(HET)ARYLATION OF SUBSTITUTED ACETONITRILES.

1. SYNTHESIS OF 2-AMINO-3-(BENZIMIDAZOL-2-YL)PYRROLO[2,3,b]-QUINOXALINES

A. P. Kozynchenko, Yu. M. Volovenko,
V. K. Promonenkov, A. V. Turov,
and F. S. Babichev

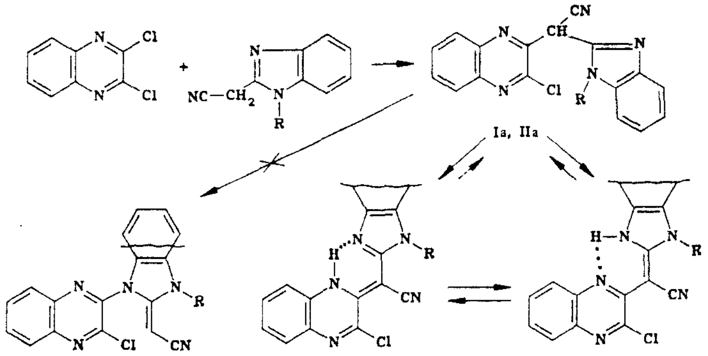
UDC 547.863.13'866.5.07

It was shown that hetarylation of benzimidazol-2-ylacetonitriles by 2,3-dichloroquinoxaline proceeds at the methylene group. The reaction of 2-chloro-3-[α-cyano-α-(benzimidazol-2-yl)methylene]-3,4-dihydroquinoxalines formed with primary amines leads to 1-R-2-amino-3-(benzimidazol-2-yl)pyrrolo[2,3-b]quinoxalines.

Products of hetarylation of the methylene group of cyanoacetic ester and malononitrile by 2,3-dichloroquinoxaline found application in the syntheses of 2-aminopyrrolo[2,3-b]quinoxalines [1] and 2-aminothieo[2,3-b]quinoxalines [2]. It was of interest to study the hetarylation of ambidentate anions, generated from benzimidzol-2-ylacetonitriles by the action of bases.

We found that in the reaction of 2,3-dichloroquinoxaline with benzimidazol-2-ylacetonitriles in aprotic organic solvents in the presence of potassium carbonate, hetarylation proceeds at the methylene group, and not at the other nucleophilic center, i.e., the nitrogen atom of the benzimidazole ring.

This path of the reaction is confirmed especially by the PMR spectra of the reaction products I and II showing signals of the NH group protons, which can undergo a deutero exchange, in the 12.5...13.5 ppm region: a two-proton signal in compound I and a one-proton signal in compound II.



Ib IIb

Ic IIc

I R=H; II R=CH_3

In the IR spectra of the two compounds, the stretching vibrations of the NH group appear in the form of broad absorption bands in the 3500...3400 cm^{-1} region (compound II) and 3500...3400, 3300...3100 cm^{-1} region (compound I). The high intensity and the position (2180 cm^{-1}) of the stretching vibrations band of the CN group indicate a conjugation of the nitrile group with the double bonds. From the above data it can be concluded that compounds I and II are not present in form Ia, IIa, either in solution or in the solid state. However, until this time it is still difficult to make a definite statement on the preferential content of tautomers Ib or Ic, IIb or IIc and on the presence of an equilibrium.

The chlorine atom at the 2-position of the quinoxaline ring in compounds I and II readily undergo nucleophilic substitution; on brief warming with excess piperidine, the chlorine atom

---

T. G. Shevchenko State University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1119-1123, August, 1988. Original article submitted February 4, 1987; revision submitted October 27, 1987.

