N,N'-Bis(2-alkoxyphenyl)ureas as By-Products in the Reaction of Tertiary Alcohols with 2-Alkoxyphenyl Isocyanates

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Received 5 October 1992

Primary and secondary alcohols are known to react with aryl isocyanates to give arylcarbamates, while tertiary alcohols produce diarylureas. In this work we used two tertiary alcohols, 2-methyl-1-dimethylamino-2-propanol and 1-dimethylaminomethylcyclohexanol, to demonstrate that when reacting with 2-alkoxyphenyl isocyanates a mixture of products was obtained, the 2-alkoxyphenylcarbamates being the main products of the reaction.

It is well known that addition of primary and secondary alcohols to aryl isocyanates leads to formation of esters of arylcarbamic acid [1—4] and this reaction is frequently used to prepare local anaesthetics and antiarrhythmics of the phenylcarbamate type (esters of 2-alkoxyphenylcarbamic acid with aminoalcohols) [2, 4, 5]. On the other hand, tertiary alcohols (*e.g. tert*-butanol) are reported to react under noncatalyzed conditions to give *N,N'*-diarylurea and the reaction is known to be accompanied by alkene formation [1, 6, 7]. Previously, however, we have found [8] that arylcarbamates can also be prepared by reaction of a tertiary alcohol, *e.g.* 1-dimethylaminomethylcyclohexanol, with aryl isocyanates (with simultaneous production of ureas). To examine the latter reaction in more detail, we recently initiated a systematic study of the reaction of a tertiary alcohol 2-methyl-1-dimethylamino-2-propanol with 2-alkoxyphenyl isocyanates and found that although ureas are really formed, 2-alkoxyphenylcarbamates were the main products of the reaction [2]. As *N,N'*-bis(2-alkoxyphenyl)ureas may also be produced, due to the presence of atmospheric moisture, in the reaction of primary and secondary aminoalcohols with 2-alkoxyphenyl isocyanates and hence lower the yield of the main products (*i.e.* 2-alkoxyphenylcarbamates), it is important to know the reaction mechanism of the formation of *N,N'*-bis(2-alkoxyphenyl)ureas as well as their physicochemical properties. To deal with these problems is the main purpose of this communication. In addition, some of these *N,N'*-diarylureas were found to show a wide spectrum of biological (*e.g.* antiviral, immunosuppressive, and sedative) activities [9].

EXPERIMENTAL

Melting points (determined with a Kofler hot-stage) and elemental analyses (determined on Elemental Analyzer Model 1102 (Erba)) agreed with theoretical values, resp. [10—15]. All compounds were checked for purity by partition TLC on silica gel Silufol UV-254 (Kavalier) plates impregnated with 5 % solution of silicone oil in n-heptane, using the 1 M-HCl—acetone mixture (φ_r = 1 : 1) as the mobile phase (detection by 254 nm UV light).

The IR spectra were measured in chloroform solution on a Specord M-80 (Zeiss, Jena) spectrophotometer. NMR spectra (^{1}H at 300 MHz and ^{13}C at 75 MHz) were obtained on a Varian VXR-300 spectrometer in $CDCl_3$, using TMS as an internal reference. To assign the signals unambiguously, the two-dimensional ^{1}H—^{1}H correlation (DQCOSY) and ^{1}H—^{13}C heteronuclear correlation (HETCOR) experiments were also carried out for some samples.

N,N'-Bis(2-alkoxyphenyl)ureas *IVa—IVj* and *N,N'*-Dicyclohexylurea *VI*

A mixture of 2-alkoxyphenyl isocyanate (0.020 mol), 2-methyl-1-dimethylamino-2-propanol (2.46 g; 0.021 mol) or 1-dimethylaminomethylcyclohexanol (3.30 g; 0.021 mol) and anhydrous toluene (15 cm^3) is heated under reflux for 16 h. After cooling to 0—5 °C, an equal volume of n-hexane is added, and the mixture is allowed to stand at this temperature for additional 10 h. The solid product that appeared was collected by filtration, washed with n-hexane, dried, and crystallized from methanol—n-heptane (φ_r = 1 : 4). Yields are given in Table 1.

The same procedure was used in the reaction of 2-methyl-1-dimethylamino-2-propanol (2.46 g; 0.021 mol) with cyclohexyl isocyanate (2.28 g; 0.02 mol) in toluene which yielded *N,N'*-dicyclohexylurea *VI*, crystallized from butanone. R_f = 0.27. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 3436, 1658, 1524. ^{1}H NMR spec-

trum ($CDCl_3$, TMS), δ: 3.48 (C-1—H), 1.07, 1.93 (C-2—H_2, C-6—H_2), 1.35, 1.69 (C-3—H_2, C-5—H_2), 1.15, 1.60 (C-4—H_2), 4.08 (NH). ^{13}C NMR spectrum ($CDCl_3$, TMS), δ: 49.2 (C-1), 34.0 (C-2, C-6), 24.9 (C-3, C-5), 25.6 (C-4), 130.7 (CO).

