# FUNCTIONAL DERIVATIVES OF THIOPHENE

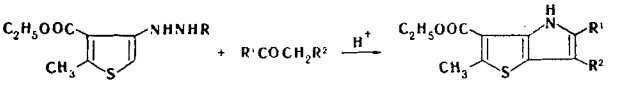
## XV.* β-THIENYLHYDRAZINE DERIVATIVES IN THE SYNTHESIS OF THIENO[3,2-b]PYRROLES

V. I. Shvedov, Yu. I. Trofimkin, V. K. Vasil'eva, and A. N. Grinev

UDC 547.734.737'74.07:542.953

A new preparative method for the synthesis of thieno[3,2-b]pyrrole derivatives by condensation of β-thienylhydrazine derivatives with diverse carbonyl compounds under the conditions of the Fischer reaction is described.

Thienopyrroles, as isosteres of indole derivatives, are of considerable theoretical and practical interest. However, the heretofore known methods for the synthesis of thienopyrroles are extremely laborious and have a number of limitations [2, 3]. We propose a new preparative method for the synthesis of thieno-[3,2-b]pyrroles that is based on the reaction of acyl derivatives of substituted β-thienylhydrazines [4] (Ia, b) with carbonyl compounds in the presence of acid catalysts, i.e., under the conditions of the Fischer reaction. A number of diverse thieno[3,2-b]pyrrole derivatives (IIa-o) were obtained in this way.



I a, b

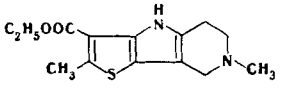
II a-o

I a R=CHO; b R=COCH$_3$

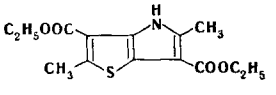
It was shown that carbonyl compounds of various classes – ketones of the aliphatic series, aliphatic aromatic and cyclic ketones, and carbonyl compounds with other functional groups, for example, levulinic acid and γ-chloropropyl methyl ketones – can be used for the synthesis of thieno[3,2-b]pyrroles.

In most cases the reaction is carried out in a methanol or acetic acid solution of hydrochloric acid and also by reaction of the carbonyl compounds with hydrazines Ia, b in the presence of p-toluenesulfonic acid. In addition to Ia, b, 2-methyl-3-carbethoxy-4-thienylhydrazine hydrochloride (III) was used in the synthesis of thieno[3,2-b]pyrroles. Heating an alcohol solution of hydrazine III with 1-methyl-4-piperidone gave 2,7-dimethyl-3-carbethoxy-5,6,7,8-tetrahydrothieno[3,2-b]pyrrolo]3,2-c]pyridine (IV) – the first representative of a new class of heterocyclic compounds – which is the thiophene analog of tetrahydro-γ-carbolines. It was established that, in contrast to the reaction of acetoacetic ester with phenylhydrazine, which gives a pyrazolone derivative, the reaction of III with acetoacetic ester gives a thieno[3,2-b]pyrrole derivative (V).

However, in an attempt to synthesize a thieno[3,2-b]pyrrole derivative from hydrazine Ia and acetylacetone we obtained only 1-(2-methyl-3-carbethoxy-4-thienyl)-2,4-dimethylpyrazole (VI). We were also un-



IV



V

*See [1] for communication XIV.

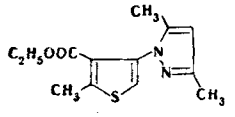
S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1324-1327, October, 1975. Original article submitted November 15, 1974.

