2-Methyl-7-phenylpyrazolo[2,3-a]pyrazine (X). The formylpyrazole (VIII) (2.2 g, 10 mmole) was dissolved in 50 ml of methanol, an equimolar amount of 25% aqueous ammonia added, and the mixture heated to 50-60°C. The crystalline (X) which separated on cooling was filtered off and recrystallized from methanol.

1-(2-Hydroxy-2-carboxypropyl)-4-phenylpyrazole (XI). To 2.2 g (10 mmole) of (IIa) in 10 ml of diethylene glycol was added 1 ml of water and 2 g of potassium hydroxide. The mixture was heated for 2 h at 130-150°C, diluted with 90 ml of water, neutralized with hydrochloric acid to pH 7, and extracted with ether (5 × 25 ml). The ether solution was dried over sodium sulfate, and the residue recrystallized from benzene to give the acid (X).

1-(2-Acetoxy-2-carboxypropyl)-4-phenylpyrazole (XII). A mixture of 2.88 g (10 mmole) of the hydroxyacid (XI) and 10 ml of acetic anhydride was boiled for 1 h. The mixture was cooled, diluted with ten times its volume of water, neutralized with sodium carbonate to pH 6, and extracted with ether (4 × 30 ml). After drying over sodium sulfate, the solution was evaporated, and the product (XII) recrystallized from acetone.

LITERATURE CITED

1. H. B. Schroter, D. Neumann, A. R. Katritzky, and F. J. Swinbourne, Tetrahedron, 22, 2895 (1966).
2. T. Onaka, Tetrahedron Lett., No. 54, 5711 (1968).
3. A. Morimoto, K. Noda, T. Watanabe, and H. Ikagusi, Tetrahedron Lett., No. 54, 5707 (1968).
4. D. G. O'Donovan and T. J. Forde, Tetrahedron Lett., No. 42, 3637 (1970).
5. S. Takano, Imamura, and K. Ogasawara, Heterocycles, 19, 1223 (1982).
6. D. Rangamathan and S. Bamezai, Synth. Commun., 15, 259 (1985).
7. A. M. Zvonok, N. M. Kuz'menok, and L. S. Stanishevskii, Khim. Geterotsikl. Soedin., No. 5, 679 (1982).
8. Beilstein's Handbuch der Organischen Chemie, Springer-Verlag, Berlin (1936), Vol. 25, p. 134.

2-SUBSTITUTED IMIDAZOLES.

1. REACTIONS OF 1-METHYL-2-(2-FURYL)IMIDAZOLE WITH ELECTROPHILES

V. M. Stoyanov, M. M. El'chaninov, A. M. Simonov, and A. F. Pozharskii

UDC 547.785.5'727.04:542.958.1'951'944.1

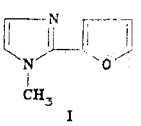
1-Methyl-2-(2-furyl)imidazole has been synthesized. Electrophilic attack (bromination, nitration, formylation, acylation, and hydroxymethylation) occurs in most cases at the free α-position of the furan ring.

The mutual effects of the heterocyclic nuclei in bihetaryls are of interest, but have received little attention. Least of all is known about the reactivity of compounds in which azole and π-excessive rings are linked. The reactivity of such compounds is sometimes totally unexpected. For example, it has recently been reported that 2-(2-furyl)- and 2-(2-thienyl)-oxazoles are formylated in the oxazole ring [1], although the π-excess is greater in the furan and thiophen rings. The purpose of the present study was to examine the reactivity towards electrophilic substitution of 1-methyl-2-(2-furyl)imidazole (I). The imidazole ring is well known to be inert to electrophiles under acid conditions, but to readily undergo electrophilic substitution in neutral media [2]. For this reason, although it is not difficult to predict that electrophilic substitution will be directed towards the furan ring under acid conditions, this is not so under neutral conditions. Electrophilic substitution in 1-methyl-2-(2-furyl)-benzimidazole (II) has been examined [3, 4]. In this case, however, all the carbon atoms of the imidazole ring are blocked, so that the reactions take place exclusively at the free α-position of the furan substituent.

