and *VIII*. The structure of *VI* was proved by means of X-ray diffraction analysis; in crystalline form the molecules of *VI* are present as H-bonded dimers (N—H···O).

In our previous communications[1,2] we described a simple one-pot reaction of $POCl_3$, KSCN, and acetaldehyde giving 2,6-dimethyl-4-isothiocyanato-1,3-dioxane (*IIIa*). This reaction can be explained by two parallel processes. The first one involves the formation of acetaldol, and it is known[3,4] that the OH group of the acetaldol being formed can easily add to the nonreacted acetaldehyde to give an equilibrium mixture of the open-chain hemiacetal *I* and its cyclic form, i.e. 2,6-dimethyl-4-hydroxy-1,3-dioxane (aldoxane, *II*). The formation of aldoxane *II* is very frequent in aldol reactions, and some authors[4] even state that this is the main reaction product. The second process[5] consists in gradual substitution of chlorine atoms in $POCl_3$ by reaction with KSCN to give $PO(NCS)_3$. The intermediates thus formed, i.e. $PO(NCS)_3$ and aldoxane *II*, can react in a subsequent step to give the final product – isothiocyanate *III* (Scheme 1). The idea that the $PO(NCS)_3$ formed can replace the hemiacetal OH group in aldoxane *II* was evoked by our earlier findings[6] showing that $PO(NCS)_3$ can effectively substitute the OH group in tertiary alcohols and in carboxylic acids to give the corresponding tert.alkyl isothiocyanates and acyl isothiocyanates, respectively.

In order to support the above-mentioned idea, we decided to verify by an independent reaction whether or not $PO(NCS)_3$ can substitute the hemiacetal OH group of aldoxane *IIa* to give the isothiocyanate *IIIa*. When trying to prepare *IIa* from



In formulae *I–IV*: *a*, $R^1 = R^2 = Me$; $R^3 = H$; *b*, $R^1 = Et$; $R^2 = Me$; $R^3 = H$; *c*, $R^1 = R^2 = Et$; $R^3 = Me$

SCHEME 1

fresh acetaldol and acetaldehyde in the known way[7,8] we found that its distillation is probably accompanied by the reverse reaction and a large loss due to escape of acetaldehyde. Therefore, in subsequent reactions we used the raw, non-distilled product. The presence of aldoxane *IIa* in the raw product was verified by converting it into the known benzoate[7,8] and measuring the ^1H and ^{13}C NMR spectra (Tables I–III). The coupling constants of hydrogen atoms at 4 and 5 positions (10·0 and 2·7 Hz) indicate that the benzyloxy group is in equatorial position. When treating the raw aldoxane *II* with $PO(NCS)_3$, we really obtained isothiocyanate *IIIa* (yield 60%) identical in all respects with the isothiocyanate obtained from the one-pot reaction[1,2] of acetaldehyde with $POCl_3$ and KSCN.

The ability of $PO(NCS)_3$ to react with hemiacetal OH groups was verified also by reactions with other derivatives of aldoxane, i.e. with 2-ethyl-4-hydroxy-6-methyl-1,3-dioxane (*IIb*) prepared in the same way as above from acetaldol and propanal, and with 2,6-diethyl-4-hydroxy-5-methyl-1,3-dioxane (*IIc*) prepared from propionaldol and propanal. In the former case, we isolated the isothiocyanate *IIIb* in the yield of 30%, in the latter case, the isothiocyanate *IIIc* was obtained in the yield of 87%. The same isothiocyanate *IIIc* (85%) was obtained from the one-pot reaction of propanal, KSCN, and $POCl_3$. Although the isothiocyanates *IIIa*, *IIIb*, and *IIIc*

prepared were sufficiently stable and could be distilled, the products obtained were not quite uniform. Their NMR spectra exhibited beside the signals of expected dominant products also those of other compounds, probably decomposition products. Nevertheless, it was possible to obtain reliable ^1H and ^{13}C NMR data of the main constituent in the isothiocyanate *IIIa* (Tables I–III). Small values of coupling constants of H-4 and H-5 protons (3·9 and 1·6 Hz in $CDCl_3$; 3·9 and 2·0 Hz in $CD_3C.OCD_3$) indicate the axial orientation of the isothiocyanate group in *IIIa* (in contrast to the equatorial position of substituent in the above-mentioned benzoate). In accordance therewith, the thioureido group of N'-benzylthiourea *IVa* (prepared by addition of benzylamine to isothiocyanate *IIIa*) adopts the axial position[3].

After the reaction of isothiocyanate *IIIb* with benzylamine, we isolated the thiourea *IVb* whose ^1H and ^{13}C NMR spectra agreed with the presumed structure. The coupling constants of the H-4 and H-6 protons with H-5 ($J(4, 5) = 4·9$ and $\leqq 2·0$ Hz; $J(6, 5) = 11·3$ and $\leqq 2·0$ Hz) prove the axial and equatorial orientations of 4-thioureido and 6-methyl groups, respectively. However, the ^1H and ^{13}C NMR spectra of the same compound measured in $CDCl_3$ revealed the presence of two isomers having the thioureido group in axial or equatorial position. Hence in chloroform solution obviously an easy epimerization takes place at C-4 carbon atom (probably catalyzed with traces of hydrochloric acid) to give a mixture of both the isomers of compound *IVb*. A similar effect was observed also with compound *IVa* in chloroform or after long-term standing in acetone solution[2]. The NMR data of both isomers of *IVb* are presented in Tables I–III.

