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INVESTIGATIONS OF 2-SUBSTITUTED IMIDAZOLES. 2.* SYNTHESIS AND ELECTROPHILIC SUBSTITUTION OF 1-METHYL-2-(THIENYL-2)IMIDAZOLE. A CONVENIENT METHOD OF METHYLATION OF 2-R-IMIDAZOLES

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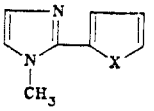
We have synthesized 2-(thienyl-2)imidazole and its N-methyl derivative. The latter product was obtained by nitration, bromination, acylation, and formylation, occurring as a rule on the thiophene ring. A general method for methylating 2-R-imidazoles with methyl iodide KOH—dimethoxy ethane is proposed.

We have previously studied electrophilic substitution reactions of 1-methyl-2-(furyl-2)imidazole (I) [1]. Here we report the synthesis and investigation of the hitherto undescribed 1-methyl-2(thienyl-2)imidazole (II).



I, II

I X=O; II X=S

Reaction of aqueous ethylenediamine with thiophene-2-carboxylic acid as in [2] gave in 84% yield 2-(thienyl-2)imidazoline (III). On reflux in diphenyl oxide in the presence of 2% palladium on carbon, the product rapidly dehydrogenated to give 2-(thienyl-2)imidazole (IV). However, the reaction did not go to conclusion, probably due to poisoning of the catalyst with sulfur-containing degradation products of the thiophene ring. The mixture of III and IV could not be separated by fractional crystallization or column chromatography. Their different reactions with silver nitrate afforded a separation. Imidazole IV formed an insoluble salt, while imidazoline III gave a complex soluble in DMF and partly soluble in other solvents.

*For Communication 1 see [1].

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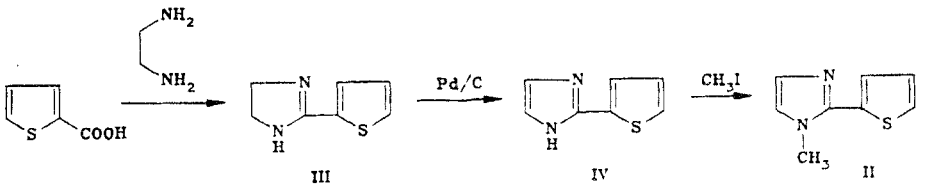
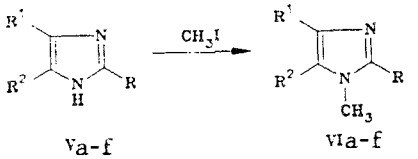
TABLE 1. Compound II and 1-Methyl-2-R-4-R^1-5-R^2-imidazoles VIa-h

Compound	Mp, °C*	Yield, %	Compound	Mp, °C*	Yield, %
II	170,5...171,5**	85	VI d	185...186**	82
VI a	179...180** (179...180 [6])***	83	VI e	(184...186 [8])*** 42...43	89
VI b	42,5...43.5 (oil [7])	90	VI f	93...94	76
VI c	178,5...179,5**	88	VI g	114...115	97
			VI h	184...185	93

*Compounds VIb, d, f were crystallized from hexane; compounds VIg, h from hexane with added benzene.
**Picrate, from ethanol.
***Picrate.

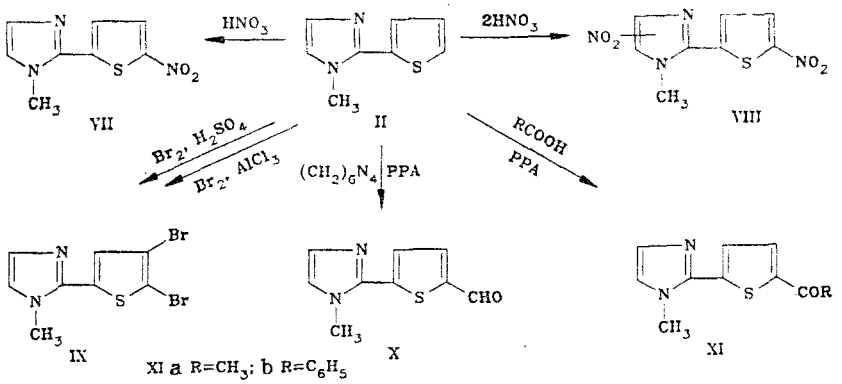


Compound IV may be methylated with methyl iodide in KOH-DMSO [3] or acetone—KOH systems [4]. The best results (highest yield and purity of product) were obtained in dimethoxyethane (DME) in the presence of powdered KOH at 3-5°C. The KOH—DME system also afforded high yields in the methylation of other 2-R-imidazoles (see Table 1).



