Chemistry of Heterocyclic Compounds, Vol. 31, No. 11, 1995

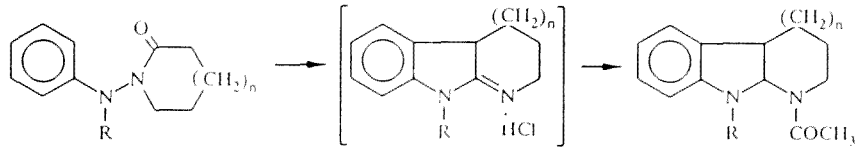
SYNTHESIS AND HETEROCYCLIZATION OF N-PHENYLAMINOLACTAMS

V. P. Zhestkov, V. V. Druzhinina, and A. V. Rudnitskikh

Intramolecular alkylation of N-phenylhydrazides of δ-chlorovaleric and ε-chlorocaproic acids was used to prepare the corresponding N-phenylaminolactams. Their reaction with phosphoryl chloride formed the corresponding condensed tricyclic systems of tetrahydro-α-carbolines and -azepino[2,3-b]indole.

We have shown previously that the Costa reaction of N-arylamino-2-pyrrolidones with phosphoryl chloride forms derivatives of 2-oxotryptamine, probably as a result of degradation of the intermediate unstable condensed structure of dihydropyrrolo[2,3-*b*]indole [1]. The extension of this reaction to N-arylaminolactams with a large-sized ring, as follows from its mechanism, may result in the formation of higher hydrogenated condensed systems containing the 2-aminoindole fragment. It was therefore of interest to synthesize N-phenylaminolactams of ring sizes 6 and 7 and to study their transformations under Costa reaction conditions.

The synthesis of N-phenylamino-2-piperidones Ia-d was carried out in accordance with a scheme which we elaborated for the preparation of N-arylamino-2-pyrrolidones [2], namely, intramolecular alkylation of phenylhydrazides of δ-chlorovaleric acid acted on by sodium ethoxide. These conditions proved inapplicable to the synthesis of the lactam of ring size 7, i.e., N-methyl-N-phenylaminoperhydroazepin-2-one (Ie). Attempts to carry out the intramolecular alkylation failed to produce the desired result, and after prolonged heating under these conditions, only substitution of the halogen at the ethoxy group was observed, accompanied by heavy tarring. N-Methyl-N-phenylaminoperhydroazepin-2-one (Ie) was obtained by cyclization of the corresponding hydrazide by ε-chlorocaproic acid with excess sodium hydride in DMFA.



Ia-e IIe IIIa-d

I, IIIa-d n = 1, a R = H, b R = CH_3, c R = $CH_2C_6H_5$, d R = C_6H_5; I, II e R = CH_3, n = 2

N-Phenylaminolactams Ia-d are soluble in organic solvents and insoluble in water. Their IR spectra contain absorption peaks of the carbonyl group in the 1635-1660 cm^{-1} range. Mass spectra of these compounds show a strong peak of a molecular ion.

The reaction of N-phenylamino-2-piperidones Ia-d with phosphoryl chloride in dioxane led to their disappearance in the reaction mass as shown by TLC (10-50 h at 60°C, 15-30 days at room temperature). However, we were unable to isolate the products of the rearrangement, either as salts or as bases after alkalization. Therefore, the compounds obtained were identified in the form of 1-acetyltetrahydro-α-carbolines IIIa-d (Table 1). Their IR spectra contain an absorption band of the

All-Russian Scientific Center for the Safety of Biologically Active Substances (VNTs BAV), Kupavna, Moscow Oblast, 142450. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1507-1510, November, 1995. Original article submitted June 9, 1995.

