A ^{15}N, ^{13}C, AND ^{1}H NMR STUDY OF REACTION PRODUCTS FROM ARYLGUANIDINES AND CHLOROFORMATE ESTERS

Antonín LYČKA[a] and Karel PALÁT, jr.[b]

[a] *Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitví*
[b] *Faculty of Pharmacy, Charles University, 501 65 Hradec Králové*

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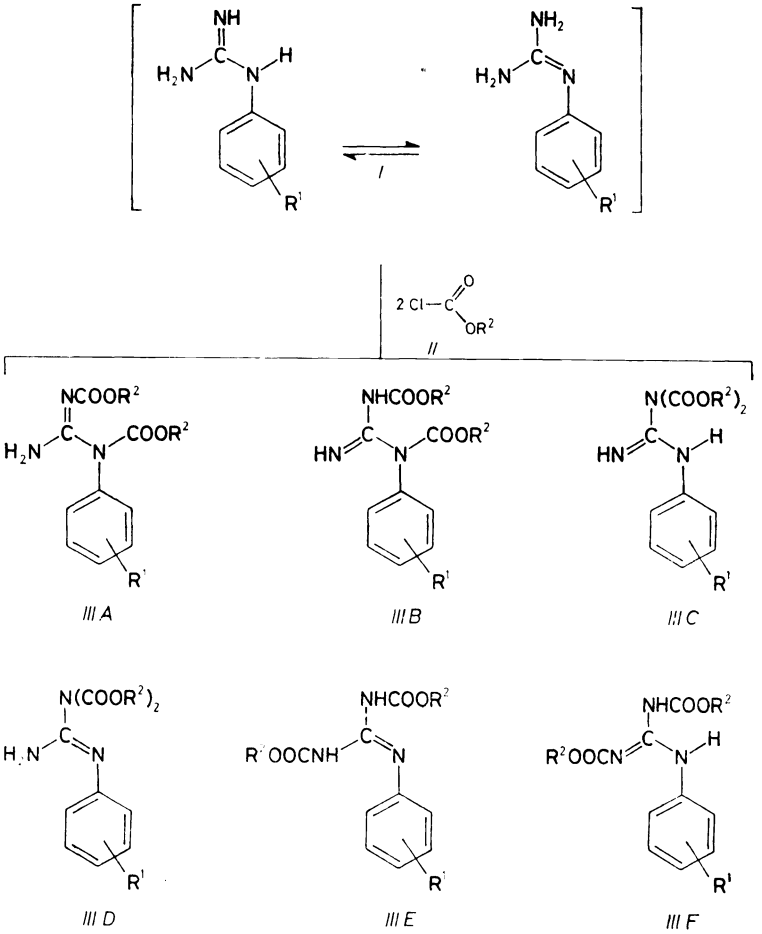
The ^{15}N, ^{13}C, and ^{1}H NMR spectra of the reaction products from arylguanidines with two mols of chloroformate esters have been measured. With application of the corresponding ^{15}N isotopomer it has been proved that the reaction products have the structures *IIIa*—*IIIo*.

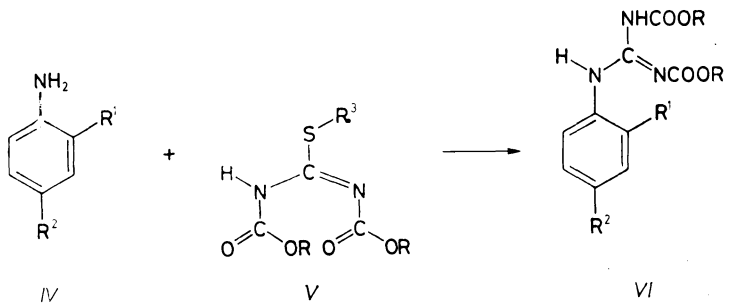
Within the attempts at finding alternative pathways to synthesis of substituted arylguanidine dicarboxylates we have used the reaction of the respective arylguanidine (*I*, R^1 = H, NO_2) with esters of chloroformic acid (*II*, R = CH_3, C_2H_5, $CH(CH_3)_2$, $CH_2C_6H_5$). The reaction was carried out at the interface of two phases (water–dichloromethane), and magnesium oxide was used to maintain the alkaline reaction medium. The products *III* were formed in the reactions without side products, and the yields were relatively high (60–97%). The IR spectra and elemental analyses of the products confirmed that they are bisalkoxycarbonyl derivatives. The alkoxycarbonylations given, of course, can theoretically produce a series of isomers and/or tautomers, as it can be seen in Scheme 1.