The analysis of ^1H NMR spectra of *IVb* is complicated by considerable broadening of signals of some protons (especially H-4 and the $-NHCSNHCH_2-$ fragment, or also H-5), which makes it impossible to determine the multiplet type and the coupling constant values. This phenomenon is probably connected with the tendency of these compounds to intermolecular association giving H-bonded dimers. Such behaviour was also proved in crystals of *IVc* (vide infra) and *IVa* (ref.[2]). With respect to these complications, the ^{13}C NMR spectra (where the broadening of signals was distinctly weaker) proved to be very useful for determination of structure of *IVb* isomers as well as of the below-mentioned *IVc* isomers. The change of orientation of C-4 substituent from axial to equatorial (e.g. with *IVb*) is accompanied by characteristic downfield shifts of carbon atoms at 2 and 6 positions (by 5·70 and 3·76 ppm, respectively) due to elimination of the well-known γ-gauche effect (in *IVb* the axial thioureido group adopts a gauche arrangement with distinct shielding effect with respect to the C-2 and C-6 carbon atoms, whereas in the isomer with equatorial thioureido group their mutual arrangement is *trans* and the shielding effect is zero).

In contrast to the isothiocyanates *IIIa* and *IIIb*, the reaction of isothiocyanate *IIIc* with benzylamine produced a mixture of three isomeric thioureas *V*, *VI*, and *VIII* (Scheme 2). Their ratio was 3 : 6 : 1 (according to reflection UV spectrophotometry of TLC chromatogram), and they were separated and isolated by means of

TABLE I

^{1}H NMR chemical shifts (δ, ppm) and coupling constants of substituted 1,3-dioxanes in CD_3COCD_3

Hydrogen	*IIa* benzoate	*IIIa*	*IVb*[a]	*IVb*[b]	*V*	*VI*	*VII*	*VIII*
H-2	4·95 q (5·1)	5·18 q (5·1)	4·87 um	4·60 t (5·1)	4·86 bt (5·1)	4·81 t (5·2)	4·64 t (5·0)	4·62 t (5·1)
H-4	6·13 dd (10·1; 2·7)	5·78 dd (3·9; 2·0)	5·64 um	5·10 um	5·33 bd (4·7; 1·0)	5·85 bdd (4·8; 7·6)	5·89 b	5·48 b
H-5ax	1·56 ddd (12·5; 10·1; 11·3)	1·80 ddd (13·8; 10·4; 3·9)	1·77 ddd (13·7; 11·3; 4·9)	[c]	—	2·03 ddq (9·5; 4·8; 7·0)	—	1·53 b
H-5eq	1·96 ddd (12·5; 2·7; 2·4)	1·84 ddd (13·8; 3·4; 2·0)	1·83 bd (13·7; ≦2; ≦2)	[c]	1·82 ddq (2·4; 1·0; 7·0)	—	1·80 tq (2·3; 7·0)	—
H-6	3·96 ddq (11·3; 2·4; 6·2)	4·07 ddq (10·4; 3·4; 6·2)	4·12 um	3·81 ddd (11·1; 2·4; 6·2)	3·96 ddd (8·2;, 5·4; 2·4)	3·61 bddd (9·5; 8·3; 2·8)	3·63 ddd (8·1; 5·7; 2·3)	3·29 ddd (9·7; 8·3; 2·7)
CH_2-2	—	—	1·50 ddq (13·7; 5·0; 7·6) 1·45 ddq (13·7; 5·1; 7·6)	1·55 dq (2 H) (5·1; 7·6)	1·51 ddq (13·7; 5·1; 7·6) 1·46 ddq (13·7; 5·1; 7·6)	1·52 ddq (13·7; 5·2; 7·5) 1·48 ddq (13·7; 5·2; 7·5)	[c]	1·51 dq (2 H) (5·1; 7·4)
CH_3-2	1·28 d (5·1)	1·25 d (5·1)	0·78 t (7·6)	0·87 t (7·6)	0·80 t (7·6)	0·83 t (7·5)	0·92 t (7·5)	0·94 t (7·4)
NH(CH)	—	—	7·50 b	≈7·30[d]	7·49 b	7·46 b	7·57 b	7·37 b
$NH(CH)_2$	—	—	7·63 b	≈7·40[d]	7·64 b	7·50 b	7·41 b	7·47 b

CH_2-4	—	—	4·98 dd (14·8; 6·1) 4·73 dd (14·8; 5·1)	[c] 4·76 bdd (≈15·0; 5·2)	4·98 dd (14·8; 6·0) 4·72 dd (14·8; 5·0)	4·93 dd (15·0; 5·9) 4·75 dd (15·0; 5·3)	4·84 bdd (15·0; 5·5) 4·77 dd (15·0; 5·4)	4·89 bdd (15·0; 5·9) 4·77 dd (15·0; 5·5)
C_6H_5	8·13 m (*o*) 7·49 m (*m*) 7·67 m (*p*)	—	7·37 m (*o*) 7·32 m (*m*) 7·25 m (*p*)	7·37 m (*o*) 7·32 m (*m*) 7·25 m (*p*)	7·23—7·39 m	7·21—7·41 m	7·23—7·39 m	7·23—7·43 m
CH_3-5	—	—	—	—	1·09 d (7·0)	0·85 d (7·0)	0·90 d (7·0)	0·86 d (6·6)
CH_2-6	—	—	—	— —	1·53 ddq (13·7; 8·2; 7·4) 1·36 ddq (13·7; 5·4; 7·4)	1·68 ddq (14·0; 2·8; 7·3) 1·35 ddq (14·0; 8·3; 7·3)	[c] [c]	1·74 ddq (14·0; 2·7; 7·5) 1·40 ddq (14·0; 8·3; 7·5)
CH_3-6	1·25 d (6·2)	1·19 d (6·2)	1·14 d (6·2)	1·18 d (6·2)	0·90 t (7·4)	0·93 t (7·3)	0·89 t (7·5)	0·88 t (7·5)

