SYNTHESIS OF 4H-THIENO[3,2-b]PYRROL-5(6H)-ONE

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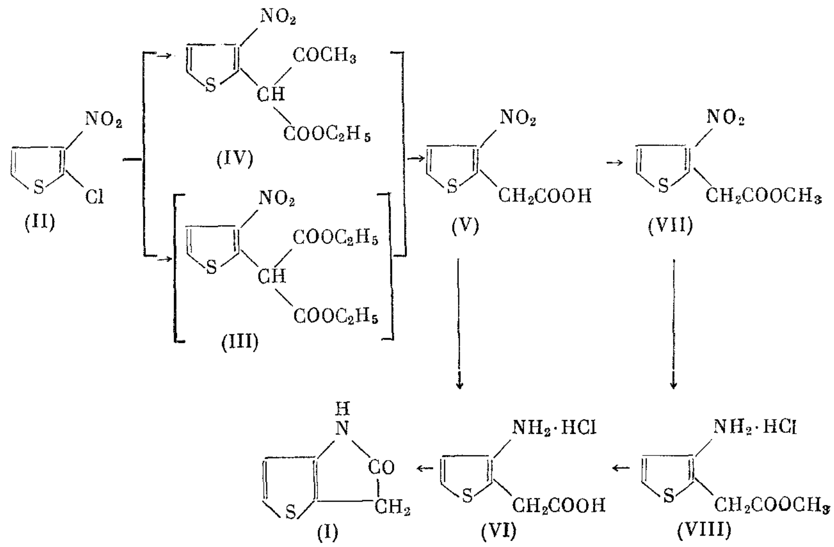
The cyclic system of indole forms the basis of a large number of compounds of practical importance. It might be supposed that the replacement of its benzene ring by the extremely similar thiophene ring would also lead to some interesting substances. The possibility of preparing compounds of this type was demonstrated by the synthesis of thieno[3,2-b]pyrrole [1].

We here report on the synthesis of a sulfur-containing isostere of oxindole — 4H-thieno]3,2-b]pyrrol-5(6H)-one (I) — which we shall refer to simply as thienopyrrolone in the further treatment. In the choice of reaction scheme for the synthesis we were guided by transformations which are well known in the benzene series. As our starting substance we took 2-chloro-3-nitrothiophene (II), whose chlorine atom is almost as active as the chlorine of 1-chloro-2,4-dinitrobenzene [2].



(II) was heated with two molecular proportions of sodiomalonic ester, the 3-nitro-2-thiophenemalonic ester (III) obtained (it was not isolated in the pure state) was hydrolyzed, and we obtained 3-nitro-2-thiopheneacetic acid (V) in 70% yield. We also obtained this acid in much lower yield by the condensation of (II) with sodioacetoacetic ester and subsequent hydrolysis of the resulting α-acetyl-3-nitro-2-thiopheneacetic ester (IC) with dilute hydrochloric acid. The identity of the samples of (V) obtained by the two methods was established on the basis of the complete identity of their IR spectra, the absence of depression in the melting point of a mixture, and identical behavior in paper chromatography.

The yield of (IV) in the condensation of (II) with acetoacetic ester was 40-47% and we were unable to increase it by varying the reaction conditions. As by-product bis(3-nitro-2-thienyl)acetic ester (IX) was formed in 5-10% yield; when the reaction was conducted in more dilute dry ether solutions, up to 15% of unchanged (II) was recovered. In view of data in the literature on the performance of nucleophilic substitution reactions in presence of alkali-metal fluorides [3], in the condensation of (II) with acetoacetic ester we used cesium fluoride, but even then, even with a large excess of acetoacetic ester, (IX) was formed in considerable amount and the yield of (IV) remained low.

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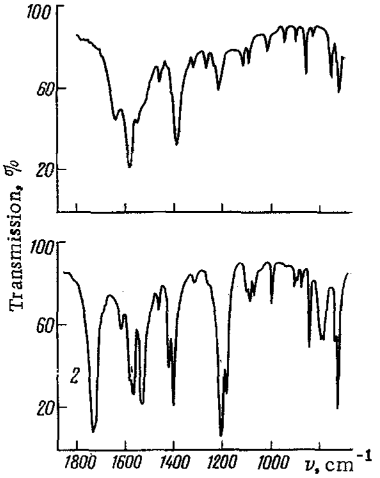

Fig. 1. IR spectra: 1) 3-amino-2-thiopheneacetic acid (VI); 2) hydrochloride of (VI).