The aim of the present work was to identify the compounds obtained by means of ^{15}N, ^{13}C, and ^{1}H NMR spectroscopy and to verify whether or not they have the same positions of substituents as those in the compounds obtained by the usual reaction of substituted anilines *IV* with dialkyl 2-alkyl-1,3-thioisoureidodicarboxylates *V* (Scheme 2). In the compounds *VI* the alkoxycarbonyl groups are bound to the nitrogen atoms N^1 and N^2 of the guanidine group[1,2] and the aryl substituent is at N^3.

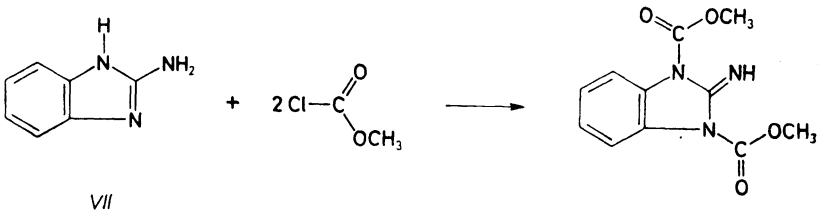
The reaction studied is – in a sense – analogous to the methoxycarbonylation of "cyclic benzoguanidine" – 2-aminobenzimidazole (*VII*) described by Klopping[3] (Scheme 3). This reaction produces dimethyl 2-imino-1,3-benzimidazolinedicarboxylate (*VIII*), i.e. the substitution takes place at the nitrogen atoms adjacent to the benzene nucleus.



SCHEME 1



SCHEME 2

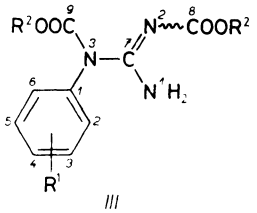


VII *VIII*

SCHEME 3

EXPERIMENTAL

The syntheses of compounds *IIIa—IIIo* (Scheme 1) and results of tests of biological activity are given in ref.[4]. The compound *IIIc* enriched with ^{15}N at the N^3 position was obtained in the same way as the nonlabelled compounds with application of ^{15}N-aniline (96% ^{15}N, Isocommerz Berlin).



III

III	R^1	R^2	*III*	R^1	R^2
a	H	CH_3	*i*	3-NO_2	CH_2CH_3
b	H	$CH(CH_3)_2$	*j*	3-NO_2	$CH(CH_3)_2$
c	H	$CH_2C_6H_5$	*k*	3-NO_2	$CH_2C_6H_5$
d	2-NO_2	CH_3	*l*	4-NO_2	CH_3
e	2-NO_2	$CHCH_3$	*m*	4-NO_2	CH_2CH_3
f	2-NO_2	$CH(CH_3)_2$	*n*	4-NO_2	$CH(CH_3)_2$
g	2-NO_2	$CH_2C_5H_5$	*o*	4-NO_2	$CH_2C_6H_5$
n	3-NO_2	CH_3			

The ^1H and ^{13}C NMR spectra were measured with a Bruker AM 400 apparatus at 400·13 and 100·6 MHz, respectively, in a 5 mm NMR tube at 300 K in a standard way, using 5—10% solutions of the substances in deuteriochloroform. The ^1H and ^{13}C chemical shifts are referred to internal tetramethylsilane ($\delta = 0{\cdot}00$).

The ^{15}N NMR spectra were measured with a JNM-FX 100 apparatus at 10·095 MHz with natural abundance of the ^{15}N isotope. At first the measurement was carried out in a 10 mm NMR tube in deuteriochloroform at 300 K with application of the proton-noise decoupling (spectral width 5 000 Hz, 8 k memory, 45° pulse, pulse repetition 3 s). After these measurements, $Cr(acac)_3$ (about 25 mg/ml) was added to the samples as relaxation agent, and the ^{15}N chemical shifts were measured for the nitrogen atoms not directly bound with protons. The ^{15}N chemical shifts are referred to external neat nitromethane ($\delta = 0{\cdot}02$). Positive values of the chemical shifts denote downfield shifts.