0009-3122/95/3111-1307$12.50

carbonyl group around 1645-1675 cm^{-1}. In addition, compound IIIa has an absorption peak of the indole-ring NH around 3350^{-1}. The ESR spectra contain a proton singlet of the acetyl group around 1.7-2.2 ppm. The proton signals of the methylene groups are manifested as three multiplets with an intensity of two proton units: at 1.6-2.4, 2.5-3, and 3.2-4.4 ppm. The mass spectra of N-acetyltetrahydrocarbolines contain peaks of molecular ions.

We carried out the dehydrogenation of compound IIIb in the presence of palladium catalyst, and thus, after chromatographic purification, isolated N-methyl-α-carboline, identical in properties to the known sample described in the literature [3]; this constitutes additional evidence of the structure of compounds IIIa-d.

Rearrangement of N-methyl-N-phenylaminoperhydroazepin-2-one (Ie) under action of phosphoryl chloride results in the formation of the hydrochloride of the corresponding tetrahydroazepino[2,3-*b*]indole IIe. In the ESR spectrum of this compound, the proton signals of the methylene groups of the saturated ring are manifested in the form of two multiplets at 1.1-2.7 and 3.0-3.8 ppm. The mass spectrum contains a peak of the molecular ion of the base.

EXPERIMENTAL

The IR spectra of a suspension in vaseline oil were recorded with a Specord IR-75 instrument. The ESR spectra in DMSO-D_6 were recorded with a Tesla BS-487C instrument with TMS as the internal standard. The mass spectra were recorded with an MKh-1303 with 70-eV ionizing electrons. The mass spectrum of bombardment with accelerated argon atoms for compound IIe was obtained with an MI 1201E instrument in a glycerin matrix. The monitoring of the reaction and of the purity of the compounds obtained were carried out on Silufol UV-254 plates in a 2:1 chloroform–2-propanol system. Silpearl silica get was used in the chromatography.

Data of the ultimate analyses of the synthesized compounds are consistent with the calculated data.

N-Phenylamino-2-piperidones (Ia-d). To a mixture of 0.05 mole of the corresponding arylhydrazine and 0.05 mole of triethylamine or pyridine in 50 ml of dry chloroform with cooling to 0-5°C was added dropwise 0.05 mole of δ-chlorovaleryl chloride. The reaction mass was stirred for 4-8 h at room temperature until the initial hydrazine disappeared as indicated by TLC, whereupon the mixture was diluted to 100 ml with chloroform and washed with water (2 × 100 ml). The organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was ground up in hexane, filtered off, and recrystallized from a benzene–hexane mixture. If necessary, the substance was chromatographed on a column, with elution with chloroform.

To a solution of sodium ethoxide, prepared from 0.01 g-atom of sodium and 30 ml of absolute ethanol, was added 0.01 mole of the corresponding phenylhydrazide of δ-chlorovaleric acid, and the mixture was agitated at 60-65°C until the hydrazide disappeared, as indicated by TLC. The reaction mass was acidified with acetic acid to pH 5-6, diluted with 100 ml of water, and extracted with chloroform (3 × 50 ml). The combined extract was dried over sodium sulfate and evaporated in a vacuum. The residue was ground up in hexane, filtered off, and recrystallized from a benzene–hexane mixture (Table 1).

N-Methyl-N-phenylaminoperhydroazepin-2-one (Ie). To a solution of 0.01 mole of N-methyl-N-phenylhydrazide of ε-chlorocaproic acid, obtained as indicated above, in 15 ml of absolute DMFA was added in small amounts 0.03 mole of a suspension of sodium hydride in 5 ml of DMFA, then the mixture was agitated for 6 h at 60°C until the initial hydrazide was shown by TLC to disappear from the reaction mass. When the reaction was complete, acetic acid was added to pH 5-6, then the mixture was diluted with water to 100 ml and extracted with chloroform (3 × 20 ml). The combined extract was washed with water (3 × 20 ml), dried over sodium sulfate, and evaporated under vacuum. The residue was chromatographed on a column with silica gel, elution with chloroform was used, and the azepinone fraction was evaporated under vacuum (Table 1).