[a] Axial thioureido group; [b] equatorial thioureido group; [c] overlapped by the signal of major isomer; [d] overlapped with the aromatic protons.

TABLE II

^{1}H NMR chemical shifts (δ, ppm) and coupling constants of substituted 1,3-dioxanes in $CDCl_3$

Hydrogen	*IIa* benzoate	*IIIa*	*IVb*[a]	*IVb*[b]	*V*	*VI*	*VII*	*VIII*
H-2	4·94 q (5·1)	5·20 q (5·1)	4·92 t (≈5·0)	4·52 t (5·3)	4·90 t (5·0)	5·15 bt (≈5·0)	4·54 t (5·1)	4·56 t (5·3)
H-4	6·14 dd (10·0; 2·7)	5·60 dd (3·9; 1·6)	5·35 bddd (5·1; ≈4·0; 2·8)	5·24 b	5·03 bd (3·6; ≦2)	4·89 b	5·26 b	5·15 b
H-5ax	1·70 ddd (12·6; 10·0; 11·3)	1·90 ddd (13·6; 10·7; 3·9)	1·85 ddd (14·3; 11·9; 5·1)	1·44 m[c]	—	2·03 ddq (10·7; 4·8; 7·2)	—	1·56[d]
H-5eq	1·91 dt (12·6; 2·7; 2·4)	1·72 ddd (13·6; 2·9; 1·6)	≈1·60	1·81 dt (12·8; 2·8; 2·2)	1·58[d]	—	1·75 tq (2·2; 6·8)	—
H-6	3·90 ddq (11·3; 2·4; 6·2)	4·10 ddq (10·7; 2·9; 6·2)	4·00 ddq (11·9; ≦2; 6·2)	3·78 ddq (11·2; 2·2; 6·2)	3·79 ddd (8·0; 5·7; 2·4)	3·48 ddt (10·7; 8·7; 2·8)	3·53 ddd (7·9; 5·7; 2·2)	3·21 ddd (9·4; 8·8; 2·7)
CH_2-2	—	—	1·54 dq (2 H) (≈5·0; 7·5)	1·46 ddq (1 H) (13·5; 5·9; 7·5) [e]	1·4—1·6 m (2 H)	1·46 ddq (1 H) (13·9; 5·3; 7·5) 1·56 ddq (1 H) (13·9; 5·1; 7·5)	1·4—1·6 m (2 H)	1·56 dq (2 H) (5·4; 7·5)
CH_3-2	1·43 d (5·1)	1·34 d (5·1)	0·77 t (7·5)	0·75 t (7·5)	0·915 t (7·4)	0·95 t (7·5)	0·91 t (7·4)	0·92 t (7·5)
NH(CH)	—	—	6·63 bd (2·8)	6·51 b	6·50 b	6·31 d (3·9)	6·22 b	6·61 b
$NH(CH_2)$	—	—	7·20 bt (5·5; 5·1)	6·80 b	7·18 bt (5·5; 5·2)	7·16 t (4·9)	6·76 bt (5·5; 5·2)	6·85 bt (≈5·0)

CH_2-4	—	—	4·90 dd (14·7; 5·5) 4·77 dd (14·7; 5·1)	4·84 um 4·69 um	4·91 dd (14·6; 5·5) 4·75 dd (14·6; 5·2)	4·92 bdd (14·6; 5·3) 4·76 dd (14·6; 5·1)	4·77 bdd (14·6; 5·5) 4·69 bdd (14·6; 5·2)	4·91 bd 4·63 bd
C_6H_5	8·10 m (*o*) 7·45 m (*m*) 7·58 m (*p*)	—	7·27—7·37 m	7·27—7·37 m	7·26—7·36 m	7·26—7·36 m	7·26—7·36 m	7·26—7·36 m
CH_3-5	—	—	—	—	1·09 d (7·0)	0·91 bd (6·8)	0·90 bd (6·8)	0·88 bd (7·2)
CH_2-6	—	—	—	—	1·57[d] 1·35 ddq (13·9; 5·7; 7·5)	1·66 ddq (14·0; 2·8; 7·5) 1·37 ddq (14·0; 8·7; 7·5)	1·57[d] 1·35[d]	1·72 dd (14·0; 2·7; 7·4) 1·39 ddq (14·0; 8·8; 7·4)
CH_3-6	1·32 d (6·2)	1·25 d (6·2)	1·22 d (6·2)	1·24 d (6·2)	0·77 t (6·2)	0·77 t (7·5)	0·78 t (7·5)	0·78 bt (7·5)