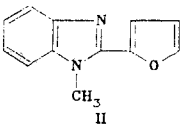
Rostov State University, Rostov-on-Don 344071.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1396-1400, October, 1989. Original article submitted May 23, 1988; revision submitted January 13, 1989.

0009-3122/89/2510-1168$12.50

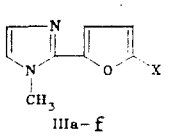


I

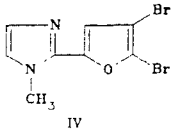


II

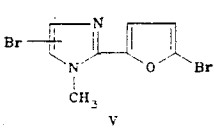
Reaction of ethylenediamine with methyl pyromucate as described in [5] gives 2-(2-furyl)-imidazoline, converted by boiling in dodecane with a Pd/C catalyst into 2-(2-furyl)imidazole, methylation of which with methyl iodide in dimethoxyethane in the presence of powdered potassium hydroxide gave (I).



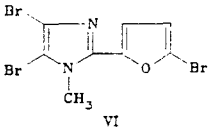
IIIa–f



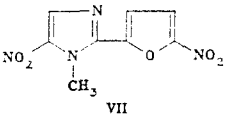
IV



V



VI



VII

III a X=Br; b X=NO_2; c X=CHO; d X=$COCH_3$; e X=COC_6H_5; f X=CH_2OH

The products of electrophilic substitution of (I) are compounds (IIIa-f)-(VIII).

As expected, bromination of the furylimidazole (I) in the presence of acid proceeds in the furan ring only. For example, with one equivalent of bromine in conc. sulfuric acid at room temperature, a 72% yield of the 5-bromofurylimidazole (IIIa) was obtained. Bromination of the complex of (I) with $AlCl_3$ results in the entry of two bromine atoms into the furan ring to give a 36% yield of the 4',5'-dibromo-compound (IV).

Bromination under neutral conditions is more complex. Unlike (II), which does not react with bromine unless heated [3], the furylimidazole (I) is brominated even at low temperatures (−10 to −15°C). The reaction could not be stopped at the monobromination stage. Reaction of (I) with two equivalents of bromine in chloroform gave a mixture of two dibromo-compounds (V) in an overall yield of 31%. The low yield of products of bromination of the imidazole ring is due to considerable losses by resinification. Since the isomeric (V) have the same R_f values, they could not be separated, but the PMR spectrum of the mixture indicates that one of the bromine atoms is in the 5-position of the furan ring, and the other in the 4- or 5-position of the imidazole ring. According to PMR, the ratio of the dibromo-compounds in (V) is 4:1, that isomer which contains bromine in the 5-position of the imidazole ring predominating (cf. [6]). Treatment of (I) with three equivalents of bromine in boiling chloroform or dichloroethane, i.e., under the conditions in which the furylbenzimidazole (II) is brominated, gives the tribromo-derivative (VI) in 14% yield.

Nitration of the furylimidazole (I) with nitric acid in acetic anhydride or in PPA, as in the case of (II), gives the 5'-nitro-compound (IIIb), but although the reaction stops at this stage in acetic anhydride, in PPA with two equivalents of nitric acid a mixture of products is obtained. The principal nitration product isolated from this mixture is, according to PMR, 1-methyl-5-nitro-2-(5-nitro-2-furyl)imidazole (VII).

Formylation of (I) by the Vilsmeier method with the DMF–$POCl_3$ complex at 95°C gives the 5'-formyl compound (IIIc) in 32% yield, approximately 50% of the starting material being recovered under these conditions. It appears that the hydrogen chloride liberated during the formylation protonates the imidazole ring in (I), and the imidazolium cation, being a strong electron acceptor, deactivates the furan ring towards formylation. In the case of (II), which in general does not undergo Vilsmeier formylation [4], the neutral 1-methylbenzimidazole grouping has the same deactivating effect.