TABLE 1. Thieno[3,2-b]pyrroles

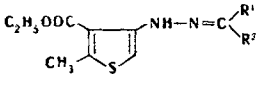
| Compound | $R^1$ | $R^2$ | mp, °C* | Reaction catalyst (solvent) | Empirical formula | Found, % | | | | Calculated, % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | S | C | H | N | S | |
| IIa | $CH_3$ | $CH_3$ | 170—171 | HCl ($CH_3OH$) | $C_{12}H_{15}NO_2S$ | 60,4 | 6,3 | 5,8 | 13,5 | 60,7 | 6,4 | 5,9 | 13,5 | 55 |
| IIb | $CH_3$ | $C_6H_5$ | 130—131 | HCl ($CH_3OH$) | $C_{17}H_{17}NO_2S$ | 68,0 | 5,5 | 4,9 | 10,5 | 68,2 | 5,7 | 4,7 | 10,7 | 80 |
| IIc | $C_6H_5$ | $C_6H_5$ | 109—110 | HCl ($CH_3OH$) | $C_{22}H_{19}NO_2S$ | 73,2 | 5,2 | 3,8 | 9,0 | 73,1 | 5,3 | 3,9 | 8,9 | 61 |
| IId | $CH_3$ | $CH_2CH_2Cl$ | 114,5—115,5 | HCl ($CH_3OH$) | $C_{13}H_{16}NO_2SCl$ | 55,1 | 5,7 | 5,1 | 11,3 | 54,7 | 5,6 | 4,9 | 11,2 | 61 |
| IIe | $CH_2C_6H_5$ | $COOCH_3$ | 94—95 | HCl ($CH_3OH$) | $C_{19}H_{19}NO_4S$ | 63,7 | 5,3 | 3,8 | 8,8 | 63,8 | 5,4 | 3,9 | 9,0 | 33 |
| IIf | $C_2H_5$ | $C_6H_5$ | 93—94 | HCl ($CH_3OH$) | $C_{18}H_{19}NO_2S$ | 69,0 | 6,0 | 4,7 | 10,4 | 69,0 | 6,1 | 4,5 | 10,2 | 67 |
| IIg | $C_6H_5$ | $CH_3$ | 84—85 | HCl ($CH_3COOH$) | $C_{17}H_{17}NO_2S$ | 67,9 | 5,7 | 4,9 | 10,7 | 68,2 | 5,7 | 4,7 | 10,7 | 47 |
| IIh | $CH_3$ | $CH_2COOH$ | 147—148 | HCl ($CH_3COOH$) | $C_{13}H_{15}NO_4S$ | 55,5 | 5,3 | 5,4 | 11,5 | 55,5 | 5,4 | 5,1 | 11,4 | 43 |
| IIi | $CH_3$ | $C_2H_5$ | 115—116 | p-Toluenesulfonic acid ($CH_3OH$) | $C_{13}H_{17}NO_2S$ | 62,3 | 6,8 | 5,6 | 12,5 | 62,1 | 6,8 | 5,6 | 12,8 | 50 |
| IIj | $CH_3$ | $CH_2CH_2OH$ | 116—117 | p-Toluenesulfonic acid ($CH_3OH$) | $C_{13}H_{17}NO_3S$ | 58,2 | 6,3 | 5,3 | 11,7 | 58,4 | 6,4 | 5,2 | 12,0 | 40 |
| IIk | $-(CH_2)_3-$ | | 170—171 | p-Toluenesulfonic acid ($CH_3OH$) | $C_{13}H_{15}NO_2S$ | 62,7 | 5,8 | 5,4 | 12,9 | 62,6 | 6,1 | 5,6 | 12,9 | 60 |
| IIl | $-(CH_2)_4-$ | | 148—149 | HCl ($CH_3OH$) | $C_{14}H_{17}NO_2S$ | 63,9 | 6,6 | 5,3 | 12,2 | 63,8 | 6,5 | 5,3 | 12,2 | 77 |
| IIm | $-(CH_2)_5-$ | | 128,5—129,5 | HCl ($CH_3OH$) | $C_{15}H_{19}NO_2S$ | 64,8 | 6,7 | 5,3 | 11,4 | 65,0 | 6,9 | 5,1 | 11,6 | 90 |
| IIn | $-(CH_2)_2CH(CH_3)CH_2$ | | 154—155 | HCl ($CH_3OH$) | $C_{15}H_{19}NO_2S$ | 65,0 | 6,7 | 5,2 | 11,7 | 65,0 | 6,9 | 5,1 | 11,6 | 65 |
| IIo | $o$-$C_6H_4(CH_2)_2$ | | 111—112 | p-Toluenesulfonic acid ($CH_3OH$) | $C_{18}H_{17}NO_2S$ | 69,4 | 5,3 | 4,5 | 10,3 | 69,4 | 5,3 | 4,5 | 10,3 | 65 |