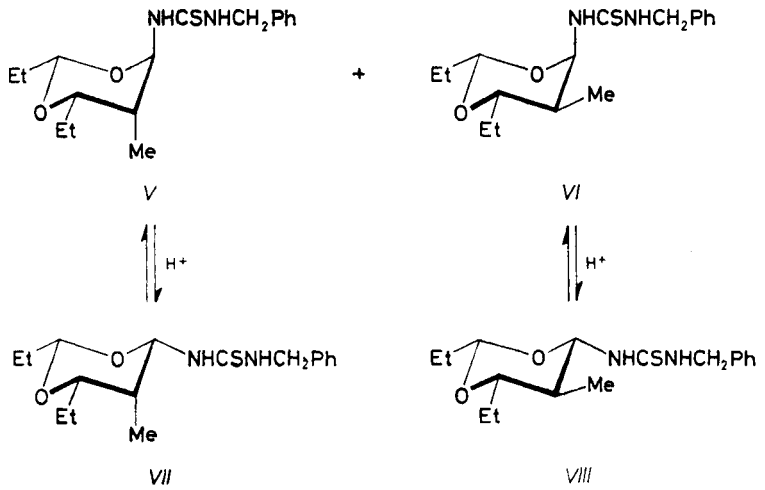
[a] Axial thioureido group; [b] equatorial thioureido group; [c] overlapped (*J*-values not obtained); [d] signal position determined from 2D-COSY spectrum; [e] the other H overlapped by the signal of major isomer.

TABLE III

^{13}C NMR chemical shifts (δ, ppm) of substituted dioxanes in CD_3COCD_3 and $CDCl_3$

Carbon	*IIa* benzoate	*IIIa*	*IVb*[a]	*IVb*[b]	*V*	*VI*	*VII*	*VIII*
				in CD_3COCD_3				
C-2	93·86	94·13	95·68	101·43	96·43	96·01	102·41	101·32
C-4	97·17	83·12	78·55	78·46	84·68	81·81	84·56	86·43[d]
C-5	37·81	37·84	36·17	38·60[d]	34·74	37·59	35·56	39·57[d]
C-6	71·49	68·62	68·53	72·20	76·29	77·97	81·30	82·64
CH_3	21·56	21·24	21·66	21·73	11·45	11·93	10·04	11·92
	21·00	20·88	8·46	8·57	9·95	9·36	8·33	9·63
					8·29	8·51	5·65	8·57
CH_2	—	—	28·46	28·53	28·38	28·52	28·40	28·56
					25·88	26·23	25·88	26·28
C=S	—	[c]	[c]	[c]	184·55	[c]	184·50	[c]
C—O	164·93	—	—	—	—	—	—	—
NCH_2	—	—	48·60[d]	—	49·02	48·95	48·95	48·67
C_6H_5: C_i	130·54	—	139·81	139·81	139·81	[c]	[c]	[c]
C_o	129·50	—	128·46	128·39	128·46	128·49	128·50	128·35
C_m	130·40	—	129·14	129·14	129·15	129·21	129·21	129·15
C_p	134·39	—	127·90	127·85	127·90	127·95	127·93	127·84
				in $CDCl_3$				
C-2	93·29	93·48	95·29	100·99	95·91	95·19	101·59	101·11
C-4	96·94	81·86	78·48	81·23	84·47	81·95	85·23	86·23
C-5	37·29	37·39	35·20	37·13	34·42	35·98	34·10	38·50[d]
C-6	71·07	67·81	67·88	71·64	75·59	77·29	80·71	82·43
CH_3	21·30	20·96	21·31	21·17	10·97	11·78	9·67	11·74
	20·71	20·50	8·09	8·14	9·58	8·93	7·98	9·42
					7·98	8·13	5·29	8·17
CH_2	—	—	27·48	27·56	27·41	27·38	27·41	27·62
					25·00	25·41	25·00	25·48
C=S	—	[c]	183·40	183·40	183·44	183·70	183·44	183·51
C=O	164·70	—	—	—	—	—	—	—
NCH_2	—	—	49·42	49·10[d]	49·63	49·70	49·23[d]	49·13[d]
C_6H_5: C_i	129·90	—	137·16	137·16	137·16	137·12	137·16	137·12
C_o	128·37	—	127·76	127·76	127·86	127·80	127·80	127·85
C_m	129·98	—	128·72	128·72	128·75	128·75	128·87	128·76
C_p	133·46	—	127·80	127·80	127·78	127·80	127·92	127·85

[a] Axial thioureido group; [b] equatorial thioureido group; [c] not detected; [d] broad.



SCHEME 1

the crystallization combined with chromatography. The ^1H and ^{13}C NMR spectra of *V*, *VI*, and *VIII* in CD_3COCD_3 (Tables I and III) proved uniformity of the products and enabled determination of relative configurations at the C-2, C-4, C-5, and C-6 carbon atoms. In compound *V* the value $J(4, 5) = 1{\cdot}0$ Hz corresponds to the diequatorial arrangement of the H-4 and H-5 protons, and the value $J(5, 6) = 2{\cdot}4$ Hz stands in accordance with equatorial and axial arrangements of the H-5 and H-6 protons, respectively. With the isomers *VI* and *VIII* we found high values of $J(5, 6) = 9{\cdot}5$ and $9{\cdot}7$ Hz, respectively, which unambiguously proves the diaxial arrangement of the H-5 and H-6 protons in the two isomers. With compound *VI*, the value of $J(4, 5) = 4{\cdot}8$ Hz indicates the equatorial position of the H-4 proton, whereas with compound *VIII* the value of $J(4, 5)$ could not be determined from the spectrum because of the extreme broadening of signals of the two protons H-4 and H-5. However, the equatorial position of thioureido group in *VIII* was proved by comparison of the ^{13}C NMR spectra of compounds *VI* and *VIII*. With compound *VII* we found distinct downfield shifts of the C-2 and C-6 carbon atoms (by 5·31 and 4·67 ppm, respectively) indicating the change of configuration of thioureido group from axial to equatorial position, which is similar to the above-discussed pair of isomers *IVb*. The configurational assignment given also agrees with the fact that *VI* can be transformed into more stable *VIII* (with all substituents in equatorial positions) by action of $NiCl_2$.