By the reduction of the nitro acid (V) we expected to obtain thienopyrrolone (I), for in the case of analogous compounds of the benzene series cyclization occurs simultaneously with the reduction of the nitro group [4]. However, in the reduction of (V) with iron filings in presence of ammonium chloride we could only isolate 3-amino-2-thiopheneacetic acid (VI). Like other amino acids of the thiophene series [5], the free amino acid (VI) proved to be of low stability: it decomposes even during recrystallization, and it was therefore characterized as its hydrochloride and its N-benzoyl derivative. The structure of (VI) was confirmed by its chemical properties: an intense color reaction with p-dimethylaminobenzaldehyde (DAB) characteristic for primary amines; the ability to form salts, which makes it possible to isolate it on a cation exchanger; and IR spectral data. The IR spectrum* of the free amino acid (VI) contains absorption bands corresponding to the carboxyl ion (1580 cm^{-1}) and to NH_3^+ deformation vibrations (1640 and 1550 cm^{-1}). The IR spectrum of the hydrochloride of (VI) contains absorption bands due to carboxyl $C = O$ (1735 cm^{-1}) and NH_3^+ vibrations (1615, 1535 cm^{-1}) (Fig. 1).

According to paper chromatography, the product obtained by the reduction of (V) with tin and hydrochloric acid was identical to (VI). By the esterification of the nitro acid (V) we obtained an almost quantitative yield of its methyl ester (VII), the reduction of which led to methyl 3-amino-2-thiopheneacetate (VIII), which was isolated as the hydrochloride and characterized in the form of the benzoyl derivative. For the reduction of (VII) we tried aluminum amalgam and catalytic hydrogenation over palladized charcoal, but the best results were obtained by reduction with iron filings in presence of ammonium chloride. By hydrolysis with dilute hydrochloric acid the ester (VIII) was converted smoothly into the acid (VI). In view of the fact that the amino acid (VI) showed no tendency to undergo cyclization into (I), for the closing of the lactam ring we used cyclohexyl[2-(4-methyl-4-morpholinio)ethyl]carbodiimide p-toluenesulfonate [4-[2-[(cyclohexylimidocarbonyl)amino]ethyl]-4-methylmorpholinium p-toluenesulfonate] (CME-carbodiimide), which has been used successfully for the formation of a peptide link [7]. The solutions which we used were more dilute than those indicated in [7] so as to reduce the possibility of the occurrence of intermolecular reactions. Under these conditions we obtained thienopyrrolone (I) as the main product. (I) is a readily sublimed white crystalline powder (needles from water, rhombs from benzene), m.p. 150-151°. (I) is readily soluble in ether and chloroform, readily stable in an acid medium, and unstable to the action of dilute alkalies. In light it gradually darkens; with DAB it gives a pale-pink spot which gradually turns brown in light. The composition and structure of (I) were confirmed by the determination of molecular weight by the mass-spectrometric method and the results of IR spectroscopy.

In the spectrum of (I) (Fig. 2) the $C = O$ absorption band is shifted relative to the band of the original (VI) hydrochloride toward low frequencies (1700 cm^{-1}), which corresponds to the absorption of amide $C = O$; CH_2 absorption bands are present (2845 and 2920 cm^{-1}). In the IR spectrum of thienopyrrolone pelleted with KBr the region of NH stretch proved to be difficult for identification, and we therefore determined also the spectrum of a dilute solution of (I) in chloroform in this region; here there is a sharp band at 3460 cm^{-1} corresponding to the free NH stretching vibrations of secondary amides. All the above-cited bands of (I) are in good accord with the corresponding bands in the spectra of oxindole determined under the same conditions.

EXPERIMENTAL

The compounds obtained were identified by means of ascending paper chromatography on Leningrad grade B paper. R_f values of compounds in the solvent systems A (isopropyl alcohol — ammonia — water, 10 : 1 : 1) and B (butyl alcohol — acetic acid — water, 4 : 1 : 2) are given in Table 1. The spots were detected by UV radiation (violet fluorescence), and also with DAB (nitro compounds were first reduced on the paper with stannous chloride) and with 0.5 N NaOH (nitro compounds).

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*All the IR spectra cited here were determined with a UR-10 spectrophotometer on samples pelleted with KBr at a concentration of 4 mg of the substance to 800 mg of KBr. Here and later all assignments of absorption bands are made in accordance with [6].