V, VI: a) R = CH_3; b) R = C_6H_5; c, g, h) R = 2-furyl; d) R = 2-pyridyl; e) R = 3-pyridyl; f) R = 4-pyridyl; a-f) $R^1 = R^2 = H$; g) $R^1 = R^2 = C_6H_5$; h) $R^1 + R^2$ = 2,2'-diphenyl

Compound II reacted with electrophiles primarily on the thiophene ring.



Nitration was carried out with nitric acid (d 1.5) in polyphosphoric acid (PPA). At room temperature with 1 equivalent of HNO_3 the mononitro derivative of VII was obtained as for compound I in 56% yield; under harsher conditions (80°C, 1 h) the dinitro derivative VIII was obtained. The PMR spectra indicate that the second nitro group attacked the imidazole ring (see Table 2). Recrystallization gave a single product, but the position of the nitro group on the imidazole ring could not be determined. Formation of the dinitro derivative VIII did not proceed as readily as with compound I [1].

TABLE 2. PMR Spectra of Compounds II, VII-XIa, b

Compound	Chemical shifts, δ, ppm (CF_3COOH)*
II	7,05 (2H, m, 3′-H, 5′-H); 6,8 (1H, d., 4′-H); 6,75 (1H, s, 4-H); 6,65 (1H, s, 5-H); 3,5 (3H, s, N—CH_3)
VII	7,7 (1H, d, 4′-H); 7,03 (1H, d, 3′-H); 7,15 (2H, s, 4-H, 5-H); 3,7 (3H, s, N—CH_3)
VIII	8,05 (1H, s, 4(5)-H); 7,75 (1H, d, 4′-H); 7,45 (1H, d, 3′-H); 4,0 (3H, s, N—CH_3)
IX	7,1 (1H, s, 3′-H); 7,07 (2H, s, 4-H, 5-H); 3,6 (3H, s., N—CH_3)
X	9,7 (1H, s., CHO); 7,8 (1H, d, 4′-H); 7,5 (1H, s, 3′-H); 7,17 (2H, s., 4-H); 3,7 (3H, s., N—CH_3)
XIa	7,7 (1H, d., 4′-H); 7,4 (1H, d, 3′-H); 7,1 (1H, d, 4-H); 6,9 (1H, m, 5-H); 3,83 (3H, s, N—CH_3); 2,45 (3H, s $COCH_3$)
XIb	7,86 (2H, m, *o*-H benzene ring); 7,75 (1H, d, 4′-H); 7,57 (4H, m, 3′-H, *m*- and *p*-H); 7,37 (1H, s, 4-H); 7,05 (1H, s, 5-H); 3,9 (3H, s, N—CH_3)

*Solvent for compound II, CCl_4; for XIa, b, DMSO-d_6.

Bromination of II under neutral conditions gave ambiguous results. Reaction with bromine even at −15 to −20°C gave a complex mixture of hydrobromides from which individual compounds could not be isolated. Probably both heterocycles undergo electrophilic attack. In the presence of acids, deactivation of the imidazole ring leaves exclusively the thiophene ring subject to electrophilic attack. Bromination of a complex of II·$AlCl_3$ in methylene chloride or the action of bromine on a solution of II in concentrated H_2SO_4 gave 45 and 60% yields of 1-methyl-2-(4,5-dibromothienyl-2)-imidazole (IX).

Formylation of thienylimidazole II with an excess of Willsmayer's reagent and prolonged (6 h) heating at 95-100°C had little effect. The formyl group was successfully introduced by heating II with 3 equivalents of urotropin in PPA, giving aldehyde X in 90% yield. Compound II was acylated with carboxylic acids in PPA at 120-160°C; ketones XIa, b were formed in 47 and 42% yields.

Comparison of the reactivity of the thiophene with the imidazole nucleus of II shows that the thiophene ring readily undergoes electrophilic attack, directed, as would be expected, at the α-position of the heterocyle. However, the thiophene ring in thienylimidazole II is deactivated and undergoes electrophilic substitution markedly less readily than unsubstituted thiophene. Compound II reacts with electrophilic reagents markedly less readily than its furan analog I.

EXPERIMENTAL

PMR spectra were taken on a Tesla BS-487 spectrometer (80 MHz) with HMDS as internal standard. Reaction progress and purity of products were monitored by TLC on Al_2O_3 with Brockmann activity II (by iodine vapor) in $CHCl_3$. Products were separated by chromatography on 1.6 × 20 cm columns packed with Al_2O_3 and eluted with methylene chloride.

The data from elemental analysis (C, H) for II, IV, and VII-XIa, b corresponded to the calculated values.

