

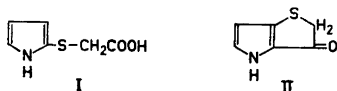
On a New Type of Rearrangement during Ring-closure

SALO GRONOWITZ and PINCHAS MOSES*

Chemical Institute, University of Uppsala, Uppsala, Sweden

Rearrangement occurs during the ring-closure of (2-thienylthio)acetic acid with sulphuric acid. The main ketone formed is 2H,3H-[3,2-b]thiophen-3-one (V), which is the only ketone obtained in the ring-closure of (3-thienylthio)acetic acid.

Gronowitz *et al.*^{1,2} have shown that a rearrangement occurs during the ring-closure of (2-pyrrolylthio)acetic acid (I) to 2H, 3H-thieno [3,2-b] pyrrole 3-one (II)



with polyphosphoric acid³.

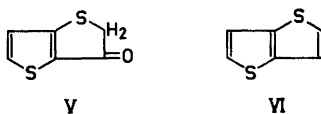
One of the mechanisms previously suggested² to account for the rearrangement involves electrophilic substitution by the cationoid carbonyl carbon at the α -carbon carrying the sulphur atom, with simultaneous rearrangement of the sulphur to the 3-position, a reaction which, as far as we know, has no precedence in the chemical literature. Granting the above mechanism, one can expect that this type of ring-closure with rearrangement will occur in other compounds having a thioglycolic acid group situated in that position, which is most reactive in electrophilic aromatic substitution, or more precisely, where the reactivity to electrophilic substitution is considerably greater than that of its *ortho* position, as is the case in the α -position of pyrrole relative to its β -position. This is also true in the thiophene series where Melander and Halvarsson⁴ have shown that the α -position is about 1000 times as reactive



* On leave of absence from the Hebrew University, Jerusalem, Israel.

as the β -position in electrophilic hydrogen exchange. We have therefore investigated the ring-closure of the isomeric (thienylthio) acetic acids III and IV.

The ring-closure of IV has been carefully studied by Challenger and Holmes⁵ in their work dealing with the structure of the thiophthenes. We could confirm their result that cyclization is best achieved with concentrated sulphuric acid. We did not obtain any defined ring-closed products when III was treated with polyphosphoric acid at 135°, or with anhydrous HF at room temperature. An attempted Friedel-Crafts ring-closure of the acid chloride in benzene, using stannic chloride as catalyst was also unsuccessful. Even in the ring-closure with sulphuric acid, the yields are low, Challenger and Holmes⁵ having obtained a yield of 14 % of the ketone * V in the best instance.



This is most probably due to extensive sulphonation of the starting acid, and possibly also of the product formed. These water-soluble by-products do not, however, interfere in the isolation and purification of the ketones. Tilak *et al.*⁶, who have extensively studied the cyclization of various (arylthio)acetaldehyde acetals, found that in the case of the (thienylthio)acetaldehydes the yields were also low^{7,9}.

We found that no rearrangement occurred in the cyclization of IV, only one ketone being produced namely 2H,3H-thieno[3,2-b]thiophene-3-one (V). There is no doubt as to the structure of this compound since Challenger and Holmes⁵ reduced it to the solid thiophene (VI), the structure of which has been determined by X-ray and dipole moment measurements^{5,9}.

In the ring-closure of III with concentrated sulphuric acid, however, we invariably obtained a mixture of two ketones, the total yields of which ranged from 9–11 %. Through fractional crystallization we managed to separate the two constituents from each other. The major constituent was shown by IR-spectroscopy and mixed m.p. to be identical with V, while the structure of the minor product (VII) analyzing correctly for C₁₀H₈O₂S₃ has not yet been determined. Quantitative analysis by means of IR-spectroscopy showed that VII and V are formed approximately in the ratio 1:9**.

It is excluded that V could have been formed from small amounts of IV possibly present in III. III was prepared through metalation of thiophene with *n*-butyllithium, followed by reaction with sulphur and chloroacetate. Since the metalation of thiophene takes place exclusively in the α -position, it is most improbable that any of the 3-isomer was formed. Furthermore IR-spectro-

* V may to some extent, exist in its tautomeric hydroxythiophene structure. The strong C=O stretching bond in its IR-spectra indicates, however, that it mainly exists in the ketoform.

** In earlier experiments when the reactions were carried out without stirring total yields were only 3–6 % and the product consisted of a mixture of VII to V in the ratio of 2:1. This procedure is to be preferred if it is desired to prepare VII.

scopy verified that, if the 2-isomer was at all contaminated with 3-isomer, the maximum quantity of the latter present was far below the amount required to account for the experimental results.

It is thus evident that the rearrangement during ring-closure first discovered by Gronowitz *et al.*^{1,2} in the pyrrole series is of a more general nature. It is possible that it might also have occurred in the cyclization of (2-thienylthio)acetaldehyde acetal with phosphorous acid and phosphorus pentoxide where Pandya and Tilak³ obtained thieno[2,3-b]thiophene in 11 % yield, and might have overlooked smaller amounts of VI during their purification of the crude product. We are continuing our investigations on the scope of this ring-closure with rearrangement and especially on its mechanism.