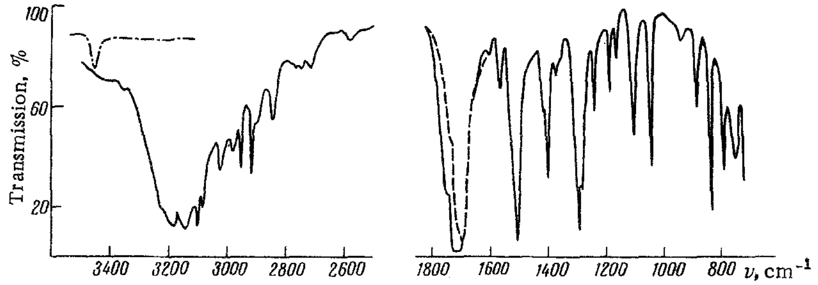

Fig. 2. IR spectrum of 4H-thieno[3,2-b]pyrrol-5(6H)-one: 1) in KBr, 0.5%; 2) in KBr, 0.09%; 3) in CHCl$_3$.

TABLE 1

Compound	R$_f$ in system	
	A	B
4H-Thieno[3,2-b]pyrrol-5(6H)-one (I)	—	0.88
2-Chloro-3-nitrothiophene (II)	0.93	—
α-Acetyl-3-nitro-2-thiopheneacetic ester (IV)	0.93	With front
3-Nitro-2-thiopheneacetic acid (V)	0.52	0.91
3-Amino-2-thiopheneacetic acid (VI)	0.27	0.70
Methyl 3-nitro-2-thiopheneacetate (VII)	Diffuse band	0.94
Methyl 3-amino-2-thiopheneacetate (VIII)	0.89	—
Bis(3-nitro-2-thienyl)acetic ester (IX)	0.9	—

2-Chloro-3-nitrothiophene (II) was prepared by the method given in [2] in 17.9% yield (based on the thiophene taken); m.p. 50.5-51.5° (hexane). The literature [2] gives m.p. 49.4-50.5°.

Condensation of (II) with Sodiomalonic Ester. 0.0366 g-atom of sodium wire was added in small portions to a solution of 0.0366 mole of freshly distilled malonic ester in 60 ml of dry ether. The mixture was stirred at room temperature for 6 h and then left overnight. With cooling with ice water a solution of 0.0183 mole of (II) in 15 ml of dry ether was added dropwise to the thick white suspension of sodiomalonic ester, and the mixture was stirred for 11 h at a bath temperature of 40-45° (the color of the mixture gradually changed from intense violet to bright red). The precipitate formed was filtered off, washed on the filter with ether, and dissolved in water; the ethereal filtrate was extracted with water and then with 2% NaOH solution until the alkaline extract became almost colorless. The combined aqueous alkaline extracts were carefully (with cooling with ice) acidified with excess of dilute hydrochloric acid (until the mixture was decolorized). (III), which then came out as an oily liquid, was separated by decantation, the acid aqueous solution was extracted several times with ether, and the combined extracts were washed with water until neutral. Ether was vacuum-evaporated completely, and 5.15 g of oily (III) remained. This was heated for 3.5 h with stirring with 100 ml of dilute (1 : 1) hydrochloric acid at a bath temperature of 110-115°; the hot turbid solution was filtered to remove resin. The needlelike crystals of (V) which came down on cooling were filtered off; weight 2.42 g [70.6%, based on the amount of (II) taken].

An analytical sample of (V) was obtained by reprecipitation from sodium carbonate solution with hydrochloric acid and subsequent crystallization from water (with active charcoal treatment) and from benzene; m.p. 156.5-157° (large glistening plates). (V) dissolves in solutions of sodium carbonate and caustic alkalies with a yellow coloration. Found: C 38.5; 38.6; H 2.69; 2.73; N 7.58; 7.59; S 16.9, 17.0%. $C_6H_5NO_4S$. Calculated: C 38.5; H 2.69; N 7.48; S 17.1%. IR spectrum: 1330, 1545 cm^{-1} (NO$_2$); 1655, 1705 cm^{-1} (carboxyl C = O). In the IR spectrum of a 3% solution of (V) in tributyl phosphate there is only one C = O absorption band at 1755 cm^{-1}.

Condensation of (II) with Sodioacetoacetic Ester. This was conducted under the conditions described above for the condensation of (II) with sodiomalonic ester. A solution of 0.0245 mole of (II) in 25 ml of dry ether was added to a suspension prepared from 0.049 mole of freshly distilled acetoacetic ester and 0.049 g-atom of sodium in 20 ml of dry ether, and the mixture was stirred for 11 h at a bath temperature of 40-45°.

