INVESTIGATIONS IN THE IMIDAZOLE SERIES

LXXIV.* ELECTROPHILIC SUBSTITUTION REACTIONS IN THE PYRROLO[1,2-a]IMIDAZOLE SERIES

A. A. Druzhinina, P. M. Kochergin, and L. M. Alekseeva

UDC 547.74'781:542.951'958:543.422.25

The formylation, acetylation, hydroxymethylation, azo coupling, nitrosation, nitration, and chloromercuration of pyrrolo[1,2-a]imidazole derivatives were studied. The PMR spectra were used to establish that all of these reactions proceed at the 5 position or, if it is occupied, at the 7 position of the two-ring system. When the 5 and 7 positions are free, the formation of 5,7-disubstituted pyrrolo[1,2-a]imidazoles is possible.

In developing the research accomplished in [2-6] in order to obtain the inaccessible (by direct synthesis) functional derivatives of pyrrolo[1,2-a]imidazole and to compare the reactivity of this heterocycle with other condensed pyrrole-containing systems with a common nitrogen atom, we studied the electrophilic substitution reactions in this series of pyrrolo[1,2-a]imidazole derivatives, which were reported only briefly in [7]. The starting substances were 1-propyl-2-chloro-6-(p-bromophenyl)-7-methyl-, 1-ethyl-2,3-diphenyl-5,6-dimethyl-, 1,2,3,6-tetraphenyl-, and 1-benzyl-6-(p-tolyl)pyrrolo[1,2-a]imidazoles (I-IV) [4-6], 1-ethyl-5,6-diphenylpyrrolo[1,2-a]-2-imidazolone (V) [4], and the 1-methyl-6-(p-chlorophenyl)- and 1-ethyl-2-chloro-5,6-diphenylpyrrolo[1,2-a]imidazoles (VIII, IX) described in this paper.

It was established that the formylation, acetylation, hydroxymethylation, azo coupling, nitrosation, and chloromercuration of I-V, VIII, and IX proceed with great ease under mild temperature conditions.

As one should expect in analogy with the electrophilic substitution reactions in the indolicine [8], pyrrolo[2,1-b]thiazole [9], and pyrrolo[1,2-a]benzimidazole [10, 11] series, in this case the pyrrole ring carbon atom adjacent to the common nitrogen atom – the 5 position of the pyrroloimidazole two-ring system – also undergoes primary electrophilic attack. Thus X, XI, XIV, XV, XVII, and XIX, respectively, are obtained from the Vilsmeier formylation of I, the acetylation of IV with acetic anhydride, and the hydroxymethylation of I with formaldehyde, the azo coupling of III with p-bromobenzenediazonium borofluoride, the nitrosation of I with nitrous acid, and the chloromercuration of IV with mercuric chloride.

If there is any substituent in the 5 position, the electrophilic substitution reactions proceed at the 7 position of the two-ring system. Thus, for example, XII and XX, respectively, are formed in the acetylation of XI with acetic anhydride in the presence of sodium acetate and in the chloromercuration of II with mercuric chloride.

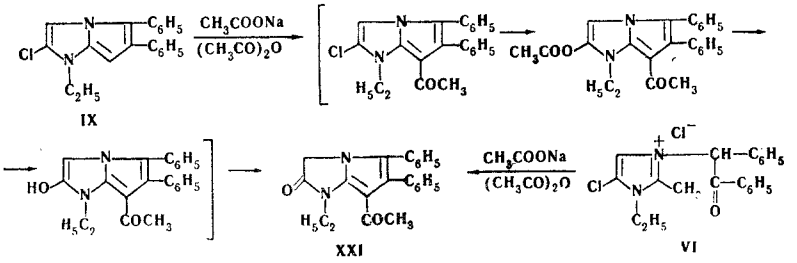
When the 5 and 7 positions are free, the substitution reactions of such pyrrolo[1,2-a]imidazoles may proceed to form 5,7-disubstituted products. Thus XII, XIII, and XVI, respectively, are obtained in the acetylation of IV and VIII with acetic anhydride in the presence of sodium acetate and in the azo coupling of IV with p-bromobenzenediazonium borofluroide.

It is interesting to note that the dimethylaminomethylation of I under the conditions of the synthesis of Mannich bases of the indolicine series [12] gives XIV, which is probably explained by the ease of the competitive hydroxymethylation or by hydrolysis of the 5-dimethylaminoethyl derivative of I.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 405-409, March, 1972. Original article submitted March 4, 1971.