Interesting results were obtained from measurements of ^1H and ^{13}C NMR spectra of compounds *V*, *VI*, and *VIII* in $CDCl_3$. In all the cases the spectra indicated the presence of two compounds in solution, their ratio being somewhat changed with

time. The spectra of compounds *VI* and *VIII* contained the signals of the same components corresponding to the structure *VI* and *VIII* of various mutual ratios. This finding shows that in chloroform solution an equilibrium is slowly established between both the isomers. In the spectrum of compound *V*, however, we also identified its C-4 epimer *VII* with equatorial thioureido group. The structure *VII* is indicated by the coupling constants $J(4, 5) = J(5, 6) = 2{\cdot}2$ Hz and by the downfield shifts of C-2 and C-6 (by 5·68 and 5·12 ppm, respectively) as compared with the isomer *V*. Hence the pairs *V*, *VII* and *VI*, *VIII* represent C-4 epimeric pairs with the same equatorial orientation of 2- and 6-ethyl groups (Scheme 2), which is indicated by the very similar upfield shifts of the axial H-2 and H-6 protons accompanying – in the pairs given – the configurational change of thioureido group axial to equatorial (−0·36 and −0·59 ppm for H-2, and −0·26 and −0·27 ppm for H-6). Hence, the data given indicate the following relative configurations: *rel*-(2*S*,4*R*,5*R*,6*S*) for *V*, *rel*-(2*S*,4*S*,5*R*,6*S*) for *VII*, *rel*-(2*S*, 4*R*, 5*S*, 6*S*) for *VI*, and *rel*-(2*S*, 4*S*, 5*S*, 6*S*) for *VIII*.

The mass spectra of the thioureas *V*, *VI*, and *VIII* confirmed that they are isomers with molecular mass of 322; in addition, however, the mass spectra also exhibited weak peaks (rel. intensity of 0·2–0·8%) of dimeric structures. From literature[9] it is known that in the presence of anhydrous $HClO_4$ 1,3-dioxane can dimerize to the more stable 1,3,7,9-tetraoxacyclododecane. In our case such dimerization cannot be fully excluded, since the relatively acidic protons of the thiourea grouping could play the role of the acidic catalyst initiating the C—O bond splitting of dioxane and, hence, its dimerization. On the other hand, the presence of the thioureido grouping allows formation of dimeric structures with the help of intermolecular hydrogen bonds, which was confirmed[2] in the case of *rel*-(2*S*,4*S*, 6*S*)-2,6-dimethyl-4-(N′-benzylthioureido)-1,3-dioxane (*IVa*). In order to obtain unambiguous information about structure of the substances formed, we submitted the best crystallizing isomer *VI* to X-ray diffraction analysis. The results obtained are given in Table IV*. Perspective view of the molecule with atom numbering is depicted in Fig. 1. Intramolecular bond lengths and angles are unexceptional. From the results given it unequivocally follows that compound *VI* really is a derivative of 1,3-dioxane (not a derivative of 1,3,7,9-tetraoxacyclododecane) which has an almost ideal chair conformation with equatorial alkyl groups and axial ureido group. In the crystal (Fig. 2) the molecules are paired through two centrosymmetrically related hydrogen bonds N42—H42···O3, with the distances N—H 0·96(1) Å, H···O 2·16(1) Å and the angle N—H···O 153(2)°. All other molecular contacts are close to or longer than the sum of the van der Waals radii of the atoms involved. Hence in crystal the molecules of *VI* form dimeric structures of a type different from that observed in *rel*-(2*S*, 4*S*, 6*S*)-2,6-dimethyl-4-(N′-

* Supplementary materials comprising hydrogen atom coordinates, anisotropic temperature factors, and structure factors are available from the author (J.P.) on request.

TABLE IV

Atomic coordinates, equivalent isotropic thermal parameters, bond lengths and bond angles in *rel*-(2*S*,4*S*,5*S*,6*R*)-2,6-diethyl-5-methyl-4-(N′-benzylthioureido)-1,3-dioxane (*VI*). Standard deviations in parentheses. $U_{eq} = 1/3\sum_i \sum_j a_i a_j a_i a_j U_{ij}$