TABLE 1. Results of Synthesis of Compounds I-VI

Compound	Method of synthesis	Time of reaction, min	mp, °C*	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N (Cl)		C	H	N (Cl)	
I	A B	720 240	309...310 (dec.)	—	—	22,0 (11,3)	$C_{17}H_{10}ClN_5$	—	—	21,9 (11,1)	56 73
II	A B	240 150	233...234	—	—	21,3 (10,7)	$C_{18}H_{12}ClN_5$	—	—	21,0 (10,6)	70 74
III	E	15	289 (разл.)	71,7	5,5	22,7	$C_{22}H_{20}N_6$	71,7	5,5	22,8	Quant.
IV	C	3	220...221	72,0	5,7	21,8	$C_{23}H_{22}N_6$	72,2	5,8	22,0	"
Va	D	240	241...242	69,9	5,3	24,3	$C_{20}H_{18}N_6$	70,2	5,3	24,5	"
Vb	E	60	265...266	70,5	5,5	23,6	$C_{21}H_{20}N_6$	70,8	5,7	23,6	"
Vc	E	30	246...247	70,9	4,7	24,9	$C_{20}H_{16}N_6$	70,6	4,7	24,7	97
Vd	E	40	309...310 (dec.)	71,9	5,8	21,8	$C_{23}H_{22}N_6$	72,2	5,8	22,0	Quant.
Ve	C	5	308...310 (dec.)	74,1	4,7	21,6	$C_{24}H_{18}N_6$	73,8	4,7	21,5	"
VIa	D	240	239...240	70,4	5,7	23,6	$C_{21}H_{20}N_6$	70,8	5,7	23,6	91
VIb	E	15	174...175	71,7	6,0	23,0	$C_{22}H_{22}N_6$	71,3	6,0	22,7	95
VIc	E	20	190...191	71,1	5,1	23,8	$C_{21}H_{18}N_6$	71,2	5,1	23,7	90
VId	C	5	285...286	72,8	6,2	21,0	$C_{24}H_{24}N_6$	72,7	6,1	21,2	Quant.
VI e	C	5	195...197	74,2	5,0	20,8	$C_{25}H_{20}N_6$	74,4	5,0	20,7	94

---

*Solvent for compounds I, Vd — DMFA; II-IV — dioxane; Va-c, e, VId, e — xylene; VIa-c — toluene.

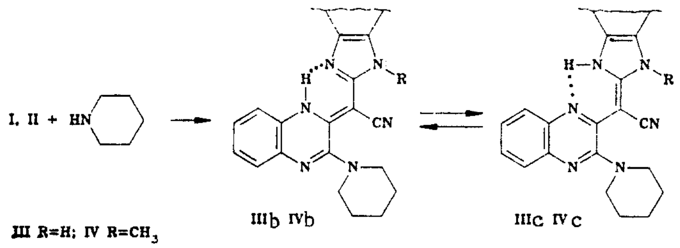
TABLE 2. Spectral Characteristics of Compounds I-VI