RESULTS AND DISCUSSION

The reaction of substituted phenylguanidines with chloroformate esters has been studied. The elemental analyses of the reaction products show that the reactants react in the molar ratio of 1 : 2, which leads to the reaction products given in Scheme 1. The ^1H and ^{13}C NMR spectra of the reaction products measured in deuteriochloroform give – in accordance with the results of elemental analysis – two sets of ^1H and ^{13}C NMR signals for the COOR groups (Tables I and II). On the basis of this information, however, it is impossible to differentiate between the structure given in Scheme 1, since even in compounds with $N(COOR)_2$ grouping the COOR groups are magnetically nonequivalent due to geometrical isomerism at the $>C=N<$ bond. In order to prove that the reaction products from arylguanidines and two mols of chloroformate esters correspond to the compounds *IIIa–IIIo*, we adopted a procedure which will be demonstrated in detail for the case of compound *IIIc*. The ^{15}N NMR spectrum of this compound was measured with application of the proton-noise decoupling and rapid pulse repetition (c. 3 s). Thus we obtained a singlet with the ^{15}N chemical shift of −288·2 ppm, and in the subsequent measurement of the proton-coupled spectrum this singlet gave a triplet with the coupling constant $^1J(^{15}N, H) = 92·8$ Hz, which is characteristical of an NH_2 group. This is a very

TABLE I

^1H chemical shifts (δ, ppm) in compounds *IIIa–IIIo*

Compound	NH_2	H arom	R^2
IIIa	9·43[a]	7·13–7·35	3·66, 3·48 (CH_3)
IIIb	9·40[a]	7·10–7·30	4·94, 4·42 (CH), 1·09, 1·01 (CH_3)
IIIc	9·20, 9·50	6·94–7·45	5·07, 4·85 (CH_2)
IIId	9·45[a]	7·28–8·16	3·71, 3·49 (CH_3)
IIIe	9·40[a]	7·29–8·11	4·16, 3·85 (CH_2), 1·05, 1·02 (CH_3)
IIIf	9·21, 9·54	7·29–8·10	4·99, 4·44 (CH), 1·08, 1·01 (CH_3)
IIIg	9·17, 9·46	6·99–8·00	5·08, 4·83 (CH_2)
IIIh	9·27, 9·48	7·52–8·23	3·73, 3·54 (CH_3)
IIIi	9·45[a]	7·50–8·17	4·19, 3·91 (CH_2), 1·13, 1·10 (CH_3)
IIIj	9·37[a]	7·50–8·17	4·99, 4·55 (CH), 1·12, 1·05 (CH_3)
IIIk	9·12, 9·45	7·02–8·10	5·08, 4·88 (CH_2)
IIIl	9·25, 9·45	7·32–8·26	3·73, 3·54 (CH_3)
IIIm	9·45[a]	7·33–8·26	4·18, 3·95 (CH_2), 1·14, 1·14 (CH_3)
IIIn	9·41[a]	7·34–8·23	5·00, 4·57 (CH), 1·13, 1·07 (CH_3)
IIIo	9·25, 9·45	7·03–8·20	5·10, 4·90 (CH_2)

[a] Broad signal.

TABLE II

^{13}C chemical shifts (δ, ppm) in compounds *IIIa*—*IIIo*

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	R^2
IIIa	137·4	128·7	128·4	128·0	128·4	128·7	160·9	156·0	164·0	54·0, 52·4
IIIb	137·9	128·4	128·4	127·4	128·4	128·4	160·7	155·0	162·9	71·4, 69·1, 21·7, 21·2
IIIc	137·5	128·6	128·5	128·1	128·5	128·6	160·9	155·2	163·4	68·3, 67·1[a]
IIId	131·7	145·0	125·5	129·5	134·2	131·7	160·0	154·9	163·7	54·5, 52·5
IIIe	131·8	144·9	125·1	129·2	134·0	131·6	159·8	154·2	163·1	63·8, 61·2, 14·1, 13·6
IIIf	132·2	145·3	125·1	129·1	133·8	131·8	160·1	153·9	163·0	72·3, 68·9, 21·3, 21·1
IIIg	131·6	145·0	125·2	129·3	133·9	131·5	160·0	154·2	163·1	69·0, 66·9[b]
IIIh	138·5	124·2	148·4	123·3	129·6	135·2	160·4	155·2	163·8	54·6, 52·6
IIIi	138·7	124·1	148·1	122·9	129·3	135·2	160·2	154·6	163·2	63·9, 61·2, 14·1, 13·7
IIIj	138·9	124·0	148·0	122·6	129·2	135·2	160·1	154·1	162·7	72·3, 68·6, 21·6, 21·2
IIIk	138·5	124·1	148·2	122·9	129·3	135·0	160·3	154·3	163·1	69·0, 66·9[c]
IIIl	143·2	129·9	124·3	147·3	124·3	129·9	160·3	155·0	163·9	54·5, 52·6
IIIm	143·3	129·8	124·0	146·9	124·0	129·8	160·1	154·3	163·1	63·8, 61·6, 14·1, 13·7
IIIn	143·7	129·8	123·9	146·8	123·9	129·8	160·2	153·9	162·8	72·3, 68·7, 21·6, 21·2
IIIo	143·2	129·8	124·1	147·1	124·1	129·8	160·2	154·3	163·2	69·0, 67·0[d]

[a] 136·8, 134·6, 128·3, 128·0, 127·9, 127·6, 127·4, 127·0; [b] 136·6, 134·1, 128·5, 128·4, 128·0, 127·5, 127·4, 127·3; [c] 136·5, 134·1, 128·5, 128·4, 128·0, 127·5, 127·4, 127·3; [d] 136·6, 134·1, 128·5, 128·4, 128·0, 127·5, 127·4, 127·3.

valuable piece of information which excludes the structures *B*, *C*, *E*, and *F* in Scheme 1. The ^{15}N chemical shifts of the other two nitrogen atoms were measured after adding the relaxation agent $Cr(acac)_3$ (Table III).