As for (II), the furylimidazole (I) is acylated by carboxylic acids in PPA at 110-140°C to give the ketones (IIId, e) (yields 35 and 54%).

Compound (I) undergoes hydroxymethylation in the 5-position of the furan ring. The reaction is, however, extremely slow, the yield of the hydroxymethyl derivative (IIIf) being only 11% after boiling for 16 h in formalin. Under these conditions, (II) fails to react with formaldehyde.

This comparison of the reactivities of the furan and benzimidazole rings in (I) shows that both in acid and neutral media the furan ring readily undergoes electrophilic attack. The imidazole ring in (I), as in (II), stabilizes the furan ring towards acids. The electrophilic substituent enters the free α-position of the furan ring. Compound (I) reacts much more readily with electrophiles than does (II).

EXPERIMENTAL

PMR spectra were obtained on a Tesla BS-487 spectrometer, internal standard HMDS. The progress of the reactions was followed, and the purity of the products checked, by TLC on Brockman grade II alumina (visualized with iodine vapor) in chloroform.

The PMR spectra of the products are shown in Table 1. The elemental analyses for C, H, and N were in agreement with the calculated values.

2-(2-Furyl)imidazoline was obtained as in [5], mp 177-178°C (from xylene); according to [5], mp 170°C. PMR spectrum (CF_3COOH): 3.73 (4H, s, CH_2CH_2); 6.30 (1H, d.d, 4'-H); 7.10 (1H, d, 3'-H); 7.35 (1H, d, 5'-H); 7.70 ppm (2H, br.s, 2NH).

2-(2-Furyl)imidazole. A mixture of 13.6 g (0.1 mole) of 2-(2-furyl)imidazoline and 6.8 g of 2% Pd/C in 200 ml of dodecane was boiled with stirring for 2 h. The mixture was cooled, diluted with twice its volume of chloroform, and the catalyst filtered off. The product was precipitated from the filtrate with hexane, and crystallized from xylene, mp 169.5-170.5°C (according to [7], mp 169.5-170.5°C). Yield 51%. PMR spectrum (CF_3COOH): 6.25 (1H, d.d, 4'-H); 6.95 (3H, m, 3'-H, 4-H, 5-H); 7.25 ppm (1H, d, 5'-H).

1-Methyl-2-(2-furyl)imidazole (I, $C_8H_8N_2O$). A. Methylation in alcoholic alkali with double the amount of methyl iodide at room temperature as described in [8] gave 46% of 1,3-dimethyl-2-(2-furyl)imidazolium hydroiodide, $C_9H_{11}IN_2O$, mp 188-189°C (from butanol). PMR spectrum (CF_3COOH): 3.53 (56H, s, $2NCH_3$); 6.35 (1H, d.d, 4'-H; 6.83 (1H, d, 3'-H); 6.93 (2H, s, 4-H, 5-H); 7.30 ppm (1H, d, 5'-H).

B. To a mixture of 1.34 g (10 mmole) of 2-(2-furyl)imidazole, 0.62 g (11 mmole) of powdered KOH, and 10 ml of dimethoxyethane was added dropwise with vigorous stirring at 3-5°C 1.56 g (11 mmole) of methyl iodide, at such a rate that the temperature of the mixture did not exceed 8°C. The mixture was then stirred at the same temperature for 30 min, poured into 100 ml of water, and extracted with chloroform (2 × 50 ml). The chloroform was removed, and the residue extracted with hot hexane (3 × 50 ml). Removal of the hexane gave a yellow oil which darkened on storage. Picrate, mp 178.8-179.5°C (from alcohol).

