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Heterocycles. CI. Syntheses and Isomerizations of Some Allylthio Nitrogen Heterocycles

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Allylthio nitrogen heterocycles were isomerized under the influence of base into the corresponding propenylthio analogs. Subsequently, isomerization of the resultant *cis*-propenylthio compounds afforded the *trans*-isomers. In the case of 2-allylthiobenzothiazole isomerization is followed by hydrolytic cleavage of the side chain. Similar behaviour was observed in the 1,2,3-benzotriazine series.

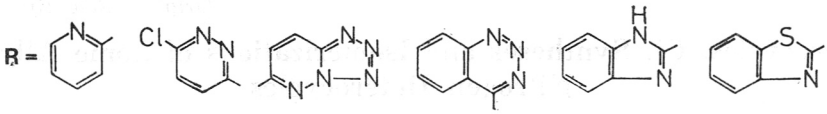
Allylthio heterocycles with an adjacent ring-nitrogen represent a class of compounds which may undergo several types of transformations. Of particular interest is the thio-Claisen rearrangement, which has been observed with 4-allylthioquinolines[1] and proceeds in a different way from the normal Claisen rearrangement. Moreover, the formation of some bi- or tricyclic products from allylthiothiophenes[2] or 4-allylthioquinolines[3] is indicative of a thio-Claisen rearrangement. Similarly, 2-allylthioquinolines were rearranged thermally or in the presence of a base into the corresponding propenylthio derivatives[4]. The formation of the latter was observed also in the aryl series[5]. Among these compounds, 2-allylthiopyridine, as the sole representative of heterocyclic compounds, was isomerized into 2-propenylthiopyridine and this was believed to exist in the *trans* form.

In connection with our studies concerning ring openings and isomerizations of some bicyclic heterocycles[6–8] it seemed of interest to investigate the possibilities of isomerizations or cyclizations of allylthio substituted heterocycles. In fact, isomerizations occurred and the conversion of allylthio heterocycles into the isomeric propenylthio derivatives with subsequent isomerization at the double bond could be followed by NMR spectroscopy or performed on preparative scale with the isolation and characterization of products.

2-Allylthiopyridine (Ia, $R_1 = H$) is isomerized in the presence of alkali into the corresponding 2-propenylthio derivative (IIa, $R_1 = H$) in 45 min. at 65 °C. The initially formed *cis*-isomer is then slowly isomerized into the corresponding *trans*-isomer and after 1 h the ratio of *cis* and *trans* isomers is about 2:3. In the analogous pyridazine series (Ib, $R_1 = H$), the isomerization to IIb ($R_1 = H$) is much easier and is complete in 10 min. However, during this time the isomerization is accompanied by nucleophilic substitution of the chlorine atom (to an extent of about 60%) and *cis-trans* isomerization of the side chain (ratio *cis* and *trans* is about 7:3). After 50 min. the formation of III is complete.

A similar hydrolytic cleavage was observed with If ($R_1 = H$). After isomerization into IIf ($R_1 = H$) hydrolysis of the propenylthio group took place

I II



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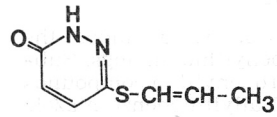

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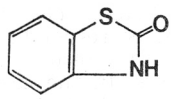
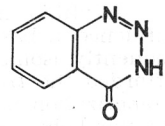
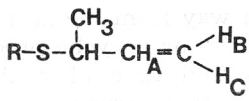


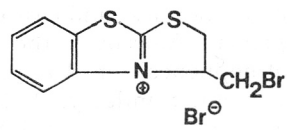
IV



V



VI



VII

and after 90 min. at 65 °C the reaction mixture consisted of 69% of IIf (R_1 = H), 14% of IV and 17% of the starting material, whereas after 150 min. these compounds were present in amounts of 67%, 22% and 11%. After 1 day only IV was present.

No hydrolytic cleavage was observed with Ie (R_1 = H). Here, the conversion into IIe (R_1 = H) was 13% after 90 min., 23% after 150 min. and 97% after 25 h. Again, the conversion is followed by *cis-trans* isomerization and after 4 h the ratio of *cis* and *trans* isomers is 4:3, after 8 h 1:2. The lack of reactivity for hydrolytic cleavage of the propenylthio group in the benzimidazole series, as observed above with the analogous benzothiazole, is due to the fact that in the presence of bases the heterocycle is in the form of the conjugated base. Moreover, studies on the reactivity of 2-halobenzothiazoles and 2-halobenzimidazoles in nucleophilic substitution reactions have shown the reactivity of the former[9,10].