EXPERIMENTAL

(2-Thienylthio)acetic acid. A solution of 190 g (2.26 moles) of thiophene in 250 ml of dry ether was introduced into the usual nitrogen-swept four-necked apparatus and 1400 ml of 1.35 N *n*-butyllithium was added with stirring. The solution was refluxed for 2 h more, cooled to -70° and treated with 57.6 g (1.80 moles) of sulphur. The mixture was stirred at -70° for 1 h, poured into water, the aqueous layer separated and washed once with water. The aqueous solution containing the lithium salt of 2-thiophenethiol was then poured into a neutral solution made up from 170 g (1.82 moles) of chloroacetic acid and 124 g of potassium carbonate.

The reaction mixture was allowed to stand over-night at room temperature, extracted with ether, the aqueous layer cooled and acidified with dilute hydrochloric acid. The desired product separated out as an oil, which was extracted with ether. The ether layer was washed twice with water, treated with anhydrous sodium sulphate and Norit, filtered and the solvent removed *in vacuo*. The oily residue was cooled in an ice-salt mixture and the resulting crystalline mass was broken up and twice washed with a 1:9 ether-petrol-ether mixture; yielding 250 g (80 %) of light brown (2-thienylthio)acetic acid m.p. $42-46^{\circ}$. Recrystallization by dissolving in ether and massively diluting with petrol-ether raised the m.p. to $47-48^{\circ}$. (Found: C 41.24; H 3.58; S 36.71. Calc for $C_8H_6O_2S_2$ (174.2): C 41.36; H 3.47; S 36.80).

Ring-closure of (2-thienylthio)acetic acid. One part (by weight) of (2-thienylthio)acetic acid was added under stirring to ten parts (by volume) of concentrated sulphuric acid at 100° and the mixture stirred at that temperature for 45 min. It was cooled, poured onto crushed ice and extracted with chloroform. The solution was dried, the chloroform distilled off *in vacuo* (nitrogen atmosphere) and the oily residue cooled in ice. The resulting yellow solid product (9–11 %) was analyzed by IR-spectroscopy.

Through the fractional crystallization from alcohol of 7.5 g of crude product, which was shown by IR-analysis to consist of a mixture of 90 % of V and 10 % of VII we obtained 1.1 g of V m.p. $93-96^{\circ}$, whose IR-spectrum was identical to that of an authentic sample of 2H,3H-thieno[2,3-b]thiophene-3-one melting at $97-98.6^{\circ}$, prepared by ring-closing(3-thienylthio)acetic acid according to Challenger and Holmes⁵. One additional recrystallization raised the m.p. to $96.5-97.5^{\circ}$.

In addition 100 mg of an unknown ketone, m.p. $111-112.5^{\circ}$ was obtained. (Found: C 46.81; H 3.19; S 37.43. Calc. for $C_{10}H_8O_2S_2$: C 46.83; H 3.13; S 37.50). Its IR-spectrum was free from the characteristic peaks of V.

The spectroscopic analyses were carried out utilizing the ratio of the absorption of a characteristic peak of one component to that of the other component (*cf.* Ref.¹⁰). The peaks at 6.65μ and at 13.75μ of VII and those at 6.75 and 13.25μ of V were used. In three experiments carried out with adequate stirring the cyclization product consisted of 90 % V and 10 % VII. Without adequate stirring, it was found in seven experiments that the cyclization product consisted of 28–42 % of V and 72–58 % of VII. The IR-spectra were recorded on a Perkin-Elmer Infracord spectrophotometer.

Acknowledgements. The authors wish to express their thanks to Professor Arne Fredga for many fruitful suggestions concerning this work and for all facilities put at their disposal. The elementary analyses were carried out at the Analytical Department of the Chemical Institute and by Dr. A. Bernhardt, Mülheim (Ruhr). A grant from the *Swedish Natural Research Council* to S. G. is gratefully acknowledged.

REFERENCES

1. Gronowitz, S., Hörnfeldt, A.-B., Gestblom, B. and Hoffman, R. A. *J. Org. Chem.* **26** (1961) 2615.
2. Gronowitz, S., Hörnfeldt, A.-B., Gestblom, B. and Hoffman, R. A. *Arkiv Kemi* **18** (1961) 133.
3. Matteson, D. S. and Snyder, H. R. *J. Org. Chem.* **22** (1957) 1500.
4. Halvarson, K. and Melander, L. *Arkiv Kemi* **8** (1955) 29.
5. Challenger, F. and Holmes, J. L. *J. Chem. Soc.* **1953** 1837.
6. Tilak, B. D. *Tetrahedron* **9** (1960) 76.
7. Ghaisas, V. V. and Tilak, B. D. *Proc. Indian Acad. Sci.* **39 A** (1954) 14.
8. Pandya, L. J. and Tilak, B. D. *J. Sci. Ind. Res., India* **18 B** (1959) 371.
9. Cox, E. G., Gillot, R. J. J. H. and Jeffrey, G. A. *Acta Cryst.* **2** (1949) 356.
10. Moses, P. and Gronowitz, S. *Arkiv Kemi* **18** (1961) 119.

Received August 29, 1961.