Compound	IR spectrum, ν, cm^{-1}		UV and visible spectrum, λ_{max}, nm (log ε)	PMR spectrum (in DMSO-D_6), δ, ppm
	NH	CN		
I	3460, 3180	2181	289 (4,17), 326 sh, 334 (4,54), 450 (4,14)	12,90 (2H, br.s, N—H); 8,4 ... 7,2 (8H, m, arom)
II	3470	2181	288 (4,12), 338 (4,35), 450 (4,09)	13,24 (1H, br. s, N—H); 8,4 ... 7,0 (8H, m, arom.); 3,82 (3H, s, N—CH_3)
III	3450, 3200	2200	282 (4,11), 316 (4,30), 333 sh; 433 (4,35), 450 (4,35), 477 sh	10,9 (2H, br.s, N—H); 8,1 ... 6,9 (8H, m, arom), 3,29 (4H, m α-H); 1,83 (4H, m, β-H); 1,64 (2H, m γ-H)
IV*	3450	2190	282 sh, 321 (4,32), 435 (4,37), 455 sh, 488 sh	15,85 (1H, br. s., N—H); 7,9 ... 7,1 (8H, m, arom .); 4,09 (3H, s, N—CH_3); 3.49 (4H, m, α-H); 1,89 (4H, m, β-H), 1,71 (2H, m, γ-H)
Va	3420, 3340, 3315, 3230	—	269 (4,43), 275 (4,44), 300 sh, 315 (4,57), 330 (4,68), 343 sh, 417 (4,10)	11.7 (1H, br.s., N—H); 8,73 (2H, br. s, NH_2); 8,2 ... 7,1 (8H, m, arom); 5,09 (1H, hept, $CH(CH_3)_2$); 1,75 (6H, d CH_3)
Vb	3450, 3380, 3280	—	269 (4,41), 275 (4,44), 300 sh, 315 (4,58), 330 (4,67), 343 sh, 417 (4,10)	11,7 (1H, br. s, N—H); 8,77 (2H, br. s, NH_2); 8,3 ... 7,0 (8H, m, arom); 4,32 (2H, t, N—CH_2); 1,76 (2H, m, CH_2—CH_2—); 1,38 (2H, m CH_2—CH_2—CH_2—); 0,94 (3H, t, CH_3)
Vc	3430, 3350, 3330	—	269 (4,56), 275 (4,58), 300 sh, 315 (4,72), 330 (4,81), 343 sh, 417 (4,10)	11,4 (1H, br. s, N—H); 8,73 (2H, br. s, NH_2); 8,3 ... 7,0 (8H, m, arom.); 6,1 (1H, m, CH_2—CH=CH_2); 5,1 (4H, m, CH_2—CH=CH_2)
Vd	3410, 3380, 3310	—	269 (4,46), 275 (4,47), 300 sh, 315 (4,61), 330 (4,71), 343 sh, 417 (4,06)	8,69 (2H, br. s, NH_2); 8,2 ... 7,1 (8H, m, arom); 4,60 (1H, m, N—CH); 2,74 (4H, m, α-H); 1,88 (4H, m, β-H); 1,48 (2H, m, γ-H)
Ve	3390, 3340, 3270	—	269 (4,53), 275 (4,56), 300 sh., 315 (4,70), 330 (4,79), 343 sh, 417 (4,06)	11,82 (1H, br. s, N—H); 8,81 (2H, br. s, NH_2); 8,3 ... 6,8 (13H, m, arom.); 5,10 (2H, s, N—CH_2—)
VIa*	3420, 3370, 3210	—	266 (4,56), 318 (4,47), 403 (4,10)	7,25 (2H, br. s, NH_2); 8,2 ... 7,1 (8H, m, arom .); 5,14 (1H, hept, $CH(CH_3)_2$); 4,34 (3H, s, CH_3); 1,75 (6H, d, $CH(CH_3)_2$)
VIb*	3440, 3360	—	266 (4,52), 318 (4,48), 403 (4,11)	7,06 (2H, br.s, NH_2); 8,3 ... 6,7 (8H, m, arom); 4,35 (3H, s, N—CH_3); 4,26 (2H, t, N—CH_2—); 1,85 (2H, m, —CH_2—CH_2—); 1,43 (2H, m, —CH_2—CH_3); 0,97 (3H, t, CH_3)
VIc*	3400, 3280, 3220	—	266 (4,50), 318 (4,40), 403 (4,04)	7,25 (2H, br. s, NH_2); 8,2 ... 6,9 (8H, m, arom .); 6,07 (1H, m, CH_2—CH=CH_2); 5,5 ... 4,9 (4H, m, CH_2—CH=CH_2); 4,38 (3H, s, N—CH_3)
VId*	3400, 3270	—	266 (4,64), 318 (4,50), 403 (4,15)	7,30 (2H, br. s, NH_2); 8,2 ... 7,0 (8H, m, arom); 4,60 (1H, m, N—CH—); 4,32 (3H, s, CH_3); 2,8 ... 1,1 (10H, cyclohexyl)
VIe*	3430, 3300	—	266 (4,55), 318 (4,45), 403 (4,10)	8,73 (2H, br. s, NH_2); 8,1 ... 7,0 (13H, m, arom); 5,62 (2H, s, N—CH_2—); 4,29 (3H, s, N—CH_3)

---

*The PMR spectrum was run in $CDCl_3$.