Attempts to nitrate the pyrrolo[1,2-a]imidazole derivatives with a nitrating mixture led to resinification, which is apparently explained by the instability of this heterocyclic system to the action of strong mineral acids. We were able to obtain dinitro compound XVIII by substitution of the acetyl groups by a nitro group by the action of HNO_3 on the corresponding 5,7-diacetyl derivative (XII) in glacial acetic acid, as described for the synthesis of nitro derivatives of indolicine [13] and pyrrolo[1,2-a]benzimidazole [11]. The nitration of VIII with concentrated HNO_3 in acetic acid does not give XVIII – the nitrate of VIII was isolated from the reaction mixture.

The acetylation of 2-chloro-substituted pyrrolo[1,2-a]imidazoles (I, IX) proceeds unusually. When these compounds were heated with acetic anhydride in the presence of sodium acetate, pyrrolo[1,2-a]imidazolones (XXI, XXII) were isolated. The formation of XXI and XXII is apparently explained by the ease of acetylation in the 5 or 7 positions and subsequent acetolysis of the chlorine atom under the influence of sodium acetate; hydrolysis of the intermediate 2-acetoxy-5(or 7)-acetylpyrroloimidazoles leads to the corresponding 2-hydroxypyrroloimidazoles, which are isomerized to XXI and XXII. Compound XXI was also synthesized by heating 1-ethyl-2-methyl-3-decyl-5-chloroimidazolium chloride (VI) [4] in acetic anhydride in the presence of sodium acetate, during which, in addition to closing of the pyrrole ring, the other processes indicated above, which are associated with acetylation of the pyrrole ring and acetolysis of the chlorine atom in the imidazole ring of the two-ring system, also took place.



It is interesting to note that the azo coupling of V with p-bromobenzenediazonium borofluoride proceeds at the 7 position of the two-ring system rather than at the active methylene group of the imidazole ring, which attests to the high aromaticity of the pyrrole ring in pyrrolo[1,2-a]-2-imidazolone derivatives.

The structures of X-XXIII were established by means of IR and PMR spectroscopy.* The IR spectra of X-XIV, XVII, XVIII, and XXI-XXIII contain absorption bands of the corresponding functional groups – CO, OH, NO, or NO_2 – while the signals of the protons in the 5 or 7 or 5,7 positions of the two-ring system that were observed in the PMR spectra of starting compounds I-V, VIII, and IX are absent in the PMR spectra of X-XVIII, and XXI-XXIII. The structures of XIX and XX were assumed by way of analogy, since it was difficult to record their PMR spectra because of the presence of a mercury atom.

Among the properties of the compounds that we obtained, one should note the ease of deacetylation of XI-XIII on heating in water in the presence of mineral acids, as is also observed in acetyl derivatives of indolicine [8], pyrrolo[1,2-b]thiazole [14], and pyrrolo[1,2-a]benzimidazole [10].

EXPERIMENTAL

1,2-Dimethyl-3-(p-chlorophenacyl)imidazolium Bromide (VII). This salt was obtained in 90% yield from 1,2-dimethylimidazole and p-chlorophenacyl bromide via the method in [3] and had mp 200-202° (from absolute ethanol). Found: N 8.3%. $C_{13}H_{14}BrClN_2O$. Calculated: N 8.5%.

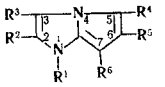
1-Methyl-6-(p-chlorophenyl)pyrrolo[1,2-a]imidazole (VIII). This compound was obtained by the cyclization of VII under the influence of sodium ethoxide via the method in [5].

1-Ethyl-2-chloro-5,6-diphenylpyrrolo[1,2-a]imidazole (IX). A solution of 3 g of V in 30 ml of $POCl_3$ was refluxed for 1 h, the $POCl_3$ was removed by vacuum distillation, and 50 ml of water was added to the residue. The mass was heated up to the boiling point and filtered. The filtrate was cooled and neutralized with $NaHCO_3$, and the precipitate was removed by filtration and washed with water to give 2.55 g of product.

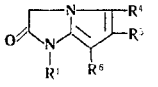
Acyl Derivatives of Pyrrolo[1,2-a]imidazole (X-XIII, XXI, and XXII). A) A 1.48-g (0.01 mole) sample of $POCl_3$ was added dropwise with stirring to 3 ml of DMF cooled to 0°, and the solution was allowed to stand at 18-20° for 15 min. A solution of 3.4 g (0.01 mole) of I in 15 ml of DMF was then added dropwise with stir-

*We thank Yu. I. Pomerantsev for recording the IR spectra of the compounds.