Atom	Coordinate . 10^4			U_{eq} . 10^4 Å^2	Bond length, Å		Bond angle, °	
	x/*a*	*y*/*b*	*z*/*c*					
S41	1387(1)	10111(1)	3230(1)	576(2)	S41—C41	1·682(2)	C2—O1—C6	111·2(2)
O1	3527(2)	6197(2)	8134(1)	477(5)	O1—C2	1·397(3)	C2—O3—C4	112·3(2)
O3	4205(2)	5880(2)	6023(1)	457(5)	O1—C6	1·445(3)	C4—N41—C41	124·6(2)
N41	1912(2)	7640(2)	5030(2)	464(6)	O3—C2	1·433(3)	C41—N42—C42	122·1(2)
N42	3575(2)	7393(2)	3309(2)	480(6)	O3—C4	1·436(4)	O1—C2—O3	110·2(2)
C2	4217(2)	6693(3)	7000(2)	447(7)	N41—C4	1·456(3)	O1—C2—C21	109·2(2)
C4	2704(3)	6094(2)	5707(2)	473(8)	N41—C41	1·351(3)	O3—C2—C21	108·0(2)
C5	1848(3)	5681(3)	6921(2)	508(8)	N42—C41	1·345(3)	O3—C4—N41	111·1(2)
C6	1948(2)	6547(3)	7941(2)	489(8)	N42—C42	1·472(3)	O3—C4—C5	110·2(2)
C21	5840(3)	6380(3)	7270(2)	525(8)	C2—C21	1·511(4)	N41—C4—C5	111·4(2)
C22	5964(3)	7221(3)	8281(3)	682(10)	C4—C5	1·521(3)	C4—C5—C6	109·2(2)
C41	2353(2)	8283(2)	3880(2)	434(7)	C5—C6	1·534(3)	C4—C5—C51	112·3(2)
C42	4260(3)	7992(3)	2121(2)	524(8)	C5—C51	1·529(4)	C6—C5—C51	115·3(2)
C43	5561(3)	8356(3)	2330(2)	514(8)	C6—C61	1·516(4)	O1—C6—C5	107·4(2)
C44	5908(3)	8467(3)	3530(3)	664(10)	C21—C22	1·517(4)	O1—C6—C61	106·8(2)
C45	7148(4)	8823(4)	3663(4)	935(13)	C61—C62	1·523(5)	C2—C21—C22	111·8(2)
C46	8035(4)	9076(4)	2613(6)	1091(20)	C42—C43	1·465(4)	C6—C61—C62	112·0(2)
C47	7669(4)	8995(4)	1411(5)	1013(17)	C43—C44	1·381(4)	S41—C41—N41	120·1(1)
C48	6456(3)	8627(3)	1257(3)	723(11)	C43—C48	1·397(4)	S41—C41—N42	123·2(1)
C51	254(3)	5844(3)	6631(3)	684(10)	C44—C45	1·383(5)	N41—C41—N42	116·7(2)
C61	1278(3)	6118(3)	9252(3)	674(10)	C45—C46	1·371(7)	N42—C42—C43	114·7(2)
C62	1509(4)	6941(4)	10240(3)	865(13)	C46—C47	1·379(8)	C42—C43—C44	122·6(2)
					C47—C48	1·371(5)	C42—C43—C48	117·9(2)
							C44—C43—C48	119·5(2)
							C43—C44—C45	119·8(3)
							C44—C45—C46	120·7(3)
							C45—C46—C47	119·4(4)
							C46—C47—C48	121·0(4)
							C43—C48—C47	119·6(3)

-benzylthioureido)-1,3-dioxane (*IVa*) with the thioureido group in equatorial position: Compound *IVa* forms intermolecular hydrogen bonds[2] without participation of oxygen atom of dioxane ring but only with participation of two thioureido groups, viz. N41—H41···S.

The results given confirm our original presumptions that the hemiacetal OH group can be transformed into respective isothiocyanate by reaction with $PO(NCS)_3$ and that the aldoxane *IIa* can represent a real intermediate in formation of isothiocyanate *IIIa* by the one-pot reaction of acetaldehyde, KSCN, and $POCl_3$.

EXPERIMENTAL

The melting points were determined with a Kofler apparatus and are not corrected. The ^1H NMR spectra were measured with an FT-NMR spectrometer Varian UNITY-500 (at 500 MHz) in $CDCl_3$ with tetramethylsilane as the internal standard or in CD_3COCD_3 (referenced to the residual solvent signal and the chemical shifts recalculated to TMS using the relationship δ(acetone) = 2·05 ppm). The interacting hydrogens were assigned with the help of the 2D-COSY spectra. The chemical shifts and coupling constants of protons were obtained by the 1st order analysis from the expanded spectra with enhanced resolution (Gauss–Lorentz apodization). The ^{13}C NMR spectra were measured with an FT-NMR spectrometer Varian UNITY-200 (at 50·3 MHz) with a brod band decoupling of protons in $CDCl_3$ or in CD_3COCD_3. The chemical shifts were referenced to the solvent signals and recalculated to TMS with the help of the relationships: $\delta(CDCl_3) = 77{\cdot}0$ ppm or $\delta(CD_3COCD_3) = 29{\cdot}8$ ppm. The "attached proton test" pulse sequence was used for the assignment of signals according to the number of directly attached hydrogen atoms. The mass spectra were measured with a JEOL apparatus DX 303/DA 5000 by the EI method at 70 eV or by the CI method.