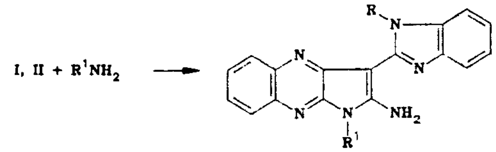
is readily substituted, while the nitrile group remains unaffected. A similar reaction with diethylamine has been described in [1].



III R=H; IV R=CH_3 IIIb IVb IIIc IVc

The spectral parameters of compounds I, II, and correspondingly, of III, IV, are similar.

The reaction of compounds I and II with primary amines proceeds more extensively, and is concluded by closing of a pyrrole ring.



V–VI a–c

V R=H; VI R=CH_3; V, VI a R^1=i-C_3H_7; b R^1=C_4H_9; c R^1=CH_2—CH=CH_2; d R^1 = cyclo-C_6H_{11}; e R^1=CH_2Ph

The reaction proceeds readily and rapidly on heating of compounds I and II with excess amine at temperatures of 120...170°C. In the case of low-boiling amines, the reaction was carried out either in DMFA or in a sealed ampule.

In the PMR spectra of compounds V and VI, signals are observed of interchanging protons of the NH and NH_2 groups, as well as the corresponding multiplets of the hydrocarbyl radicals. In the IR spectra, the stretching vibration band of the C≡N group is absent, which indicates that an intermolecular interaction of the nitrile and amino groups takes place with the formation of a heterocyclic system of pyrrolo[2,3-b]quinoxaline.

EXPERIMENTAL

The PMR spectra were recorded on a WP-100 SY Bruker spectrometer, using TMS as internal standard. When the signal of the amino group fails in the absorption region of the aromatic protons, the position of this signal is determined by the method of differential spectroscopy, based on the spectrum of the sample with and without the addition of heavy water. The IR spectra were run on a SP3-300 Pye Unicam spectrophotometer in KBr tablets. The electronic spectra of the methanolic solutions of compounds I-VI were recorded on a Specord UV-vis spectrometer.

2-Chloro-3-[α-cyano-α-benzimidazol-2-yl)methylene]3,4-dihydroquinoxalines (I, II).*
A. A 6.9 g portion (50 mmoles) of a calcined and finely ground potassium carbonate is added to a solution of 10 g (50 mmoles) of 2,3-dichloroquinoxaline and 50 mmoles of the corresponding benzimidazol-2-ylacetonitrile [3, 4] in 150 ml of dioxane. On the surface of contact of potassium carbonate with the reagent solution, an orange-red coloration gradually develops. The reaction mixture is boiled, then cooled, and the precipitate is filtered, washed with a cold dioxane (30 ml), and suspended in 150 ml of water with the addition of 15 ml of acetic acid, then filtered, washed with water and dried.

B. A 1.38 g portion (10 mmoles) of a calcined finely ground potassium carbonate is added, with stirring, to a solution of 2 g (10 mmoles) of 2,3-dichloroquinoxaline and 10 mmoles of the corresponding benzimidazol-2-ylacetonitrile in 75 ml of DMSO. A deep pink-red coloration develops at once. The mixture is stirred at room temperature and at the end of the reaction is poured into 500 ml of cold water, and 7 ml of concentrated HCl are added. The precipitate that separates out is filtered, washed with water, and dried.

---

*The time of the reaction, the yield and characteristics of the compounds synthesized are given in Table 1, and the spectral data in Table 2. The melting points given in Table 1 are uncorrected.