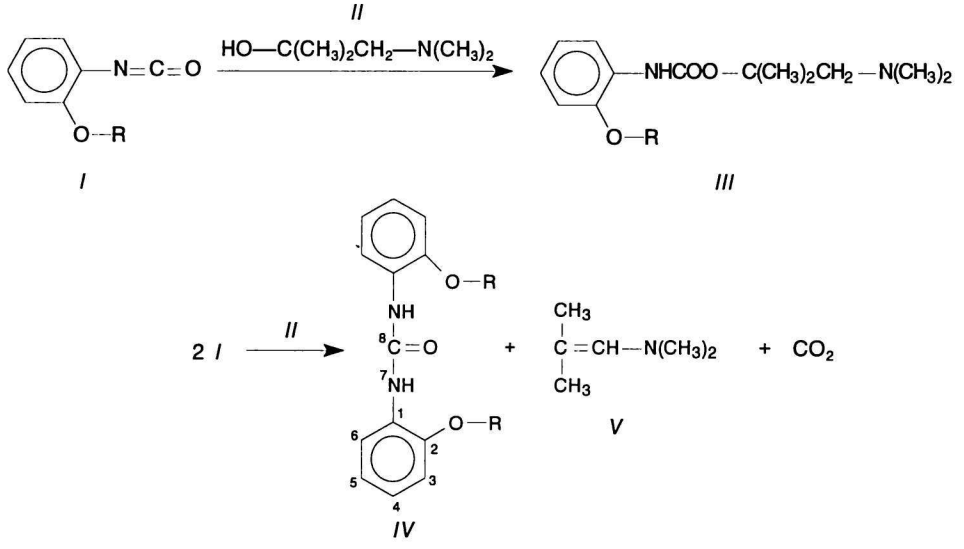
RESULTS AND DISCUSSION

It was found that the reaction of a tertiary alcohol 2-methyl-1-dimethylamino-2-propanol (*II*; Scheme 1) with 2-alkoxyphenyl isocyanates (*I*) leads to the formation of not only *N,N′*-bis(alkoxyphenyl)ureas (*IV*) as stated in the literature [6, 7], but also of 2-alkoxyphenylcarbamates (*III*), the latter being the main product of the reaction. Obviously, two parallel reactions occur in the system. As the presence of alkene (*V*) was identified in the reaction mixture, it is obvious that the reaction leading to the production of *N,N′*-bis(alkoxyphenyl)ureas is initiated by an elimination of H_2O from alcohol *II*, followed by an addition of the water molecule to the isocyanate *I*. The corresponding 2-alkoxyphenylcarbamic acid so obtained is readily decarboxylated to give 2-alkoxyphenylaniline and after addition of the latter to another molecule of 2-alkoxyphenyl isocyanate, the final product *IV* is obtained. Alkyl isocyanates react with tertiary alcohols in a similar way, as demonstrated by the synthesis of *N,N′*-dicyclohexylurea. Similarly, replacing 2-methyl-1-dimethylamino-2-propanol by another tertiary alcohol, 1-dimethylaminomethylcyclohexanol, analogous results were obtained. Compounds *IVa*, *IVb*, *IVd*, *IVh* (Table 1) are described in [10—15].

As shown in Table 1, yields obtained by using the two aminoalcohols differ only slightly and range from 10 to 20 %. Yields of *N,N′*-dicyclohexylurea fall into the same range.

Structures of diarylureas obtained were confirmed by ^1H and ^{13}C NMR spectra (Tables 2 and 3) [16, 17] and by IR spectroscopy. In the IR spectra of all compounds *IV* the following characteristic absorption bands are observed [18—20]: a band of medium intensity at $\tilde{\nu}$ = 3420 cm^{-1} due to NH stretching vibration, an intense band at 1677—1679 cm^{-1} (ν(C=O) vibration), and a medium intensity band at 1600—1605 cm^{-1} ($\nu(C—C)_{arom}$ vibration).

Products *IV* were also studied by thin-layer partition chromatography. We have found such experimental conditions that allow not only the resolution of separate members within the homologous series *IV*, but also the resolution of these *N,N′*-bis(2-alkoxyphenyl)ureas from the corresponding compounds *III* which are the main products of the reaction studied (Scheme 1). The R_f values decrease gradually with the length of the chain and, similarly as in other homologous series [21, 22], there is a linear relationship between $R_M = \log [(1/R_f) - 1]$ [23] and the number of carbons (n) of the alkoxy group: R_M = 0.193 n − 0.238 (r = 0.995, s = 0.040).