TABLE 1



VIII–XX



XXI–XXIII

Compound	R¹	R²	R³	R⁴	R⁵	R⁶	Mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
									C	H	N	halogen	C	H	N	halogen	
VIII	CH_3	H	H	H	*p*-ClC_6H_4	H	144—146	$C_{18}H_{11}ClN_2$*	67,5	4,9	12,1	15,4	67,7	4,8	12,1	15,4	35
IX	C_2H_5	Cl	H	C_6H_5	C_6H_5	H	94—95	$C_{20}H_{17}ClN_2$	74,5	5,7	8,9	10,8	74,9	5,3	8,7	11,0	80
X	C_3H_7	Cl	H	CHO	*p*-BrC_6H_4	CH_3	138—140	$C_{17}H_{16}BrClN_2O$	54,2	4,3	7,4	—	53,8	4,2	7,4	—	57
XI	$C_6H_5CH_2$	H	H	CH_3CO	*p*-$CH_3C_6H_4$	H	111—113	$C_{22}H_{20}N_2O$	80,6	6,2	8,5	—	80,5	6,1	8,5	—	87
XII	$C_6H_5CH_2$	H	H	CH_3CO	*p*-$CH_3C_6H_4$	CH_3CO	157—159	$C_{24}H_{22}N_2O_2$	78,2	5,9	7,7	—	77,8	6,0	7,6	—	86
XIII	CH_3	H	H	CH_3CO	*p*-ClC_6H_4	CH_3CO	218—219	$C_{17}H_{15}ClN_2O_2$	64,9	4,7	8,6	11,0	64,9	4,8	8,9	11,3	58
XIV	C_3H_7	Cl	H	CH_2OH	*p*-BrC_6H_4	CH_3	165—167	$C_{17}H_{18}BrClN_2O$	53,8	4,6	7,8	—	53,5	4,8	7,3	—	54
XV	C_6H_5	C_6H_5	C_6H_5	*p*-$BrC_6H_4N_2$	C_6H_5	H	202—204	$C_{36}H_{24}BrN_4$	72,5	4,3	9,9	13,5	72,9	4,1	9,5	13,5	87
XVI	$C_6H_5CH_2$	H	H	*p*-$BrC_6H_4N_2$	*p*-$CH_3C_6H_4$	*p*-$BrC_6H_4N_2$	252—253	$C_{32}H_{24}Br_2N_6$	58,5	3,7	12,8	24,7	58,9	3,7	12,9	24,5	35
XVII	C_3H_7	Cl	H	NO	*p*-BrC_6H_4	CH_3	167—168	$C_{16}H_{15}BrClN_3O$	50,8	3,8	10,7	—	50,5	4,0	11,0	—	92
XVIII	CH_3	H	H	NO_2	*p*-ClC_6H_4	NO_2	232,5—233,5	$C_{13}H_9ClN_4O_4$	48,8	2,9	17,2	10,8	48,7	2,8	17,5	11,0	50
XIX	$C_6H_5CH_2$	H	H	HgCl	*p*-$CH_3C_6H_4$	H	133—135	$C_{20}H_{17}ClN_2Hg$	—	—	—	6,7	—	—	—	6,8	80
XX	C_2H_5	C_6H_5	C_6H_5	CH_3	CH_3	HgCl	135—137	$C_{22}H_{21}ClN_2Hg$	—	—	—	6,3	—	—	—	6,4	71
XXI	C_2H_5	—	—	C_6H_5	C_6H_5	CH_3CO	188—189	$C_{22}H_{20}N_2O_2$	76,2	6,1	7,9	—	76,7	5,8	8,2	—	38
XXII	C_3H_7	—	—	CH_3CO	*p*-BrC_6H_4	CH_3	125—126	$C_{18}H_{19}BrN_2O_2$	57,2	4,8	7,6	20,5	57,6	5,1	7,5	21,3	53
XXIII	C_2H_5	—	—	C_6H_5	C_6H_5	*p*-$BrC_6H_4N_2$	196—198	$C_{26}H_{21}BrN_4O$	64,0	4,0	11,4	16,3	64,3	4,4	11,5	16,5	71

* The nitrate of VIII had mp 171–173° (from ethanol). Found: N 13.8%. $C_{13}H_{11}ClN_2 \cdot HNO_3$. Calculated: N 14.3%.

ring and cooling (2-5°). The reaction mass was stirred at 18-20° for 1 h and poured over ice. The mixture was neutralized with 2 N NaOH and allowed to stand overnight. The precipitate was removed by filtration and washed with water to give 2.09 g of X.