Bromination of 1-Methyl-2-(2-furyl)imidazole under Neutral Conditions. To a solution of 1.48 g (10 mmole) of (I) in 20 ml of chloroform was added with stirring at −15°C 3.2 g (20 mmole) of bromine. The mixture was stirred for 30 min at −10°C, and washed with 50 ml of 5% ammonia and 2 × 50 ml of water. The chloroform layer was dried over anhydrous sodium sulfate for ten minutes, and chromatographed on a column (h 20 cm, d 2.5 cm) with 70 g of alumina, eluent chloroform. The fraction with R_f 0.7-0.8 contained the mixed dibromo-compounds (V). Yield 31%. The ratio of the isomeric 1-methyl-4-bromo-2-(5-bromo-2-furyl)imidazole and 1-methyl-4-bromo-2-(5-bromo-2-furyl)imidazole was 4:1, mp of the isomer mixture 97-98°C (from hexane).

1-Methyl-4,5-dibromo-2-(5-bromo-2-furyl)imidazole (VI, $C_8H_5Br_3N_2O$). To a boiling solution of 1.48 g (10 mmole) of (I) in 20 ml of chloroform was added 4.8 g (30 mmole) of bromine. After 30 min, the reaction mixture was cooled, and worked up as in the preceding example. The fraction with R_f 0.8-0.9, which contained the tribromo-compound (VI), was evaporated, and the residue crystallized from hexane to give 14% of product, mp 131-132°C.

1-Methyl-2-(5-bromo-2-furyl)imidazole (IIIa, $C_8H_7BrN_2O$). To a solution of 1.48 g (10 mmole) of (I) in 20 ml of conc. sulfuric acid (d 1.84) was added dropwise with stirring at 20°C 1.6 g (10 mmole) of bromine. The mixture was stirred for 30 min, poured into 100 g of ice, neutralized with concentrated ammonia to pH 7, and extracted with 50 ml of chloroform. The extract was dried over anhydrous sodium sulfate, and chromatographed on a column the dimensions of which are given above, with 50 g of alumina, eluent chloroform. The chloroform was evaporated, and the residue crystallized from hexane to give a 72% yield of product, mp 56-57°C.

1-Methyl-2-(4,5-dibromo-2-furyl)imidazole (IV, $C_8H_6Br_2N_2O$). A mixture of 1.48 g (10 mmole) of (I) and 1.33 g (10 mmole) of $AlCl_3$ in 20 ml of methylene chloride was stirred until the solution be-

TABLE 1. PMR Spectra of (I), (IIIa-f), (IV), (VI), and (VII)

Compound	Chemical shifts, δ, ppm (in CF_3COOH)*
I	3,7 (3H, s, N—CH_3); 6,3 (1H,d.d 4′-H); 6,65 (2H, m, 3′-H, 5-H); 6,8 (1H, s, 4-H); 7,3 (1H,d, 5′-H)
IIIa	3,75 (3H,s N—CH_3); 6,25 (1H, d 4′-H); 6,62 (2H, m, 3′-H, 5-H); 6,73 (1H, s, 4-H)
IIIb	3,8 (3H,s N—CH_3); 7,1 (1H, d, 4′-H); 7,2 (3H, m, 3′-H, 4-H, 5-H)
IIIc	3,8 (3H,s N—CH_3); 6,9 (1H,d 3′-H); 7,15 (2H, m., 4-H, 5-H); 7,35 (1H, d, 4′-H); 9,3 (1H, s, CHO)
IIId	2,34 (3H, s, $COCH_3$); 3,81 (3H, s N—CH_3); 7,06 (1H, d 3′-H); 7,11 (2H, m, 4-H, 5-H); 7,3 (1H,d, 4′-H)
IIIe	3.8 (3H, s N—CH_3); 7.15 (5H, m,arom.); 7,25 (2H,m 4-H, 5-H); 7,33 (1H,d, 3′-H); 7,57 (1H, d, 4′-H)
IIIf	3,7 (3H, s N—CH_3); 5,1 (2H, s. CH_2OH); 6,4 (1H, d 4′-H); 6,8 (1H, d 3′-H); 6,9 (2H, m, 4-H, 5-H)
IV	3,67 (3H, s N—CH_3); 6,9 (1H, s, 3′-H); 6,95 (1H, s 5-H); 7,0 (1H, s 4-H)
VI	3,7 (3H, s N—CH_3); 6,3 (1H,d, 4′-H); 7,0 (1H, d, 3′-H)
VII	4,05 (3H, s N—CH_3); 7,2 (1H, d 3′-H); 7,4 (1H,d, 4′-H); 8,1 (1H, s 4-H)