		R			R
I, III, IV	*a*	CH_3		*f*	$(CH_2)_2CH(CH_3)_2$
	b	CH_2CH_3		*g*	$(CH_2)_5CH_3$
	c	$(CH_2)_2CH_3$		*h*	$(CH_2)_6CH_3$
	d	$(CH_2)_3CH_3$		*i*	$(CH_2)_7CH_3$
	e	$(CH_2)_4CH_3$		*j*	$(CH_2)_8CH_3$

Scheme 1

Table 1. Characterization of Compounds Studied

Compound	Formula	M_r	M.p./°C	Yield/%[a]	R_M
IVa				11, 20	− 0.045
IVb				10, 19	0.122
IVc	$C_{19}H_{24}N_2O_3$	328.40	139	12, 19	0.335
IVd				14, 17	0.535
IVe	$C_{23}H_{32}N_2O_3$	384.50	122	15, 15	0.711
IVf	$C_{23}H_{32}N_2O_3$	384.50	164	17, 15	0.650
IVg	$C_{25}H_{36}N_2O_3$	412.55	94	16, 16	1.016
IVh				18, 17	1.123
IVi	$C_{29}H_{44}N_2O_3$	468.65	75	16, 16	1.492
IVj	$C_{31}H_{48}N_2O_3$	524.75	72	15, 16	1.690
VI				16	

a) The first number corresponds to the reaction with aminoalcohol *II*, the second one to that with 1-dimethylaminomethylcyclohexanol.

Table 2. ^{1}H NMR Chemical Shifts of Compounds Studied with the Number of Protons in Parentheses

Compound	H-3	H-4	H-5	H-6	H-7	Alkyl
IVa	6.88	7.01	6.97	8.12	7.15	3.87
IVb	6.86	6.99	6.97	8.04	7.20	4.06, 1.40
IVc	6.86	7.00	6.96	8.02	7.15	3.94, 1.78, 0.99
IVd	6.86	7.00	6.95	8.02	7.16	3.98, 1.74, 1.42, 0.94
IVe	6.86	7.00	6.96	8.02	7.14	3.98, 1.75, 1.40, 1.33, 0.92
IVf	6.87	7.01	6.95	8.02	7.08	4.02, 1.66, 1.74 (1H), 0.94 (6H)
IVg	6.87	7.01	6.96	8.01	7.07	3.99, 1.77, 1.39, 1.32 (4H), 0.90
IVh	6.86	7.00	6.96	8.02	7.09	3.98, 1.76, 1.38, 1.29 (6H), 0.90
IVi	6.86	7.00	6.96	8.02	7.08	3.98, 1.76, 1.38, 1.28 (8H), 0.89
IVj	6.86	7.01	6.95	8.01	7.06	3.99, 1.77, 1.37, 1.27 (10H), 0.88

Table 3. ^{13}C NMR Chemical Shifts of Compounds Studied

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-8	Alkyl
IVa	128.1	148.2	110.1	122.9	121.2	119.7	152.4	55.7
IVb	128.1	148.1	111.3	123.3	121.1	120.2	152.7	64.2, 14.8
IVc	128.0	148.2	111.3	123.4	121.0	120.3	152.6	70.1, 22.5, 10.6
IVd	128.0	148.3	111.3	123.4	121.0	120.3	152.8	68.3, 31.2, 19.3, 13.8
IVe	128.0	148.2	111.3	123.4	121.0	120.3	152.8	68.6, 28.8, 28.3, 22.4, 14.0
IVf	128.0	148.2	111.2	123.3	121.0	120.2	152.9	67.0, 37.9, 25.1, 22.6 (2C)
IVg	128.0	148.2	111.2	123.4	121.0	120.2	152.7	68.6, 29.2, 25.7, 31.5, 22.6, 14.0
IVh	128.0	148.3	111.3	123.4	121.0	120.3	152.7	68.6, 29.2, 26.0, 29.0, 31.8, 22.6, 14.1
IVi	128.0	148.3	111.3	123.4	121.0	120.3	152.7	68.6, 29.2, 26.1, 29.4, 29.3, 31.8, 22.7, 14.1
IVj	128.0	148.3	111.3	123.4	121.0	120.3	152.7	68.6, 29.2, 26.1, 29.4, 29.5, 29.3, 31.8, 22.7, 14.1

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Translated by V. Kettmann