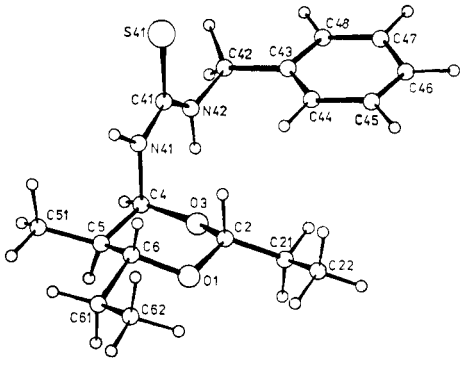


FIG. 1

Perspective view of the molecule *VI* with numbering of atoms

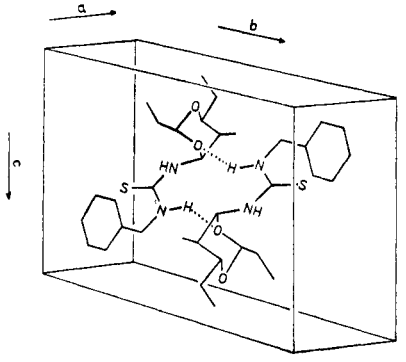


FIG. 2

Crystal packing of the molecules *VI*

The solvents used were dried by standard procedures and distilled. $PO(NCS)_3$, b.p. 120 to 122°C/160 Pa, was prepared according to ref.[6]. The other chemicals used were commercial products and were redistilled before use. Before use, KSCN was dried 24 h.

rel-(2*S*,4*R*,6*S*)-4-Benzoyloxy-2,6-dimethyl-1,3-dioxane

A mixture of 4·4 mg (50 mmol) fresh acetaldol, b.p. 63—65°C/1·5 kPa, and 2·2 g (50 mmol) freshly redistilled acetaldehyde was left to stand at room temperature 2 days. The raw aldoxane *IIa* thus obtained was treated with benzoyl chloride by a known procedure[7,8] and the product was submitted to chromatography (silica gel, $CHCl_3$–hexane 2 : 1) to give benzoate *IIa*, yield 70%, m.p. 89—91°C (methanol–water; ref.[8] gives m.p. 92—93°C, ref.[7] gives m.p. 90—91°C). The ^1H and ^{13}C NMR data are given in Tables I—III.

2,6-Dimethyl-4-isothiocyanato-1,3-dioxane (*IIIa*)

A solution of 6·6 g (50 mmol) raw aldoxane *IIa* (vide supra) in 50 ml benzene was cooled to 5°C, and 5·53 g (25 mmol) $PO(NCS)_3$ was added thereto under nitrogen during 1 h. The reaction mixture was stirred at 5°C 3 h, then it was left to attain room temperature, and, after 24 h, 30 ml hexane was added. The solution was decanted from the separated viscous oil which was additionally washed twice with 20 ml hexane. The combined hexane solutions were evaporated and the residue was distilled to give 4·25 g (50%) isothiocyanate *IIIa*, b.p. 80—83°C/267 Pa, which was in all respects identical with the isothiocyanate prepared[1,2] from $POCl_3$, KSCN, and acetaldehyde.

2-Ethyl-4-isothiocyanato-6-methyl-1,3-dioxane (*IIIb*)

Raw hemiacetal *IIb* was prepared from 4·4 g (50 mmol) acetaldol and 2·9 g (50 mmol) propanal as in above case and was treated with 5·5 g (25 mmol) $PO(NCS)_3$ as above to give 2·5 g (27%) isothiocyanate *IIIb*, b.p. 70—73°C/270 Pa. IR spectrum ($CHCl_3$): 2 040 cm^{-1} (NCS).

2,6-Diethyl-4-isothiocyanato-5-methyl-1,3-dioxane (*IIIc*)

a) *From hemiacetal* IIc *and* $PO(NCS)_3$. The above procedure was applied to 5·8 g (50 mmol) fresh propionaldol, b.p. 84—86°C/1·5 kPa, and 2·9 g (50 mmol) propanal to give the raw hemiacetal *IIc* which was then treated with 5·5 g (25 mmol) $PO(NCS)_3$ and worked up in the same way to give 9·34 g (87%) isothiocyanate *IIIc*, b.p. 106—110°C/530 Pa. IR spectrum ($CHCl_3$): 2 050 cm^{-1} (NCS).

b) *From* $POCl_3$, KSCN, *and propanal*. A suspension of 8·73 g (0·1 mol) KSCN in 33·5 g (0·6 mol) propanal was cooled to —40°C, stirred under nitrogen, and treated with 4·6 g (30 mmol) $POCl_3$ added drop by drop. The reaction mixture was left to reach room temperature and stand overnight. Then it was shaken with water and ether, the ethereal layer was dried and evaporated, and the residue was distilled to give 5·5 g (86%) isothiocyanate *IIIc*; the product was in all respects identical with that of the procedure *a*).

rel-(2*S*,4*R*,6*S*)-2-Ethyl-6-methyl-4-(N′-benzylthioureido)-1,3-dioxane (*IVb*)

A solution of 2·5 g (13 mmol) isothiocyanate *IIIb* in 15 ml ether was cooled to —10°C, stirred under nitrogen, and treated with a solution of 1·4 g (13·1 mmol) benzylamine in ether added drop by drop. Within 1 h, the temperature of the mixture was left to reach the room temperature and

10 ml hexane was added. The precipitate formed (2·8 g) was collected by filtration and recrystallized from acetonitrile to give 2·5 g (64%) *IVb*, m.p. 154–156°C. For $C_{15}H_{22}N_2O_2S$ (294·4) calculated: 61·19% C, 7·53% H, 9·52% N; found: 61·48% C, 7·21% H, 9·43% N. For the ^1H and ^{13}C NMR spectra see Tables I–III. Mass spectrum (EI), *m/z* (%): 294 (M^+, 22), 237 (11), 218 (13), 192 (39), 149 (13), 111 (12), 106 (54), 97 (15), 95 (11), 92 (13), 91 (100), 88 (18), 86 (14), 79 (13), 71 (28), 69 (21), 66 (14), 57 (42), 55 (26), 44 (37), 41 (23).