B) A mixture of 1 g of I, IV, VI, or VII, 1 g of sodium acetate, and 10 ml of acetic anhydride was refluxed for 30 min (in the preparation of XI) or 2 h (XII, XIII, XXI, XXII). The excess acetic anhydride was removed by vacuum distillation, and the residue was extracted with ether. The ether solution was washed with water and dried over $MgSO_4$, and the solvent was removed by distillation. Compound XII was similarly obtained from XI in 67% yield.

C) A mixture of 2 g of VI, 0.9 g of sodium acetate, and 20 ml of acetic anhydride was refluxed for 2 h and worked up as described in experiment B to give 0.7 g (38%) of XXI.

Compound XII is readily converted to starting IV in high yields on refluxing in 10% HCl.

1-Propyl-2-chloro-5-hydroxymethyl-6-(p-bromophenyl)-7-methylpyrrolo[1,2-a]imidazole (XIV). A) A 0.4-ml (5 mmole) sample of 37% CH_2O was added to a solution of 0.35 g (1 mmole) of I in 2 ml of DMF or ethanol, and the mixture was allowed to stand at 18-20° for 15 min. The resulting precipitate was removed by filtration and washed with acetone.

B) A 1.13-g (0.01 mole) sample of 40% aqueous dimethylamine was added to 0.82 g (0.01 mole) of 37% CH_2O in 20 ml of DMF, and the mixture was stirred at 18-20° for 15 min. A 3.5-g (0.01 mole) sample of I was added, and the precipitate was removed by filtration and washed with acetone to give 2 g of product. This product did not depress the melting point of XIV obtained as described in experiment A.

Arylazo Derivatives of Pyrrolo[1,2-a]imidazole (XV, XVI, XXIII). A suspension of 5 mmole of p-bromobenzenediazonium borofluoride in 5-10 ml of methanol was added to a solution of 5 mmole of III or V in 5-10 ml of acetic acid, and the resulting solution was allowed to stand for 24 h (in the preparation of XXIII) or for 5 days (XV) in a dark place. The resulting precipitate was removed by filtration. Compound XVI was similarly obtained from IV as in the preparation of XXIII, except that the reaction was carried out with the addition of 6 mmole of sodium acetate and 2 ml of acetic anhydride.

1-Propyl-2-chloro-5-nitroso-6-(p-bromophenyl)-7-methylpyrrolo[1,2-a]imidazole (XVII). A solution of 0.07 g (1 mmole) of sodium nitrite in 1 ml of water was added with stirring at 18-20° to a solution of 0.35 g (1 mmole) of I in 5 ml of acetic acid. The reaction mixture was stirred at the same temperature for 15 min, cooled, and made alkaline to pH 9 with 2 N NaOH. The orange precipitate was removed by filtration and washed with water. The substance became bright-green after drying at 50°.

1-Methyl-5,7-dinitro-6-(p-chlorophenyl)pyrrolo[1,2-a]imidazole (XVIII). A 5.4-g (0.084 mole) sample of 98% HNO_3 was added dropwise with stirring to a solution of 3.95 g (0.0125 mole) of VI in 45 ml of acetic acid. The reaction mass was stirred at 18-20° for 30 min and diluted with 50 ml of water. The precipitate was removed by filtration and washed with water. The nitrate of VIII was isolated from the reaction of VIII with HNO_3 under the indicated conditions.

Chloromercuri Derivatives of Pyrrolo[1,2-a]imidazole (XIX, XX). A solution of 5.5 mmole of mercuric chloride in 5 ml of ethanol was added to a solution of 0.5 mmole of II or IV in 25 ml of absolute ethanol, and the mixture was heated to the boiling point and cooled. The precipitate was removed by filtration and washed with ethanol.

Compounds VIII-XXIII are colorless, dark-red (XV, XVI, XXIII), green (XVII), or yellow (XVIII) substances. They were purified for analysis by crystallization from ethanol (VIII, IX, XI-XIII, XVII, XXI, XXII), cyclohexane (X), ethyl acetate (XIV), aqueous DMF (XV, XVI), nitromethane (XVIII), or benzene (XXIII). Crude XIX and XX were analyzed without purification.

IR Spectra (cm^{-1}). The IR spectra of mineral-oil suspensions were recorded with a UR-10 spectrometer: X – 1615 (CO); XI – 1610 (CO); XII – 1610, 1640 (CO); XIII – 1600, 1630 (CO); XIV – 3150 (OH); XVII – 1490 (NO); XVIII – 1310, 1460 (NO_2); XXI – 1650, 1734 (CO); XXII – 1630, 1740 (CO).

