CONVERSIONS OF PERIMIDINE 2-CARBAMATES ON ACETYLATION AND THEIR ANTHELMINTIC PROPERTIES

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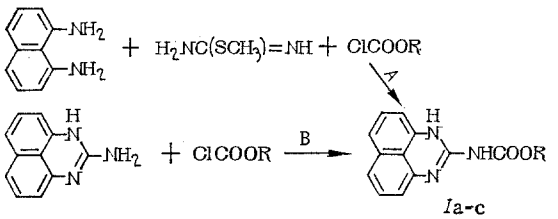
UDC 615.284:[547.853.3+547.495.1

Esters of perimidine 2-carbamic acid (Ia-c) have been synthesized by two methods with the aim of searching for new compounds possessing anthelmintic properties.



Ia-c

a: R = CH_3, b: R = C_2H_5, c: R = C_4H_9

Method A included reacting 1,8-diaminonaphthalene with S-methylisothiourea and a chlorocarbonate ester and was analogous to the method of obtaining benzimidazole carbamates in [1]. Method B is based on our data in accordance with which acylation of 2-aminoperimidine with acid chlorides occurs on the exocyclic nitrogen atom.

Of the obtained perimidine carbamates compounds, Ia, b showed reduced activity on trichocephalosis in white mice. To increase their hydrophilicity and possibly strengthen their anthelmintic activity we attempted to acylate compounds Ia-c by heating with freshly distilled acetic anhydride under conditions excluding moisture from the air. However it turned out that a complex transformation occurred with the release of carbon dioxide and the formation of a quantitative yield of 2-acetylaminoperimidine.

It was established on investigating this reaction that the appropriate alkyl acetate was formed simultaneously as was shown by gas-liquid chromatography (GLC) in the case of perimidine 2-carbamic acid butyl ester [Ic]. By thin-layer chromatography (TLC) of test samples taken out during the reaction it was established that an intermediate (R_f 0.42) was formed. It is proposed that this product is an N-acetyl derivative of the starting carbamate and we have obtained it from carbamate (Ib) under mildly acylating conditions with acetyl chloride in anhydrous medium. The substance was identical by TLC with the product detected in the reaction mixture and by elemental analytical data corresponded to the ethyl ester of perimidine 2-N-acetylcarbamic acid (II). The latter was unstable on heating in an open vessel, was hydrolyzed and was further converted with release of carbon dioxide forming 2-aminoperimidine. If heated in glacial acetic acid under conditions excluding moisture of the air then carbon dioxide was released and 2-acetylaminoperimidine was formed.

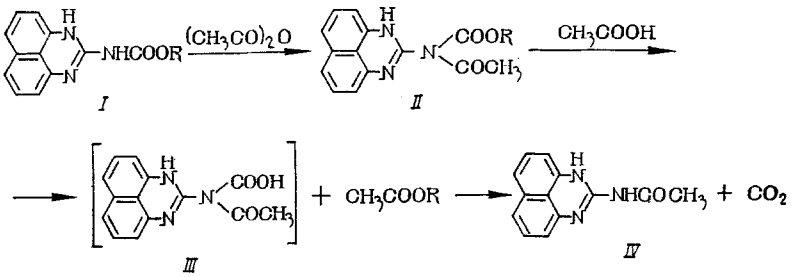
The data obtained and also the high acidity of the exocyclic N–H bond permit the hypothesis that the acetyl group in this product is on the exocyclic nitrogen atom. This hypothesis was confirmed by IR spectroscopic data. In the IR spectrum of a solid sample of perimidine 2-N-acetylcarbamic acid ethyl ester (IIb) there were two intense bands at 1760 and 1690 cm^{-1} ($\nu_{C=O}$), one intense band in the 3270 cm^{-1} region (ν_{NH}), and a very intense band at 1271 cm^{-1} (ν_{C-O}). The frequency value 1760 cm^{-1} was significantly greater than that usually observed in spectra of carbamates [2] which may denote the presence of a second carbonyl at the same nitrogen atom [3]. The small increase of frequency of the C=O of the acetyl group is also in favor of the proposed structure for (IIb). This increase is seemingly linked with the concurrent influence of the other

E. I. Martsinovskii Institute of Medical Parasitology and Tropical Medicine, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 13, No. 2, pp. 54-57, February, 1979. Original article submitted May 3, 1978.