*Compound IIc was recrystallized from methanol—acetone (1 : 1), IIk was recrystallized from methanol—dioxane (1 : 1), and the remaining compounds were recrystallized from methanol.

able to synthesize thieno[3,2-b]pyrrole derivatives by reaction of hydrazines Ia, b with acetone and acetophenone. As a result of this reaction we obtained substituted thienylhydrazones VIIa, b, which we were unable to cyclize to thieno[3,2-b]pyrroles.



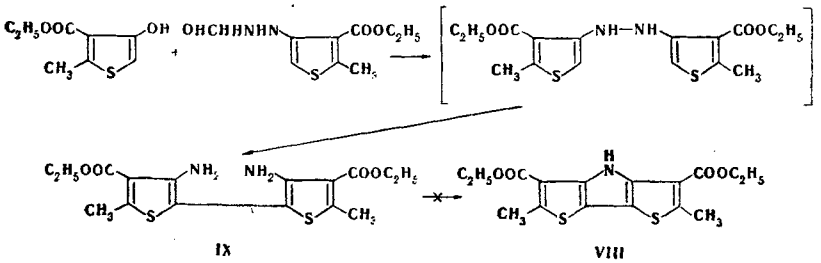
VI



VII a, b

VIIa $R^1=R^2=CH_3$, b $R^1=CH_3$, $R^2=C_6H_5$

In order to synthesize dithienopyrrole derivative VIII, we subjected Ia to reaction with 4-hydroxy-2-methyl-3-carbethoxythiophene. However, instead of VIII, we obtained 4-amino-2-methyl-3-carbethoxy-5-(4-amino-2-methyl-3-carbethoxy-5-thienyl)thiophene (IX), which we previously obtained in [4] as a side product in the synthesis of β-thienylhydrazine derivatives.



IX

VIII

The presence of intermolecular hydrogen bonds between the amino and carbethoxy groups in IX probably hinders cyclization of IX to dithienopyrrole VIII.

The IR spectra of IIa-o, IV, and V contain the absorption band of an NH group at 3310-3380 $cm^{-1}$. The magnitude of the absorption band is somewhat depressed, and this can be explained by the presence of an intermolecular hydrogen bond. As compared with the spectra of concentrated solutions of thieno-[3,2-b]pyrroles, one observes a sharp shift in the absorption band of the NH group to higher frequencies

(from 3340 and 3370 to 3470 and 3480 $cm^{-1}$) in the IR spectra of dilute solutions of these compounds, and this is in agreement with the literature data [5]. The absorption at 3100 $cm^{-1}$ associated with the vibrations of the aromatic CH bond of the thiophene ring vanishes in the spectra of IIa-o, IV, and V. The UV spectra of thieno[3,2-b]pyrroles contain two absorption maxima at 232 and 292-294 nm. The absorption bands at 3280 and 3340 $cm^{-1}$ that characterize the vibrations of the NH groups vanish in the IR spectrum of thienylpyrazole VI, and absorption at 975 $cm^{-1}$ due to vibrations of the pyrazole ring appears.

## EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with a Hitachi EPS spectrophotometer.

General Method for the Preparation of Thieno[3,2-b]pyrrole Derivatives. A solution of 0.005 mole of Ia, b, 0.005 mole of the carbonyl compound, and 0.005 mole of the catalyst in 50 ml of solvent (methanol) was refluxed (for the synthesis of IIa-f and IIi-o) or heated at 100° in acetic acid solution (for the synthesis of IIg, h),* after which the reaction solution was cooled, and the resulting precipitate was removed by filtration. Data on IIa-o and the reaction catalysts are presented in Table 1.