4-Allylthio-1,2,3-benzotriazine (Id, R_1 = H) was also readily hydrolyzed to the corresponding 4-one (V), in 30 min. at 65 °C. When the reaction was followed by NMR at 46 °C, it could be observed that no isomerization took place, but that allyl mercaptan was slowly liberated with the direct formation of the 4-one. Under the action of alkali the latter is then decomposed into anthra-

nilic acid. On the other hand, it could be observed that the starting allylthio compound remained unchanged in a solution of quinoline or *N,N*-dimethylformamide at 160 °C during 25 h.

Similar experiments with some methylallylthio (VIa, VIe) and phenylallylthio compound (Ia, R_1 = Ph; Ie, R_1 = Ph) failed and there was no observable isomerization at 65 °C after 20 h. This is understandable if we take into consideration the stabilization of the intermediate carbanion by electronic effects of the groups present.

In this connection it is of interest to note that allyl ethers are isomerized in the presence of strong base into *cis*-vinyl ethers[11] and in a likewise manner, terminal olefins give with potassium *t*-butoxide in dimethyl sulfoxide olefins of predominantly *cis*-configuration[12]. Although the *cis*-isomer is thermodynamically less stable, its formation is due to a greater stability of the *cis*-allylic anion. This is in contrast to the more stable *trans*-allylic cation and results from a minimization of dipole-dipole repulsion between the allyl system and the electron donating alkyl group, if present[13].

Although a direct comparison of the ease of isomerization with the related allyl ethers cannot be made, it appears that with the compounds under investigation isomerization takes place with greater ease than with allyl ethers[14]. The ready isomerization of allylthio compounds was interpreted in terms of resonance forms involving a decet of electrons around sulfur[5,15]. Moreover, the isomerization can be interpreted solely as base-catalyzed reaction.

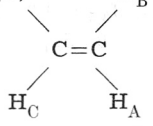
Finally, it should be mentioned that bromination of If (R_1 = H) led to VII, a derivative of the tricyclic system which we have described recently[16].

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage and are corrected. NMR spectra were recorded on a JEOL JNM-C-60HL spectrometer (TMS as internal standard) and mass spectra were obtained on a CEC 21—110 C instrument.

2-Allylthiopyridine (Ia, R_1 = H) was prepared according to the procedure described in the literature[5]. NMR spectrum ($CDCl_3$),

2-pyridyl—S—CH_2(D) H_B :



τ = 3.05 (ddd, H_3), 2.73 (ddd, H_4)
3.22 (ddd, H_5), 1.75 (ddd, H_6)
5.07 (m, H_A), 4.85 (m, H_B),

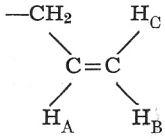
4.15 (tdd, H_C), 6.20 (deg. ddd., CH_2 (D)); = 8.4, $J_{3,4}$ = 8.4, $J_{3,5}$ = 1,7, $J_{3,6}$ = 1.0, $J_{5,6}$ = 4.8, $J_{4,5}$ = 7.2, $J_{4,6}$ = 1.8, $J_{A,B}$ = 11.7, $J_{A,C}$ = 9.0, $J_{B,C}$ = 16.2, $J_{C,D}$ = 6.3, $J_{A,D}$ = 1.0, $J_{B,D}$ = 1.0 Hz. Syntheses of 6-mercaptotetrazolo(1,5-*b*)pyridazine[17] and 6-chloropyridazine-3(2H)thione[18], used for the preparation of allylthio derivatives, were described previously.

General Procedure for the Preparation of Allylthio Heterocycles

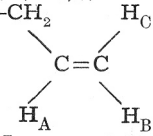
The corresponding thione (0.05 mole) was dissolved in a methanolic solution of sodium methoxide (prepared from 1.15 g of sodium and 50—70 ml of methanol), the corresponding allyl bromide (0.05 mole) was added and the mixture was heated at 50—60 °C for a few min. The solvent was evaporated *in vacuo* and the residue was extracted with chloroform. After evaporation of the solvent the product was crystallized or distilled *in vacuo*. The compounds obtained are listed in Table I, yields were 62—91%. In the case of Ie (R_1 = H or Ph), the product obtained after

evaporation of methanol was treated with water and the filtered product was crystallized from ethanol and water.