N-Acetyltetrahydro-α-carbolines (IIIa-d). To solution of 0.01 mole of the corresponding phenylaminopiperidone Ia-d in 20 ml of absolute dioxane was added 0.02 mole of phosphoryl chloride, then the mixture was agitated at 60°C until the initial substance was shown to disappear by TLC (10-50 h). The reaction mass was evaporated under vacuum, 10 ml of ethanol and 0.2 g of activated carbon were added to the residue, and the mixture was heated for 20 min. The carbon was filtered off and washed on a filter with 2 ml of ethanol. The filtrate was evaporated under vacuum with 10 ml of toluene, traces of alcohol being removed. To the oily residue was added 30 ml of dry chloroform, the temperature was lowered to 0-5°C, and 0.03 mole of triethylamine was added with stirring, followed by 0.02 mole of acetic anhydride. The

TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	T_{mp}, °C	IR spectrum, cm^{-1}	Mass spectrum, m/z	PMR spectrum, δ, ppm, J, Hz	Yield, %
Ia	$C_{11}H_{14}N_2O$	117...118	3260, 1635, 1600	190 (M^+)	1,6...2,1 (4H, m, $2CH_2$), 2,2...2,7 (2H, m, CH_2CO), 3,3...3,8 (2H, m, CH_2—N), 6,5...7,4 (5Hm, arom.)	58
Ib	$C_{12}H_{16}N_2O$	Oil	1660, 1595	204 (M^+)	1,6...2 (4H, m, $2CH_2$), 2,1...2,5 (2H, m, CH_2CO), 3,0 (3H, s, N—CH_3), 3,1...3,6 (2H, m, CH_2—N) 6,4...7,5 (5H, m, arom.)	93
Ic	$C_{18}H_{20}N_2O$	105...106	1655	280 (M^+)	1,4...1,9 (4H, m, $2CH_2$), 2,2...2,6 (2H, m, CH_2CO), 2,8...3,6 (2H, m, CH_2—N), 4,7 (2H, m, $CH_2C_6H_5$), 6,4...7,5 (10H,m, arom.)	86
Id	$C_{17}H_{18}N_2O$	117...118	1660	260 (M^+)	1,6...2 (4H, m, $2CH_2$), 2,3...2,6 (2H, m, CH_2CO), 3,3...3,8 (2H, m, CH_2—N), 6,8...7,5 (10H, m, arom.)	85
Ie	$C_{13}H_{18}N_2O$	Oil	1680, 1605	218 (M^+)	1,5...2 (6H, m, $3CH_2$), 2,1...2,5 (2H, m, CH_2CO), 3,1 (3H, s, N—CH_3), 3,2...3,6 (2H, m, CH_2—N), 6,5...7,3 (5H, m, arom.)	70
IIe	$C_{13}H_{17}ClN_2$	238...240	2750 (br.), 1695, 1655	201 (M−HCl +H$^+$)	1,07...2,7 (6H, m, $3CH_2$), 3...3,8 (5H, m, CH_2—N, N—CH_3), 7...7,6 (4H, m, arom.), 11,2 (NH, br.)	52
IIIa	$C_{13}H_{14}N_2O$	167...169	3350, 1645, 1615	214 (M^+)	1,7...2,4 (2H, m, CH_2), 2,2 (3H, s, CH_3CO), 2,7 (2H, t, 4-CH_2, J = 8), 3,7 (2H, t, CH_2—N, J = 8), 7...7,6 (4H, m, arom.), 10,6 (NH, br.)	37
IIIb	$C_{14}H_{16}N_2O$	133...135	1675, 1620, 1580	228 (M^+)	1,7...2,2 (2H, m, CH_2), 2,1 (3H, s, CH_3CO), 2,5...2,9 (4H, m, 4-CH_2), 3,2...3,9 (5H, m, N—CH_3, CH_2—N), 6,9...7,3 (4H, m, arom.)	62
IIIc	$C_{20}H_{20}N_2O$	125...130	1660, 1610	304 (M^+)	1,6...2,4 (2H, m, CH_2), 2,2 (3H, s, CH_3CO), 2,9 (4H, t, 4-CH_2, J = 7), 3,2...4 (2H, m, CH_2—N), 5,3 (2H, s, $CH_2C_6H_5$), 6,8...7,7 (9H, m, arom.)	7
IIId	$C_{19}H_{18}N_2O$	125...126	1675, 1620, 1600	290 (M^+)	1,7 (3H, s, CH_3CO), 1,9...2,3 (2H, m, CH_2), 3,0 (2H, t, 4-CH_2, J = 8), 3,6...4,4 (2H, m, CH_2—N), 6,8...8,1 (19H, m, arom.)	24