In order to differentiate between the structures *A* and *D*, we prepared the N-3. (96% ^{15}N) selectively enriched compound *IIIc*, using the ^{15}N-aniline in its synthesis. The ^{15}N isotope has the spin number $I = 1/2$ and causes splitting of the adjacent carbon signals into doublets. The assignment can be completed on the basis of the coupling constants $^{n}J(^{15}N\text{-}3, ^{13}C)$. With respect to the similarity of the coupling constants $^{1}J(^{15}N\text{-}3, ^{13}C\text{-}7) = 22{\cdot}7$ Hz and $^{1}J(^{15}N\text{-}3, ^{13}C\text{-}9) = 24{\cdot}9$ Hz it is evident that the reaction took place at the nitrogen atom N-3, whereas the coupling constant $^{3}J(^{15}N\text{-}3, C\text{-}8)$ is equal to 5·9 Hz. Other coupling constants $^{n}J(^{15}N\text{-}3, ^{13}C)$ can be observed for the carbon atoms C-1, C-2, C-3, which enables differentiation between the signals of the phenyl groups C_6H_5N and $C_6H_5CH_2$.

In the ^{13}C proton-coupled spectrum the carbon atom C—NH_2 ($\delta = 160{\cdot}9$) gives a broadened singlet, whereas the carbon atoms of carboxylic groups ($\delta = 155{\cdot}2$ and 163·4) are split into broadened triplets by the influence of the protons of CH_2 group. The signals of the $COOCH_2C_6H_5$ group were differentiated on the basis of the coupling constant $^{n}J(^{15}N\text{-}3, ^{13}C)$ (vide supra). Their unambiguous assignment was carried out by adopting[5] the selective INEPT to ascribe the signals of CH_2 groups. The selective excitation of the CH_2 protons with the ^1H chemical shift $\delta = 4{\cdot}85$ gave the carboxylic group signal with the shift $\delta(^{13}C\text{-}8) = 163{\cdot}4$ in the selective INEPT spectrum. On the basis of the result of selective decoupling, this CH_2 group was ascribed the ^{13}C chemical shift $\delta = 68{\cdot}30$. In a similar way we

TABLE III

^{15}N chemical shifts (δ, ppm) in compounds *IIIa*, *IIIc*, *IIIk*, and *IIIm*

Compound	N-1	N-2	N-3
IIIa		−288·8	
	−245·7[a]	−289·7[a]	−209·0[a]
IIIc		−288·2[b]	
	−246·0[a]	−289·7[a]	−209·6[a]
IIIk[c]		−288·4[d]	
	−247·5[a]	−289·0[a]	−207·3[a]
IIIm		−288·0	

[a] With addition of $Cr(acac)_3$ (25 mg/ml); [b] $^{1}J(^{15}H, H) = 92{\cdot}8$ Hz; [c] $\delta(NO_2) = -12{\cdot}9$; [d] $^{1}J(^{15}N, H) = 93{\cdot}0$ Hz.

proved the coupling of protons of CH_2 group (δ = 5·07) with the carbon of carboxylic group C-9 (δ = 155·2) and δ = 67·1.

The ^1H and ^{13}C NMR spectra of the other derivatives were measured, too. The comparison of ^{13}C chemical shifts, especially those of C-7, C-8, C-9 carbon atoms, shows that the structure of reaction product is the same for all the derivatives, which is additionally confirmed by the ^{15}N chemical shifts of selected derivatives (Table III).

The ^{13}C chemical shifts of carbon atoms in 2- and 3-phenyl groups were assigned on the basis of the analysis of two-dimensional H,H-COSY and H,C-COSY spectra[6], whereas the values of substituent chemical shifts[7] were used for the 4-nitro derivatives.

The formation of the products *IIIa–IIIo*, i.e. compounds whose preparation from 3-substituted guanidines involves the acylation at N^2 and N^3 nitrogen atoms, is in accordance with the products of reactions of arginine with usual alkylation reagents which give analogously substituted compounds[8].

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