2-(Thienyl-2)imidazoline (III). A mixture of 12.8 g (100 mmoles) of thiophene-2-carboxylic acid, 7.32 g (55 mmoles) ethylenediamine hydrochloride, 0.25 g p-toluenesulfonic acid, and 55 mmoles of a 50-70% aqueous solution of ethylenediamine in 45 ml ethylene glycol was refluxed 8 h, then the aqueous ethylene glycol was distilled off until the vapor temperature reached 196°C. The reaction mixture was concentrated under vacuum (5-7 mm Hg) until crystallization began. The residue was diluted with cold water (1:6) and while cooling in ice was strongly basified with solid KOH until the reaction product separated. This was filtered off and crystallized from benzene. Mp 179-180°C; according to [5], the mp is 175-177°C. Yield 12.8 g (84%).

2-(Thienyl-2)imidazole (IV, $C_7H_6N_2S$). A mixture of 15.2 g (100 mmoles) of III and 7.6 g of 2% Pd/C in 150 ml diphenyl oxide was refluxed with stirring for 2 h. The mixture was cooled to 150°C and diluted to half strength with p-xylene and the catalyst was filtered out. The reaction product was precipitated from the filtrate with hexane, filtered off, washed with hexane, and dried. Into a solution of 10 g of a mixture of III and IV in 100 ml EtOH was poured 25 ml of a 30% solution of silver nitrate. The precipitated silver salt of 2-(thienyl-2)imidazole was filtered off, washed with 50 ml DMF and 100 ml EtOH, and suspended in 100 ml EtOH. The suspension was

bubbled with hydrogen sulfide to complete dissociation of the salt. The silver sulfide was filtered off and the filtrate, after brief boiling, was diluted to one-third strength with H_2O. The precipitated imidazole IV was filtered off and recrystallized from H_2O. Mp 197-198°C. PMR (CF_3COOH): 7.4 (1H, d, 5′-H); 7.3 (1H, d, 3′-H); 7.0 (2H, s, 4-H, 5-H); 6.85 ppm (1H, t, 4′-H). Yield 5.6 g (37%).

General Method for Methylating 2-R-Imidazoles. To a mixture of 10 mmoles 2-R-imidazole, 0.62 g (11 mmoles) of KOH in powder form, and 10 ml DME at 3-5°C and vigorous stirring was added dropwise 0.68 ml (11 mmoles) of methyl iodide such that the reaction temperature did not rise above 8°C. The mixture was stirred at this temperature 0.5 h (in the case of 4,5-diaryl-2-R-imidazoles, 1 h at 15-20°C) and poured into 100 ml H_2O, and the precipitated product was filtered off or extracted with chloroform (2 × 50 ml). The extract was dried with $CaCl_2$, the chloroform distilled off, the residue extracted with hot hexane (3 × 50 ml), and the hexane distilled off to leave the 1-methyl-2-R-imidazoles.

1-Methyl-2-(5-nitrothienyl-2)imidazole (VII, $C_8H_7N_3O_2S$). To a solution of 0.41 g (2.5 mmoles) of II in 50 g PPA at 20°C was added dropwise with stirring 0.11 ml (2.5 mmoles) nitric acid (d 1.5). The reaction mixture was stirred at 20°C for 1 h, poured into 100 ml H_2O, and made to pH 5 with concentrated ammonia solution. The precipitated crystals were filtered off, washed with water, dried, and chromatographed on the column. A yellow fraction was evaporated and the residue crystallized from a methanol—water mixture. Mp 182-183°C. Yield 0.29 g (56%).

1-Methyl-4(5)-nitro-2-(5-nitrothienyl-2)imidazole (VIII, $C_8H_6N_4O_4S$). A mixture of 0.41 (2.5 mmoles) of II, 0.21 ml (5 mmoles) HNO_3 (d 1.5), and 50 g PPA was heated to 80°C with stirring for 1 h. The hot reaction mixture was poured into 200 ml H_2O and the precipitated crystals were filtered off, washed with water, dried, and chromatographed on the column. The yellow fraction was evaporated and the residue crystallized from n-butanol. Mp 196-197°C. Yield 0.27 g (42%).

1-Methyl-2-(4,5-dibromothienyl-2)imidazole (IX, $C_8H_6Br_2N_2S$). A. Compound II (0.41 g, 2.5 mmoles) and 0.33 g (2.5 mmoles) of anhydrous $AlCl_3$ were stirred in 20 ml of methylene chloride to complete homogeneity. To the complex thus formed was added dropwise at 20°C 0.26 ml (5 mmoles) of bromine; after 0.5 h the reaction mixture was poured into 100 ml H_2O, the solution made to pH 7 with concentrated ammonia solution, the aluminum hydroxide filtered off, and the organic layer separated, dried with $CaCl_2$, evaporated, and chromatographed on the column. The eluent was evaporated and the solvent crystallized from heptane. Mp 117-118°C. Yield 0.25 g (45%).