The reaction mixture was carefully extracted with water and with 2% NaOH solution (until the alkaline extract became almost colorless).* The aqueous alkaline extracts were carefully (with cooling with ice) acidified with excess of dilute HNO_3 (until the color changed from dark red to yellow). The precipitate of (IV) formed was filtered off after a few hours and crystallized from aqueous alcohol. The weight of (IV) was 2.89 g (46.1%); m.p. 73-74° (after several crystallizations). (IV) dissolves in alkalies with a red coloration. Found: C 46.7; 46.9; H 4.39; 4.36; N 5.56; 5.49; S 12.4; 12.6%. $C_{10}H_{11}NO_5S$. Calculated: C 46.7; H 4.31; N 5.45; S 12.5%. IR spectrum: 1630 cm^{-1} (ketone C = O in β-keto ester); 1670 cm^{-1} (ester C = O in β-keto ester); 1330, 1555 cm^{-1} (NO_2).

3-Nitro-2-thiopheneacetic Acid (V). 1 g of (IV) was heated with stirring with 25 ml of dilute (1 : 15) HCl for 3 h at a bath temperature of 100-110°. The hot solution was filtered to remove resin and then cooled. The precipitated crystals of (V) were filtered off; weight 0.64 g [78.5%, based on the (IV) taken]. After reprecipitation from sodium carbonate solution with hydrochloric acid and crystallization from water (with active charcoal treatment) and from benzene it had m.p. 156.5-157.5°.

Methyl 3-Nitro-2-thiopheneacetate (VII). 5.6 g of (V) was dissolved in 110 ml of absolute methanol, and with cooling with ice the solution was saturated with dry hydrogen chloride for 6 h, left overnight at room temperature, and then boiled for 1 h at a bath temperature of 60-70°. Methanol was vacuum-distilled off, the residue was dissolved in ether, the solution was filtered, and ether was evaporated. The residue consisted of 5.86 g of crystals, m.p. 33-38.5°. After recrystallization from heptane the weight of (VII) was 5.19 g (72%); m.p. 38-40°. A sample for analysis was obtained by crystallization from a mixture of benzene and hexane; m.p. 39-40°. Found: C 41.5; 41.8; H 3.43; 3.40; N 6.97; 6.97; S 16.0; 16.0%. $C_7H_7NO_4S$. Calculated: C 41.8; H 3.51; N 6.96; S 16.0%. IR spectrum: 1760 cm^{-1} (ester C = O); 1350, 1560 cm^{-1} (NO_2).

3-Amino-2-thiopheneacetic Acid (VI) [8]. A suspension of 1 g of (V) in 4.2 ml of ethanol was added in the course of 30 min with stirring to a warm (60°) suspension of 1.07 g of iron filings in 1.8 ml of 0.78 N NH_4Cl. The reaction mixture was stirred at a bath temperature of 80-90° for 2 h 45 min, diluted with water, and filtered. The precipitate was washed repeatedly with 0.5 N ammonia until the reaction with DAB was negative, and the filtrate was then partially evaporated in a vacuum at 30° until the ammonia had been removed. The solution was passed through a column of KU-2 in the H^+ form; the column was washed with water, acetone, and again water; and (VI) was then eluted with 2 N ammonia [the passage of (V) into the eluate was checked by tests with DAB]. The ammoniacal eluate was evaporated partially in a vacuum at 30° until the ammonia had been removed, dilute HCl was added, the solution was evaporated to dryness, and as a residue we obtained 0.61 g (59%) of the hydrochloride of (VI). After reprecipitation from ethanol (with active charcoal treatment) with dry ether the weight was 0.4 g. To obtain an analytical sample the hydrochloride of (VI) was dissolved in the least possible amount of water, the solution was filtered to remove insoluble impurities, and a stream of hydrogen chloride was passed through the solution. The precipitate formed was filtered off, washed with concentrated HCl, and dried in a vacuum desiccator over potassium hydroxide and diphosphorus pentoxide; m.p. 167-169° (decomp.). Found: C 36.6; 36.7; H 3.94; 3.65; Cl 18.6; 18.6; N 7.38; 7.24; S 16.1; 16.0%. $C_6H_7NO_2S \cdot HCl$. Calculated: C 37.2; H 4.16; Cl 18.3; N 7.23; S 16.5%.

Free (VI) was obtained in low yield by evaporating the ammoniacal eluate to dryness and crystallizing the residue from water heated to 70° (with active charcoal treatment); m.p. 154-156° (decomp.).