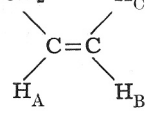
NMR data for allylthio heterocycles: Ic ($R_1 = H$) (DMSO-d_6): $\tau = 2.42$ (d, H_7), 1.58 (d, H_8), 6.06 (deg. ddd, CH_2), 4.75 (m, $=CH_2$), 4.15 (tdd, —CH=);



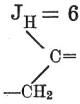
$J_{A,C} = 16.2$, $J_{A,B} = 9.3$, $J_{CH_2,A} = 6.3$, $J_{B,C} = 12.0$, $J_{CH_2,B} \approx 0.6$, $J_{CH_2,C} \approx 0.6$ Hz;
Id ($R_1 = H$) (DMF-d_7): $\tau = 2.0$. (m, $H_{5,6,7,8}$), 5.85 (deg. ddd, —CH_2—), 4.70 (m, CH_2=), 3.95 (tdd, —CH=); Ie ($R_1 = H$) ($CDCl_3$): $\tau = 2.60$ (m, $H_{4,7}$), 2.90 (m, $H_{5,6}$), 6.11 (deg. ddd, —CH_2—), 4.80 (m, CH_2=), 4.15 (tdd, —CH=);



$J_{A,C} = 16.2$, $J_{A,B} = 9.3$, $J_{B,C} = 12.0$, $J_{CH_2A} = 6.3$, $J_{CH_2,B} \approx 0{,}6$, $J_{CH_2C} \approx 0.6$ Hz;
If ($R_1 = H$) ($CDCl_3$): $\tau = 2.65$ (m, $C_{4,5,6,7}$), 6.10 (deg. ddd, —CH_2—), 4.80 (m, CH_2=), 4.15 (tdd, —CH=);

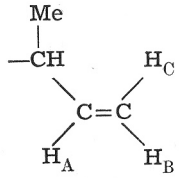


$J_{A,C} = 16.2$, $J_{A,B} = 9.3$, $J_{B,C} = 12.0$, $J_{CH_2A} = 6.3$, $J_{CH_2B} \approx 0.6$, $J_{CH_2,C} \approx 0.6$ Hz; Ia ($R_1 = Ph$) ($CDCl_3$): $\tau = 1.75$ (ddd, H_6), 3.1 (m, $H_{3,4,5}$), 6.07 (d, —CH_2—), 3.82 (deg. td, —CH_2—**CH**=), 3.52 (d, =**CH**—Ph), 2.90 (m, Ph); $J_{CH=CH,\ trans} = 14.5$, $J_{3,6} = 0.9$, $J_{5,6} = 4.8$, $J_{4,6} = 2.1$,

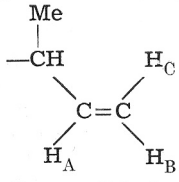


$J_H = 6.0$ Hz; Ie ($R_1 = Ph$) (DMSO-d_6): $\tau = 2.82$ (m, $H_{4,5,6,7}$), 5.90 (d, —CH_2—), 3.70 (deg. td, —CH_2**CH**=), 3.45 (d, =**CH**—Ph), 2.80 (m, Ph), $J_{CH=CH,\ trans} = 14.5$, $J_H = 6.0$ Hz;

VIa ($CDCl_3$): $\tau = 2.95$ (ddd, H_3), 2.65 (ddd, H_4), 3.12 (ddd, H_5), 1.65 (ddd, H_6), 8.52 (d, CH_3), 5.50 (m, **CH**—CH_3), 4.10 (ddd, H_A), 5.01 (ddd, H_B), 4.85 (ddd, H_C); $J_{A,B} = 9.6$, $J_{A,C} = 16.8$, $J_{B,C} = 12$, $J_{3,4} = 8.4$, $J_{3,5} = 1.7$, $J_{3,6} = 1.0$, $J_{4,5} = 7.2$, $J_{5,6} = 4.8$, $J_{4,6} = 1.8$, $J_{CHCH_3} = 6.7$, $J_{CH,A} = 6.6$, $J_{CH,B} = 0.9$, $J_{CH,C} = 0.9$ Hz;



VIe ($CDCl_3$): $\tau = 2.45$ (m, $H_{4,7}$), 2.80 (m, $H_{5,6}$), 2.52 (d, CH_3), 5.58 (m, **CH**CH_3), 4.08 (ddd, H_A), 5.06 (ddd, H_B), 4.88 (ddd, H_C); $J_{A,B} = 9.6$, $J_{B,C} = 12.0$, $J_{A,C} = 16.8$;



$J_{CH,A} = 6.6$, $J_{CH,B} = 0.9$, $J_{CH,C} = 0.9$, $J_{CHCH_3} = 6.7$ Hz.