rel-(2*S*,4*R*,5*R*,6*S*)-, *rel*-(2*S*,4*R*,5*S*,6*S*)- and *rel*-(2*S*,4*S*,5*S*,6*S*)-2,6-Diethyl-5-methyl-4-(N′-benzylthioureido)-1,3-dioxanes (*V*, *VI*, and *VIII*)

A solution of 3·2 g (14 mmol) isothiocyanate *IIIc* in 10 ml ether was cooled to −10°C, stirred under nitrogen, and treated with a solution of 1·75 g (16 mmol) benzylamine in ether added drop by drop. The reaction mixture was stirred at room temperature 2 h. The precipitated solid (2·2 g) was collected by filtration and the filtrate was submitted to flash chromatography (silica gel; benzene–acetone 3 : 1) to give another portion of crystals (1·3 g). The combined products (3·5 g) contain three substances (TLC). A recrystallization from acetone gave 1·6 g (35%) *VI*, m.p. 161–163°C. The chromatography of mother liquors (silica gel; ether–hexane 2 : 1) gave 1·12 g (25%) *V*, m.p. 104–105°C (ether) and 0·75 g mixture *VI* + *VIII* which was rechromatographed (silica gel; chloroform). This procedure provided further 0·37 g (8%) *VI* and 0·31 g (7%) *VIII*, m.p. 148–151°C (acetone). For the ^1H and ^{13}C NMR spectra see Tables I–III. For $C_{17}H_{26}N_2O_2S$ (322·5) calculated: 63·31% C, 8·13% H, 8·69% N.

V: found: 63·51% C, 8·32% H, 8·42% N. Mass spectrum (CI), *m/z* (%): 646 (2 M^+ + 2, 0·8), 324 (20), 323 (M^+ + 1, 100), 265 (10), 247 (21), 207 (26).

VI: found: 63·28% C, 8·22% H, 8·43% N. Mass spectrum (CI), *m/z* (%): 646 (2 M^+ + 2, 0·4), 324 (21), 323 (M^+ + 1, 100), 305 (14), 265 (37), 195 (11), 91 (10), 59 (23).

VIII: found: 63·41% C, 8·29% H, 8·35% N. Mass spectrum (CI), *m/z* (%): 642 (2 M^+ + 2, 0·2), 324 (19), 323 (M^+ + 1, 93), 305 (13), 265 (33), 207 (90), 195 (20), 156 (20), 91 (29), 59 (100).

Epimerization of *VI* to *VIII*

A solution of 640 mg (2 mmol) *VI* in 25 ml nitromethane was treated with 480 mg (2 mmol) $NiCl_2.6\,H_2O$. The intensively green solution formed was left to stand at room temperature 24 h, filtered, and the filtrate was treated with hexane to give 400 mg (69%) crystalline *VIII*, m.p. 148–150°C.

Crystal Structure Determination of *rel*-(2*S*,4*R*,5*S*,6*S*)-2,6-Diethyl-4-(N′-benzylthioureido)-1,3-dioxane (*VI*)

Colourless prismatic crystals (from acetone–heptane). Triclinic $P\bar{1}$, $a = 9{\cdot}583(1)$, $b = 9{\cdot}693(2)$, $c = 10{\cdot}597(1)$ Å, $\alpha = 77{\cdot}55(1)$, $\beta = 84{\cdot}53(1)$, $\gamma = 67{\cdot}84(1)°$, $V = 890{\cdot}1(6)$ Å^3, $Z = 2$, $\varrho_m = 1{\cdot}19(1)$, $\varrho_x = 1{\cdot}203$ g cm^{-3}. A 0·40 × 0·22 × 0·10 mm crystal was measured with a CAD4 diffractometer at room temperature. Lattice parameters were refined from 21 reflections in the range of $16 < \theta < 20°$. The intensities were measured between $-11 < h < 11$, $-11 < k < 11$, $0 < l < 13$; four standard reflections were monitored every 30 min and showed no significant fluctuation. The absorption of the MoK_α radiation used ($\lambda = 0{\cdot}71069$ Å) was neglected, $\mu = 0{\cdot}18$ mm^{-1}. Out of 3 488 symmetrically independent reflections, 2 425 fulfilling the criterion $I > 1{\cdot}96\sigma(I)$ were used in the further treatment.

The structure was solved by direct methods[10] and refined by full-matrix least squares[11]. All hydrogen atoms were clearly discernible in the electron density map. The N-bonded hydrogens were then fixed in the positions found from the map and the remaining hydrogens in the theoretical positions assuming the C—H distance of 1·08 Å and the proper hybridization at the carbon atoms. In the final refinement cycles, scale factors, atomic coordinates of non-H atoms, and temperature factors (anisotropic for non-H, isotropic for H) were refined simultaneously. The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = (\sigma^2(F) + 0{\cdot}0009F^2)^{-1}$. At convergence, $R = 0{\cdot}045$, $wR = 0{\cdot}054$; the final difference map was featureless with extreme values of 0·25 and $-0{\cdot}18$ eÅ^{-3}.

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