reaction mass was stirred for 2 h at room temperature, then diluted to 100 ml with chloroform, washed with water (2 × 100 ml), and dried over sodium sulfate. The solvent was driven off under vacuum, the residue was chromatographed on a column with silica gel, and the elution was carried out with chloroform. The acetylcarboline fraction was evaporated off, and the residue was ground up in hexane and filtered off (Table 1).

10-Methyl-3,4,5,5a-tetrahydro-2H-azepino[2,3-*b*]indole Hydrochloride (IIe). To a solution of 0.35 g (1.5 mmole) of N-methyl-N-phenylaminoperhydroazepin-2-one (Ie) in 5 ml of absolute dioxane was added 0.3 ml (3.3 mmole) of phosphoryl chloride, and the mixture was stirred for 12 h at 60°C. The reaction mass was evaporated under vacuum, 15 ml of dry toluene was added to the residue, and the mixture was evaporated once again, the phosphoryl chloride vapor being driven off. To the residue were added 10 ml of ethanol and 0.1 g of activated carbon, the mixture was heated for 20 min, the carbon was filtered off, and the filtrate was evaporated under vacuum. The residue was ground up in dry ether, filtered, and dried in a vacuum (Table 1).

N-Methyl-α-carboline. To a suspension of 50 mg of 10% palladium on carbon in 5 ml of cymene was added 100 mg of compound IIIb, and the mixture was boiled for 4 h. The catalyst filtered off, the solution chromatographed on a column with silica gel, with elution initially with benzene, cymene being driven off, then with a 1:1 benzene–acetone mix-

TABLE 2. Ultimate Analyses of Synthesized Compounds

Compound	Found, % / Calculated, %		
	C	H	N
I a	69,5 69,5	7,4 7,4	14,4 14,7
I b	70,8 70,6	7,7 7,9	13,6 13,7
I c	76,9 77,1	6,9 7,2	9,8 10,0
Id	77,4 76,7	7,0 6,8	10,2 10,5
I e	71,7 71,4	8,7 8,3	12,6 12,8
II f	66,0 66,0	7,6 7,2	11,7 11,8
III a	73,0 72,8	7,0 6,6	13,0 13,1
III b	73,8 73,7	6,8 7,1	12,5 12,3
III c	78,7 78,9	6,7 6,6	9,1 9,2
III d	78,6 78,6	6,2 6,2	9,7 9,7

ture. The fraction exhibiting intense fluorescence on Silufol in UV light was evaporated off, and the residue was dried under vacuum. A substance with mp 51-53°C was obtained in an amount of 55 mg. According to reported data, mp is 53°C [3].

REFERENCES

1. V. P. Zhestkov, V. V. Druzhinina, and A. V. Rudnitskikh, Khim. Geterotsikl. Soedin., No. 3, 325 (1995).
2. A. V. Blokhina, V. G. Voronin, V. V. Druzhinina, V. P. Zhestkov, and Yu. N. Portnov, Khim. Geterotsikl. Soedin., No. 4, 474 (1987).
3. K. Abramovitch, D. Hey, and R. Mully, J. Chem. Soc., No. 11, 4263 (1954).