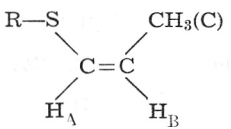
TABLE I

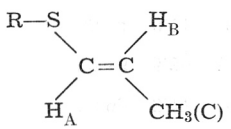
Allylthio Heterocycles

Compound	R_1	M. p./°C or b. p./°C	Crystallized from	Formula	Analysis					
					Calculated			Found		
					% C	% H	% N	% C	% H	% N
I b	H	66	*n*-hexane	$C_7H_7ClN_2S$	45.06	3.78	15.01	45.22	3.98	15.10
I c	H	90—91	ethanol/water	$C_7H_7N_5S$	43.52	3.65	36.26	43.46	3.54	35.75
I d	H	85—87	*n*-hexane	$C_{10}H_9N_3S$	59.10	4.46	20.68	58.65	4.23	20.56
I e	H	141—143	ethanol/water	$C_{10}H_{10}N_2S$	63.15	5.30	14.73	62.76	5.22	15.06
I f	H	121 (0.3 mmHg)	—	$C_{10}H_9NS_2$	57.97	4.38	6.76	58.08	4.48	6.93
I a	Ph	38—41	—	$C_{14}H_{13}NS$	73.99	5.77	6.16	73.69	5.94	6.36
I e	Ph	172—3	ethanol	$C_{16}H_{14}N_2S$	72.16	5.30	10.52	71.91	5.63	10.62
VI a	—	64 (9 mmHg)	—	$C_9H_{11}NS$	65.44	6.71	8.48	65.62	6.90	8.60
VI e	—	107	*n*-heptane	$C_{11}H_{12}N_2S$	64.69	5.92	13.72	64.82	6.04	13.36

TABLE II

NMR Data for cis- *and* trans-*Propenylthio Heterocycles*





Compound	Chemical shifts			Coupling constants, J/Hz			Ring protons τ/ppm and J/Hz	Chemical shifts			Coupling constants, J/Hz		
	H_A	H_B	$CH_3(C)$	J_{AB}	J_{AC}	J_{BC}		H_A	H_B	$CH_3(C)$	J_{AB}	J_{AC}	J_{BC}
II a, R_1 = H ($CDCl_3$)	3.35 (qd)	4.10 (qd)	8.12 (dd)	9.1	1.3	6.6	2.95 (ddd, H_3), 2.72 (ddd, H_4), 3.20 (ddd, H_5), 1.75 (ddd, H_6); $J_{3,4}$ = 8.4, $J_{3,5}$ = 1.7, $J_{3,6}$ = 1.0, $J_{4,5}$ = 7.2, $J_{4,6}$ = 1.8, $J_{5,6}$ = 4.8	3.55 (qd)	4.05 (qd)	8.18 (dd)	15.0	1.3	6.3
II e, R_1 = H (DMSO-d_6)	3.25 (qd)	3.90 (qd)	8.22 (dd)	7.5	1.4	6.3	2.65 (m, $H_{4,7}$), 3.00 (m, $H_{5,6}$)	3.48 (qd)	4.05 (qd)	8.16 (dd)	13.5	1.0	5.7

General Procedure for Isomerization of Allylthio Compounds into Propenylthio Analogs

The corresponding allylthio compound (2.0 g) was heated with Claisen alkali (30—40 ml, prepared from 35 g. of potassium hydroxide in 25 ml of water and adding methanol to 100 ml) in an atmosphere of nitrogen under reflux for several hours. For NMR measurements (at 65 °C) deuterated methanol was used.