Benzoyl Derivative (X) of (VI). This was prepared by the Schotten — Baumann method from the hydrochloride of (VI); m.p. 155.5-158.5° (reprecipitation from sodium carbonate solution with hydrochloric acid and crystallization from aqueous alcohol). Found: C 60.0; 59.5; H 4.38; 4.34; N 5.16; 5.39; S 12.5; 12.4%. $C_{13}H_{11}NO_3S$. Calculated: C 59.8; H 4.24; N 5.36; S 12.31.

Methyl 3-Amino-2-thiopheneacetate (VIII). This was prepared by the reduction of (VII) under the conditions used for the reduction of (VI). (VIII) was extracted from the slurry with a large amount of boiling water (until the reaction with DAB was negative) and then from the aqueous extracts with ether. The

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*The ether layer was evaporated to dryness, and the residue was treated with cold alcohol. The precipitated crystals of (IX) were filtered off and washed on the filter with alcohol; weight 0.4 g (9.6%); m.p. 119-120° (mixture of ethanol and ethyl acetate). (IX) gives a dark-violet coloration in alkaline solution. Found: C 42.0; 42.3; H 2.87; 3.02; S 18.3; 18.4%. $C_{12}H_{10}N_2O_6S_2$. Calculated: C 42.1; H 2.94; S 18.7%.

ethereal solution was dried over magnesium sulfate, and dry hydrogen chloride was passed in.* The precipitate of the hydrochloride of (VIII) was filtered off (60.8%); m.p. 176.5-180° (decomp.) (reprecipitation from methanol with dry ether). IR spectrum: 1755 cm^{-1} (ester C = O); 1605, 1530 cm^{-1} (NH_3^+).

Benzoyl Derivative (XI) of (VIII). This was prepared in presence of triethylamine by the method given in [9]; m.p. 96.5-99° (mixture of benzene and petroleum ether). Found: C 61.5; 61.4; H 4.79; 4.92; N 5.34; 5.31; S 11.7%. $C_{14}H_{13}NO_3S$. Calculated: C 61.1; H 4.76; N 5.09; S 11.6%. IR spectrum: 1750 cm^{-1} (ester C = O); 1650 cm^{-1} (amide C = O); 2840, 2930 cm^{-1} (CH_2); 3260 cm^{-1} (secondary amine NH).

4H-Thieno[3,2-b]pyrrol-5(6H)-one (I). 0.056 g of the hydrochloride of (VI) was dissolved in 8.7 ml of water, and the pH of the solution was brought to 4.9 by the addition of 5 N NaOH. 0.244 g of CME-carbodiimide was then added rapidly. The solution rapidly became alkaline, and a constant pH of 4.9 was maintained by the addition of 5 N H_2SO_4. The reaction was practically complete in 30 min. The reaction mixture was stirred in the cell of the pH meter for 40 min further. The precipitate formed during the reaction (2.1 mg; m.p. 172-178°) was centrifuged off and washed with water several times. The combined wash waters were extracted repeatedly with ether, ether was vacuum-evaporated at room temperature, and the residue was dried in a vacuum desiccator over diphosphorus pentoxide. The weight of (I) was 0.017 g (42.5%), m.p. 142-149°. An analytical sample was prepared by sublimation (60-110°, 3 mm) and subsequent crystallization from benzene; m.p. 150-151°. Found: C 52.2; 51.9; H 3.63; 3.84; N 10.18; S 23.0; 23.1%; mol.wt. 139. C_6H_5NOS. Calculated: C 51.8; H 3.62; N 10.07; S 23.0%. Mol.wt. 139. UV spectrum (in ethanol), λ_{max} (log ε): 222-224 mμ (4.068), 280-282 mμ (3.32).

CONCLUSIONS

1. The thiophene analog of oxindole — 4H-thieno[3,2-b]pyrrol-5(6H)-one — was synthesized.

2. It was found that 3-amino-2-thiopheneacetic acid, which we prepared, is cyclized with much greater difficulty than (o-aminophenyl)acetic acid.

3. By the condensation of 2-chloro-3-nitrothiophene with the sodium derivatives of malonic and acetoacetic esters and subsequent hydrolysis of the condensation products, 3-nitro-2-thiopheneacetic acid was prepared.

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*When the ether extract was treated with dilute HCl and the acid extracts were evaporated at 70°, (VIII) was completely hydrolyzed (the progress of hydrolysis was followed by paper chromatography). We isolated the hydrochloride of (VI) in 57.2% yield.