2,7-Dimethyl-3-carbethoxy-5,6,7,8-tetrahydrothieno[3,2-b]pyrrolo[3,2-c]pyridine (IV). A solution of 1.2 g (0.005 mole) of III and 0.6 ml of (0.005 mole) of 1-methyl-4-piperidone in 50 ml of ethanol saturated with hydrogen chloride was refluxed for 4 h, after which it was cooled, and the resulting precipitate was removed by filtration and dissolved in water. Compound IV was isolated from the solution by the addition of ammonium hydroxide to give 1 g (76%) of a product with mp 131.5-132.5° (from methanol). Found: C 60.2; H 6.5; N 10.2; S 11.5%. $C_{14}H_{18}N_2O_2S$. Calculated: C 60.4; H 6.5; N 10.1; S 11.5%.

2,5-Dimethyl-3,6-dicarbethoxythieno[3,2-b]pyrrole (V). A solution of 1 g (0.004 mole) of III and 0.6 ml (0.004 mole) of acetoacetic ester in 30 ml of glacial acetic acid was refluxed for 3 h, after which it was cooled and diluted with water. The resulting precipitate was removed by filtration to give 0.7 g (55%) of thienopyrrole V with mp 120-121° (from hexane). Found: C 57.0; H 5.5; N 4.7%. $C_{14}H_{17}NO_4S$. Calculated: C 57.0; H 5.6; N 4.7%.

1-(2-Methyl-3-carbethoxy-4-thienyl)-2,4-dimethylpyrazole (VI). A solution of 1.1 g (0.005 mole) of Ia, 0.52 ml (0.005 mole) of acetylacetone, and 0.4 ml (0.005 mole) of concentrated HCl in 15 ml of methanol was refluxed for 3 h, after which it was cooled and diluted with water. The resulting precipitate was removed by filtration to give 0.8 g (63%) of pyrazole VI with mp 72-73° (from hexane). Found: C 58.9; H 6.1; N 10.4; S 12.1%. $C_{13}H_{16}N_2O_2S$. Calculated: C 59.1; H 6.1; N 10.6; S 12.1%.

Acetone 2-Methyl-3-carbethoxy-4-thienylhydrazone (VIIa). A solution of 1.1 g (0.005 mole) of Ia, 0.36 ml (0.005 mole) of acetone, and 0.4 ml (0.005 mole) of concentrated HCl in 15 ml of methanol was refluxed for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration to give 0.5 g (45%) of hydrazone VIIa with mp 84.5-85.5° (from methanol). Found: C 55.0; H 6.6; N 11.5; S 13.3%. $C_{11}H_{16}N_2O_2S$. Calculated: C 55.0; H 6.6; N 11.7; S 13.3%.

Acetophenone 2-Methyl-3-carbethoxy-4-thienylhydrazone (VIIb). As in the preceding case, a solution of 1.1 g (0.005 mole) of Ia, 0.6 ml (0.005 mole) of acetophenone, and 0.9 g (0.005 mole) of p-toluenesulfonic acid in 15 ml of methanol gave 0.7 g (51%) of hydrazone VIIb with mp 117-118° (from methanol). Found: N 9.4; S 10.6%. $C_{16}H_{18}N_2O_2S$. Calculated: N 9.3; S 10.6%.

4-Amino-2-methyl-3-carbethoxy-5-(4-amino-2-methyl-3'-carbethoxy-5-thienyl)thiophene (IX). A solution of 0.8 g (0.0035 mole) of Ia, 0.68 g (0.0035 mole) of 4-hydroxy-2-methyl-3-carbethoxythiophene, and 0.65 g (0.0035 mole) of p-toluenesulfonic acid in 15 ml of methanol was refluxed for 4 h, after which it was cooled, and the resulting precipitate of IX was removed by filtration to give 0.5 g (41%) of a product with mp 144-145° (from dioxane). No melting-point depression was observed for a mixture of this product with a sample previously obtained in [4].

## LITERATURE CITED

1. V. I. Shvedov, I. A. Kharizomenova, N. V. Medvedeva, and A. N. Grinev, Khim. Geterotsikl. Soedin., 918 (1975).

*The reaction was carried out for 30 min for the synthesis of IIa-f and IIl-n and for 3 h for the synthesis of IIg-k and IIo.