0091-150X/79/1302-0161 $07.50

carbonyl group linked to the same nitrogen atom and also by the satisfactory proximity of the NH group absorption bands to the position of the analogous band in the spectrum of 2-dimethylaminoperimidine (ν_{NH} 3252 cm^{-1}). The band for the exocyclic NH group in spectra of 2-aminoperimidine derivatives lies appreciably higher [4]. An additional argument in favor of structure (IIb) may be the fact that on deuteration of the amino group in the (IIb) molecule the frequency of the C=O vibration is unchanged while in the spectrum of (Ic) replacement of hydrogen by deuterium in the NH groups led, as might have been expected according to [5], to a small (3 cm^{-1}) reduction in the frequency of the ester C=O group.

Thus the conversion which occurs may be represented by the following scheme:



On reaction with acetic anhydride the N-acetyl derivative of the initial carbamate (II) and acetic acid are formed. The latter enters into a transesterification reaction with N-acetylcarbamate (II) and in this way, in addition to the corresponding alkyl acetate, there is formed N-acetylcarbamic acid (III) which is decarboxylated and converted into 2-acetylaminoperimidine (IV).

The presence of the ongoing conversions with the participation of acetic acid was confirmed by experiment on heating the initial carbamate (Ia) with glacial acetic acid. The release of carbon dioxide was established in this way as was the formation of 2-aminoperimidine and traces of 2-acetylaminoperimidine (according to TLC data).

The anthelmintic action of the synthesized carbamates (Ia-c) was studied on trichocephalosis of white mice at maximally tolerated doses [6]. Compound (Ia) at a dose of 2 g/kg proved to be active. Carbamate (Ib) at a dose of 0.5 g/kg displayed intense effectiveness. Carbamate (Ic) was found to be highly effective in the limits of 51-88% and extense effectiveness was established amounting to 10-28%.

EXPERIMENTAL

IR spectra were measured on a UR-20 spectrophotometer (in potassium bromide disks and in chloroform solution). Deuteration was conducted directly on preparing solutions by the method described in [7]. GLC analysis was achieved on a Tsvet-2 instrument, column length 3 m, diameter 6 mm, containing 5% SE-30 on chromaton AW, 60-80 mesh, carrier gas nitrogen, flow rate 50 ml/min. TLC was carried out on Silufol plates in the system benzene–alcohol (22:3), visualization was with iodine vapor.

Esters of Perimidine 2-Carbamic Acid (Ia-c). Method A. To a suspension of thiourea (3.8 g: 0.05 mole) in water (2 ml) was added dropwise dimethyl sulfate (4 g: 0.0315 mole) during 10-15 min. The temperature rose thereby from 20 to 52°C. The clear solution was boiled for 30 min and cooled to 3°C (the entire mass crystallized). At this temperature 25% sodium hydroxide solution (14.5 ml) and the appropriate chlorocarbonate ester (0.09 mole) were added simultaneously with stirring, regulating the rate of addition such that the temperature did not exceed 25°C and the pH 6.0-7.0. The reaction mass was kept below 25°C for 10 min, then glacial acetic acid (5.8 ml) was added dropwise during 20 min (pH of reaction solution was 3.5), 1,8-naphthalenediamine (7.9 g: 0.05 mole) was added portionwise, the mixture maintained at 80°C for 30 min, cooled, the solid filtered off, washed with water, and crystallized from alcohol (see Table 1).