*The solvent for (I) and (IV) was CCl_4.

came homogeneous. To the resulting complex was added 3.2 g (20 mmole) of bromine at room temperature (~20°C). After 30 min, the mixture was poured into 100 ml of water, the pH brought to 7 by adding concentrated ammonia, the alumina filtered off, and the organic layer separated and the product (IV) isolated as for the bromo-compound (IIIa). Yield 36%, mp 108-109°C (from hexane).

1-Methyl-2-(5-nitro-2-furyl)imidazole (IIIb, $C_8H_7N_3O_3$). A. To a solution of 1.48 g (10 mmole) of (I) in 15 ml of freshly distilled acetic anhydride was added dropwise at 0°C 3.8 g (60 mmole) of nitric acid (d 1.5). The mixture was stirred at ~20°C for 1 h, and poured onto 100 g of ice. The product was then isolated as described for (IIIa), yield 60%, mp 153-154°C (from benzene).

B. Compound (I) (1.48 g, 10 mmole) was dissolved in 50 g of PPA at room temperature, and 0.63 g (10 mmole) of nitric acid (d 1.5) added with stirring. The mixture was stirred at ~20°C for 1 h, and the nitro-compound (IIIb) isolated as for (IIIa), yield 66%, mp 153-154°C (from benzene).

1-Methyl-5-nitro-2-(5-nitro-2-furyl)imidazole (VII), $C_8H_6N_4O_5$). Nitration of (I) (1.48 g, 10 mmole) was carried out as in the preceding example, with 1.89 g (30 mmole) of nitric acid. The reaction mixture was mixed with 100 ml of ice, and the solid which separated was filtered off, washed with water, dried, and crystallized. Yield 4%, mp 163-164°C (from butanol).

1-Methyl-2-(5-formyl-2-furyl)imidazole (IIIc, $C_9H_8N_2O_2$). To 1.48 g (10 mmole) of (I) in 4.75 g (65 mmole) of DMF was added dropwise with stirring at 0-5°C 9.2 g (60 mmole) of $POCl_3$, and the mixture stirred at the same temperature for 10 min, then for 5 h at 95°C. After cooling, the mixture was worked up at for (IIIa). Yield 32%, mp 107-108°C (from hexane).

1-Methyl-2-(5-acyl-2-furyl)imidazoles (IIId, e). A mixture of 1.48 g (10 mmole) of (I) and 40 mmole of the carboxylic acid was stirred in 40 g of PPA at 110°C (with acetic acid, or 140°C (with benzoic acid) for 6-8 h, until starting material was no longer present (TLC). Workup as for (IIIa) gave 1-methyl-2-(5-acetyl-2-furyl)imidazole (IIId, $C_{20}H_{20}N_2O_2$) [yield 35%, mp 114-115°C (from hexane)] and 1-methyl-2-(5-benzoyl-2-furyl)imidazole (IIIe, $C_{15}H_{12}N_2O_2$) [yield 54%, mp 75-76°C (from hexane)].

1-Methyl-2-(5-hydroxymethyl-2-furyl)imidazole (IIIf, $C_9H_{10}N_2O_2$). A solution of 1.48 g (10 mmole) of (I) in 25 ml of 40% formalin was heated on a boiling water bath for 16 h. The mixture was evaporated under reduced pressure, and the residue chromatographed on a column (h 15 cm, d 2.5 cm) with 40 g of alumina, eluent chloroform, the fraction with R_f 0.15 being collected. Yield 11%, mp 139-140°C (from alcohol).