PMR Spectra. The PMR spectra of $CDCl_3$, CCl_4, or CF_3COOH solutions were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

The chemical shifts in parts per million were as follows: VIII – 3.40 (CH_3); 5.53 (H_7); 6.84 (H_5); 6.75 (H_3); 6.42 (H_2); 7-7.5 (C_6H_4). X – 2.17 (CH_3); 9.1 (CHO); 7.94 (H_3); 0.98 ($\mathbf{CH_3}CH_2CH_2$); 1.78 ($CH_3\mathbf{CH_2}CH_2$); 3.97 ($CH_3CH_2\mathbf{CH_2}$); 7-7.5 (C_6H_4). XI – 1.96 ($COCH_3$); 2.36 ($C_6H_4\mathbf{CH_3}$); 5.01 ($\mathbf{CH_2}C_6H_5$); 6.82 (H_2); 8.13 (H_3); 7-7.5 (C_6H_4);

5.48 (H_7). XII – 1.63 ($COCH_{3(5)}$); ($COCH_{3(7)}$); 2.44 ($C_6H_4CH_3$); 5.87 ($CH_2C_6H_5$); 6.81 (H_2); 8.1 (H_3). XIV – 0.86 ($CH_2CH_2CH_3$); 1.66 ($CH_2CH_2CH_3$); 3.85 ($CH_2CH_2CH_3$); 2.10 (CH_3); 4.00 (CH_2OH); 7.38 (CH_2OH). XVI – 2.71 ($C_6H_4CH_3$); 5.86 ($CH_2C_6H_5$); 7-7.8 (C_6H_4); 8.23 (H_3). XVII – 0.96 ($CH_2CH_2CH_3$); 1.78 ($CH_2CH_2CH_3$); 3.94 ($CH_2CH_2CH_3$); 2.13 ($CH_{3(7)}$); 8.12 (H_3); 7-7.5 (C_6H_4). XXI – 1.22 (CH_2CH_3); 4.20 (CH_2CH_3); 1.81 ($COCH_3$); 4.42 ($CH_{2(3)}$). XXII – 0.94 ($CH_2CH_2CH_3$); 1.61 ($CH_2CH_2CH_3$); 3.99 ($CH_2CH_2CH_3$); 4.35 ($CH_{2(3)}$); 1.83 ($COCH_3$); 1.67 ($CH_{3(7)}$). XXIII – 1.36 (CH_2CH_3); 4.29 (CH_2CH_3); 4.59 ($CH_{2(3)}$); and 7-7.5 (C_6H_5, C_6H_4).

LITERATURE CITED

1. R. M. Palei and P. M. Kochergin, Khim. Geterotsikl. Soedin., 403 (1972).
2. P. M. Kochergin, A. A. Druzhinina, and R. M. Palei, Khim. Geterotsikl. Soedin., 149 (1966).
3. A. A. Druzhinina and P. M. Kochergin, Khim. Geterotsikl. Soedin., 527 (1967).
4. A. A. Druzhinina and P. M. Kochergin, Khim. Geterotsikl. Soedin., 532 (1967).
5. A. A. Druzhinina, P. M. Kochergin, and N. P. Bychkova, Khim. Geterotsikl. Soedin., 856 (1969).
6. P. M. Kochergin, Yu. N. Sheinker, A. A. Druzhinina, R. M. Palei, and L. M. Alekseeva, Khim. Geterotsikl. Soedin., 826 (1971).
7. P. M. Kochergin, A. A. Druzhinina, R. M. Palei, A. M. Tsyganova, G. N. Pershin, N. A. Novitskaya, F. N. Ismailov, Yu. I. Syrneza, A. I. Tareeva, and G. P. Sukhinina, Summaries of Papers Presented at the Conference on the Relationship between Structure and Properties in Nitrogen-Containing Heterocyclic Compounds [in Russian], Izd. UPI, Sverdlovsk (1967), p. 80.
8. W. L. Mosby, Heterocyclic Systems with Bridgehead Nitrogen Atoms, Vol. 1, New York (1961), p. 239.
9. V. K. Kibirev and F. S. Babichev, Ukr. Khim. Zh., 30, 488 (1964).
10. F. S. Babichev, G. P. Kutrov, and M. Yu. Kornilov, Ukr. Khim. Zh., 34, 1020 (1968).
11. F. S. Babichev, G. P. Kutrov, and M. Yu. Kornilov, Ukr. Khim. Zh., 36, 909 (1970).
12. W. B. Harrell and R. F. Doerge, J. Pharm. Sci., 56, 1200 (1967).
13. E. T. Borrows, D. O. Holland, and J. Kenyon, J. Chem. Soc., 1077 (1946).
14. B. B. Molloy, D. H. Reid, and F. S. Skelton, J. Chem. Soc., 65 (1965).