2-(Piperidin-1-yl)-3-[α-cyano-α-benzimidazol-2-yl)methylene]3,4-dihydroquinoxalines (III, IV) and 1-R^1-2-Amino-3-(benzimidazol-2-yl)pyrrolo[2,3-b]quinoxalines (V, VI).* C. A 5 ml portion of the corresponding amine is added to 10 mmoles of compound I or II. The solution over the precipitate immediately becomes deep pink-red colored. The reaction mixture is boiled, and on completion of the reaction, the color of the solution brightens, turns red (in thin layer, into yellow), while the precipitate becomes transformed. The reaction mixture is cooled, 100 ml of water and 5 ml of acetic acid are added. The separated precipitate is filtered, washed with water, and dried.

D. A mixture of 3 mmoles of compound I or II, 3 ml of DMFA was heated for 4 h at 130°C in a sealed ampul (length 150 ml, external diameter 17 mm, internal diameter 14 mm). The ampul is then cooled, opened, and the reaction product is isolated as described in method C.

E. A mixture of 3 mmoles of compound I or II, 3 ml of the corresponding amine and 15 ml of DMFA is boiled, and at the end of the reaction, treated in the same way in methods C and D.

LITERATURE CITED

1. O. Hirotaka, O. Shigeru, S. Toshie, and T. Hiroshi, Chem. Pharm. Bull., 18, 2065 (1970).
2. A, P. Kozynchenko, F. S. Babichev, V. . Promonenkov, A. I. Zubenko, and L. I. Savranskii, Ukr. Khim. Zh., 53, 401 (1987).
3. R. A. B. Copeland and A. R. Day, J. Am. Chem. Soc., 65, 1072 (1943).
4. G. Buchi, H. Zwicky, and A. Aebi, Arch. Pharm., 293, 758 (1960).

---

*See footnote on previous page.

SYNTHESIS AND PROPERTIES OF N-SUBSTITUTED AMINOFUROXANS IN THE ADAMANTANE SERIES

M. I. Kalinina, I. K. Moiseev,
and V. I. Pavskii

UDC 547.793.2'516'441:543.422.25

3-N,N-Disubstituted aminofuroxans in the adamantane series have been obtained by the oxidation of anti[1,(3-R-adamantyl)]-amphi-glyoximes with excess $K_3Fe(CN)_6$ in the presence of the corresponding amines. Preparation of 3-amino and 3-methylamino-4-(1-adamantyl)furoxans requires initial synthesis of 2-(1-adamantyl)-2-hydroximinoacetonitrile oxide followed by addition of the corresponding amines and oxidation of the resulting glyoximes. Substituent positions in the furoxan ring were determined by PMR spectroscopy.

Aminofuroxans attract the attention of investigators because of their known depressive effect on the central nervous system and their anti-spasmodic activity [1]. A single stage preparation of arylaminofuroxans from amphi-glyoximes in the presence of potassium ferricyanide and the amine has been reported [2]. It was therefore of interest to study the use of [2] for synthesis of N-substituted aminofuroxans of the adamantane series.

We have shown that anti-[1-(3-R-adamantyl)]-amphi-clyoximes [3] (Ia-e, a R = H, b R = CH_3, c R = p-$CH_3C_6H_4$, d R = Cl, e R = OH) form the N,N-dimethylaminofuroxans IIa-e in 50-65% yield when treated with a 30 fold excess of dimethylamine in the presence of an 8 fold excess of $K_3Fe(CN)_6$ for 2-3 h at room temperature. Decrease in the amount of oxidant to a 4-5 fold excess leads to a decreased yield of the furoxans IIa-e. The N,N-substituted furoxans IIf-h are formed by treatment of glyoxime Ia with diethylamine, morpholine, and piperidine under the conditions above.

V. V. Kuibyshev Polytechnic Institute, Kuibyshev 443010. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1124-1127, August, 1988. Original article submitted January 28, 1987.

0009-3122/88/2408-0927$12.50