LITERATURE CITED

1. L. I. Belen'kii, M. A. Cheskis, V. P. Zvolinskii, and A. E. Obukhov, Khim. Geterotsikl. Soedin., No. 6, 826 (1986).
2. K. Schofield, M. Grimmett, and B. Keene. Heteroaromatic Nitrogen Compounds. The Azoles, Cambridge Univ. Press, Cambridge (1976), p. 437.
3. M. M. El'chaninov, L. Ya. Oleinnikova, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 8, 1047 (1979).
4. M. M. El'chaninov, A. M. Simonov, and L. Ya. Oleinikova, Khim. Geterotsikl. Soedin., No. 10, 1311 (1983).
5. V. I. Isagulyants, A. Yu. Adzhiev, and L. L. Vasil'eva, Izv. Vuzov. Khim. Khim. Tekhnol., 16, 1059 (1973).
6. A. F. Pozharskii, Theoretical Fundamentals of the Chemistry of Heterocycles [in Russian], Khimiya, Moscow (1985), p. 205.
7. H. Schubert, E. Hagen, and G. Lahman, J. prakt. Chem., 17, 173 (L962).
8. Z. N. Nazarva (editor), Essays in the Chemistry of Azoles [in Russian], Izd. RGU, Rostov-on-Don (1965), p. 17.

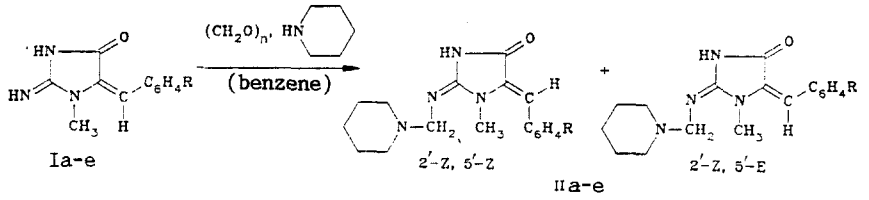
GEOMETRICAL ISOMERISM OF 2'-PIPERIDINOMETHYL-5-ARYLIDENECREATININES

S. M. Ramsh, N. G. Zheltonog, and E. S. Khrabrova

UDC 547.781.5.07:542.953.2:541.621:543.422.25

The aminomethylation of 5-arylidenecreatinines with paraformaldehyde and piperidine in benzene leads to 2'-piperidinomethyl-5-arylidenecreatinines, in which the geometrical isomerism in relation to the $C_{(2)} = N_{(2')}$ and $C_{(5)} = C$ bonds was observed.

The 5-arylidenepseudothiohydantoins are aminomethylated at the exocyclic nitrogen atom by secondary amines in hydroxyl-containing mediums [1], and give the products of the bisaminomethylation at the exo- and endocyclic nitrogen atoms in benzene [2]. The piperidinomethyl derivatives of the aza analogs of these compounds – the 5-arylidenecreatinines (Ia-e) – could not be obtained in hydroxyl-containing mediums. The procedure for the isolation of the Mannich bases, analogous to that utilized in the case of the thia analogs [1], led to viscous oils not undergoing separation into the individual substances. The 2'-piperidinomethyl-5-arylidenecreatinines (IIa-e) (Table 1) were obtained by performing the reaction in abs. benzene with paraformaldehyde as the methylene component.



I—II a R=H; b R=*p*-OCH_3; c R=*p*-F; d R=*p*-Cl; e R=*p*-Br

The site of the aminomethylation was established by the comparison of the PMR spectra of the Mannich bases (IIa-e) with the spectra of their thia analogs [1] and the corresponding imidazolo[3,2-a]triazines [3], the products of the aminomethylation of the compounds (Ia-e) by primary amines: the absorption of the methylene protons at 4.16 ppm (Table 1) corresponds unconditionally to the $N_{(2')}$-substitution, whereas the resonances of the $N_{(3)}CH_2$ protons should occur at a lower field.

Leningrad Lensovet Technological Institute, Leningrad 198013. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1401-1404, October, 1989. Original article submitted April 4, 1988.

 0009-3122/89/2510-1172$12.50