2. W. W. Gale, A. N. Scott, and H. R. Snyder, J. Org. Chem., 29, 2160 (1964).
3. V. I. Shvedov, A. N. Grinev, and V. K. Vasil'eva, Khim. Geterotsikl. Soedin., 276 (1970).
4. V. I. Shvedov, Yu. I. Trofimkin, V. K. Vasil'eva, T. F. Vlasova, and A. N. Grinev, Khim. Geterotsikl. Soedin., 914 (1975).
5. W. Carpenter and H. R. Snyder, J. Amer. Chem. Soc., 82, 2592 (1962).

# SYNTHESIS OF 2-(ACYLMETHYL)BENZO-1,3-OXATHIOLS FROM ACETYLENIC KETONES

V. N. Elokhina, A. S. Nakhmanovich, I. D. Kalikhman, N. P. Sokol'nikova, and M. G. Voronkov

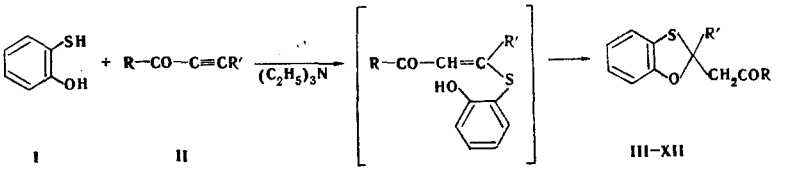
UDC 547.77.07

2-(Acylmethyl)benzo-1,3-oxathiols were synthesized by reaction of acetylenic ketones with o-mercaptophenol in alcohol in the presence of a catalyst – triethylamine.

It has been shown [1-3] that the formation of cyclic products as a result of "double addition" to the acetylenic bond is possible in the addition of some bifunctional compounds to acetylenes.

In developing our earlier research [4-6] we have studied the reaction of acetylenic ketones of various structures with o-mercaptophenol, which proceeds readily in alcohol in the presence of a catalyst – triethylamine – to give the hard-to-obtain 2-(acylmethyl)benzo-1,3-oxathiols (III-XII, Table 1) in high yields (70-98%).

The reaction of o-mercaptophenol with acetylenic alcohols probably proceeds through an intermediate step involving the formation of ketovinyl sulfides (addition of the thiol to the acetylenic bond) and cyclization of the latter to the corresponding benzo-1,3-oxathiols.




I II III-XII

III R=$C_4H_3S$, R′=$C_6H_5$; IV R=R′=$C_6H_5$; V R=$C_4H_3S$, R′=H; VI R=$CH_3$, R′=$C_6H_5$; VII R=$C_4H_3S$, R′=$C_4H_9$; VIII R=5-$C_2H_5$—$C_4H_2S$, R′=$C_4H_3S$; IX R=$C_4H_3S$, R′=$p$-$C_6H_4OCH_3$; X R=$C_4H_3S$, R′=$p$-$C_6H_4CH_3$; XI R=$C_6H_5$, R′=$C_4H_9$; XII R=$C_4H_3Se$, R′=$C_6H_5$

The structure of the compounds obtained was established by IR and PMR spectroscopy.

The IR absorption band of the C=O group lies at 1652-1681 $cm^{-1}$ for III-V and VII-XII and at 1705 $cm^{-1}$ for VI. The absorption band at 1070-1100 $cm^{-1}$ corresponds to the stretching vibrations of the C—O bond, whereas an absorption band at 680-710 $cm^{-1}$ is characteristic for the stretching vibrations of the C—S bond of the oxathiol ring. The absorption bands of the C=C bond and the OH group are absent in the IR spectra of III-XII.

Signals of olefinic and hydroxyl protons are absent in the PMR spectra of III-XII. The geminal protons of the methylene group in the $\alpha$ position relative to the C=O group give a quartet at $\delta$ 4.15 ppm; J = 18.6 Hz for IV and $\delta$ = 4.01 ppm; J = 16.8 Hz for III and V-XII. The multiplet at weak field, 6.64 +7.85 ppm,

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1328-1329, October, 1975. Original article submitted December 2, 1974.