B. To a solution of 0.41 g (2.5 mmoles) of II in 20 ml concentrated H_2SO_4 (d 1.83) at 20°C was added dropwise with stirring 0.26 ml (5 mmoles) of bromine. The reaction mixture was stirred 1 h at 50-60°C, poured onto 100 g of ice, and made to pH 7 with concentrated ammonia solution and the reaction product was extracted with methylene chloride (3 × 50 ml). The extract was dried with $CaCl_2$, concentrated, and chromatographed on the column. The eluent was evaporated and the solvent crystallized from heptane. Mp 117-118°C. Yield 0.33 g (60%).

1-Methyl-2-(5-formylthienyl-2)imidazole (X, $C_9H_8N_2OS$). A mixture of 0.41 g (2.5 mmoles) of II, 1.15 g (7.5 mmoles) urotropin, and 20 g PPA was stirred 3 h at 75-80°C. The reaction mixture was poured into 100 ml H_2O and the solution made to pH 7 with concentrated ammonia solution and extracted with methylene chloride (3 × 50 ml). The organic layer was separated, dried with $CaCl_2$, concentrated, and chromatographed on the column. The light yellow fraction was evaporated and the residue crystallized from a mixture of heptane—benzene. Yield 0.41 g (90%), mp 114-115°C. Thiosemicarbazone, mp 217-218°C.

1-Methyl-2-(5-acylthienyl-2)imidazoles (XIa, b). A mixture of 0.41 g (2.5 mmoles) of II and 10 mmoles of carboxylic acid was stirred with 20 g PPA (at 120°C with acetic acid, 150°C with benzoic acid) for 16 h. Separation was analogous to that of X.

1-Methyl-2-(5-acetylthienyl-2)imidazole (XIa, $C_{10}H_{10}N_2OS$), mp 131-132°C (heptane—benzene). Yield 0.24 g (47%).

1-Methyl-2-(5-benzothienyl-2)imidazole (XIb, $C_{15}H_{12}N_2OS$), mp 135-137°C (heptane—benzene). Yield 0.28 g (42%).

Respectively 15 and 17% of starting compound II were regenerated from the head fractions.

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SYNTHESIS OF A MODEL PHOTOSYNTHETIC SYSTEM OF THE "COVERED" TYPE BASED ON MESOPORPHYRIN II

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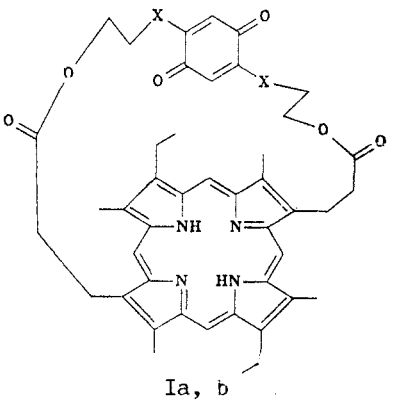
The synthesis of a porphyrinquinone compound of the "covered" type based on mesoporphyrin II was accomplished. Spectral investigations of the compound obtained were carried out.

In connection with the search for alternative sources of energy, much attention is given to the investigation of the primary stages of the absorption of light in photosynthesis. Porphyrinquinone compounds of varying structural organization are widely utilized for the simulation of these processes [1, 2]. Among the models of this class, interest is presented by the "covered" porphyrinquinones in which the acceptor of electrons (the quinone) is oriented exactly over the center of the photosensitizer (the porphyrin [1, 2]) due to two or four covalent bonds between them. The advantages of such systems consist of the possible control of the relative oxidation—reduction potentials of the fragments in the synthesis, the distance between them, and their mutual orientation, and therefore the unambiguous interpretation of the experimental results for the phototransfer of electrons.

Porphyrins of a symmetrical structure are utilized for the synthesis of the "covered" porphyrinquinones. We synthesized the porphyrinquinone (Ia) on the basis of the symmetrical mesoporphyrin II. The substance (Ia) differs from known compounds of a similar type [1] [e.g., (Ib)] by the presence of the sulfur atom directly connected to the quinone structure. It was previously shown [3] for the porphyrinquinone compounds with a flexible covalent bridge that the heteroatom directly connected with the quinone exerts significant influence on the effectiveness of the process of the photoinduced transfer of the electron. The sulfur-containing quinones thereby exhibit the greatest acceptor



Ia, b

Ia X=S; b X=CH_2

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