2-Propenylthiobenzimidazole (IIe, $R_1 = H$)

Compound Ie ($R_1 = H$) (2.0 g.) was heated with Claisen alkali (40 ml) for 4 and 8 h. In each experiment the mixture was evaporated *in vacuo* to dryness, the residue was dissolved in water and acidified with hydrochloric acid (1 : 1) to *p*H = 7. The precipitate was filtered, dissolved in hot ethanol, and filtered from insoluble residue. The crystals which separated on cooling were collected. Purification was performed with TLC (PSC-Fertigplatten, Kieselgel F 245, Merck) with chloroform as the mobile phase. For elution, ethanol was used. After evaporation of the solvent *in vacuo*, the crystals were recrystallized from aqueous ethanol. M. p. about 135 °C. NMR analysis revealed that after 4 h reaction time the *cis* and *trans* products were formed in a ratio of 4 : 3, whereas after 8 h this ratio was 1 : 2.

3-Propenylthiopyridazin-6(1H)one (III)

Compound Ib ($R_1 = H$) (0.5 g) was heated with Claisen alkali (20 ml) under reflux for 2 h. The mixture was then evaporated *in vacuo* to dryness, the residue was dissolved in water and acidified with hydrochloric acid to *p*H = 4. The separated product was crystallized from *n*-hexane (yield 52%), m. p. 105 °C. Mass spectrum: $M^+ = 168$. NMR ($CDCl_3$): $\tau = 3.30$ (d, H_4), 3.02 (d, H_5), 3.66 (qd, —SC**H**=), 4.10 (qd, =C**H**—CH_3), $J_{4,5} = 9{,}5$, $J_{CH=CH,\ cis} = 9.0$ Hz.

Anal. $C_7H_8N_2OS$ (168.22) calc'd.: C 50.00; H 4.80; N 16.66%
found: C 49.55; H 4.65; N 16.61%.

Benzothiazolin-2(3H)one (IV)

The compound was prepared in a similar manner from If ($R_1 = H$). The product was dissolved in hot benzene and filtered. The filtrate was heated to boiling and then *n*-hexane was added until the solution became turbid. The separated crystals had m. p. 137 °C (lit.[19] gives m. p. 138 °C). The compound is identical with an authentic specimen. Mass spectrum: $M^+ = 151$. NMR ($CDCl_3$): $\tau = 2.95$ (m, $H_{4,5,6,7}$).

Isomerization of 4-Allylthio-1,2,3-benzotriazine (Id, $R_1 = H$)

Compound Id ($R_1 = H$) (0.7 g) was heated with Claisen alkali (30 ml) for 4 h. The solvent was evaporated *in vacuo* and the residue was treated with sulfuric acid (1 : 1) to *p*H = 4. Water (200 ml) was added and the product filtered off (there was obtained 0.03 g of unidentified compound with m. p. over 290 °C). The filtrate was extracted with chloroform (100 ml).

After evaporation of the solvent the residue (0.15 g) was sublimed at 110 °C/0.03 mmHg. The residue in the tube was crystallized from water, m. p. 222—225 °C, and was identified as compound V. The sublimate was sublimed again and it was identified as anthranilic acid.

3-Bromomethyl-2,3-dihydrothiazolo(2,3-b)benzithiazol-4-ium bromide (VII)

To a solution of compound If ($R_1 = H$) (2.0 g) in methylene chloride (25 ml) was added portionwise a solution of bromide in the same solvent. After addition of 3 moles of bromine no further consumption of bromine was observed. The separated product was filtered off and crystallized from *N*,*N*-dimethylformamide and toluene (yield 1.9 g, 54%), m. p. 239 °C. Mass spectrum: $M^+ = 286$, 288 ($M^+ + 2$, ^{81}Br). NMR (D_2SO_4): $\tau = 2.75$ (m, $H_{5,6,7,8}$), 5.70 (m, 2-CH_2), 5.60 (m, H_3), 6.70 (m, CH_2Br).

Anal. $C_{10}H_9Br_2NS_2$ (367.14) calc'd.: C 32.71; H 2.47; N 3.82%
found: C 32.65; H 2.62; N 3.89%.

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IZVLEČEK

Heterocikli. CI. Sinteze in izomerizacije nekaterih aliltio dušik vsebujočih heterociklov

Aliltio dušik vsebujoči heterocikli se pod vplivom baze izomerizirajo v ustrezne propeniltio analoge. Nato sledi izomerizacija nastale *cis*-propeniltio spojine v *trans* izomero. V slučaju 2-aliltiobenzotiazola se po izomerizaciji hidrolizira stranska veriga in podobno obnašanje je bilo mogoče opaziti tudi v vrsti 1,2,3-benzotriazina.

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