Method B. To a solution containing 2-aminoperimidine (about 0.02 mole) and triethylamine in dry acetone (250 ml) was added dropwise with stirring at room temperature an equimolar quantity of the appropriate ester of chlorocarbonic acid and the mixture was maintained under these conditions for 3 h. The solid was filtered off and washed with water to remove triethylamine hydrochloride. Acetone was removed from the mother liquor in vacuum. The residue was filtered off, washed with water, combined with the first solid, dried, and crystallized from alcohol (see Table 1). Esters (Ia-c) obtained by methods A and B were identical, were colorless crystalline substances, moderately soluble in the majority of organic solvents, and insoluble in water.

TABLE 1. Esters of Perimidine 2-Carbamic Acid (Ia-c)

Compound	R	Yield, %		Mp °C	IR spectra, cm^{-1}		Found, %			Empirical formula	Calculated		
		method A	method B		ν_{CO}	ν_{NH}	C	H	N		C	H	N
Ia	CH_3	82,7	55	236—8	1632	[3280] 3190	65,6	4,6	17,2	$C_{13}H_{11}N_3O_2$	64,8	4,6	17,4
Ib	C_2H_5	88,5	quant.	200—1	1632	[3280] 3175	67,1	5,6	16,7	$C_{14}H_{13}N_3O_2$	66,0	5,2	16,5
Ic	C_4H_9	53	75	153—4	1632	[3280] 3180	68,7	6,9	14,4	$C_{16}H_{17}N_3O_2$	67,9	6,1	14,8

Note. Spectral data for solid substances (potassium bromide disks) include the position of unresolved bands (shoulders) in square brackets. A band at 1721 cm^{-1} was observed in spectra of chloroform solutions of (Ia-c) in the region of C=O vibrations in addition to the band at 1632 cm^{-1}.

Perimidine 2-N-acetylcarbamic Acid Ethyl Ester (II). To a solution of (Ib) (1.28 g: 0.005 mole) and triethylamine (0.7 ml: 0.005 mole) in dry benzene (100 ml) was added dropwise with stirring at room temperature freshly distilled acetyl chloride (0.35 ml: 0.005 mole). The reaction mixture was maintained under these conditions for 4 h. The resulting solid was filtered off, dissolved in cold water, filtered off once again, and washed with water to remove chloride ion. The residue was dried in a vacuum desiccator at room temperature. The yellow crystalline powder was soluble in chloroform, carbon tetrachloride, and alcohol, moderately soluble in benzene, insoluble in water, and had mp 139-140°C (previously softening at 95-98°C). Yield was 0.92 g (62%). Found, %: C 64.1; H 5.1; N 14.1. $C_{16}H_{15}N_3O_3$. Calculated, %: C 64.7; H 5.1; N 14.2.

Heating Esters of Perimidine 2-Carbamic Acid in Acetic Anhydride. A solution of (Ia-c) (0.005 mole) in freshly distilled acetic anhydride (10 ml), in an apparatus fitted with a calcium chloride tube, was boiled until evolution of CO_2 had finished (3-5 h). The resulting solid (IV) was filtered off and washed with water. Yield was 1.0-1.1 g (quantitative), mp 215-216°C. The product was identical in R_f value (0.32) with 2-acetylaminoperimidine a mixing test with which gave no depression of melting point. In the experiment with (Ic) test samples of the reaction mixture were taken before heating and 10, 30 min, and 5 h after the start of heating. Beginning with the second sample and subsequently the formation of butyl acetate, identified by GLC, was established. The retention times of a known sample and of the formed butyl acetate coincided and were equal to 110 sec. Thermostat temperature was 90°C.

Heating Perimidine 2-Carbamic Acid Methyl Ester in Glacial Acetic Acid. A solution of (Ia) (1.2 g: 0.005 mole) in freshly distilled glacial acetic acid (10 ml) was boiled until evolution of CO_2 had finished (25 h). The solid was filtered off, treated with 10% sodium carbonate solution, filtered off, and washed with water. 2-Aminoperimidine (0.64 g: 70%) was obtained and had mp 230-235°C (238-240°C after purification). By TLC the solid contained 2-aminoperidine (R_f 0.52) and traces of 2-acetylaminoperimidine (R_f 0.32). A mixing test with 2-aminoperimidine gave no depression of melting point.

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