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PREPARATION OF N-ARYLAMINO-2-PYRROLIDONES FROM ARYLHYDRAZIDES OF γ-CHLOROBUTYRIC ACID

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Intramolecular alkylation of the arylhydrazides of γ-chlorobutyric acid in the presence of sodium ethoxide leads to the formation of N-arylamino-2-pyrrolidones. The direction of the reaction is not altered by the absence of a substituent on the aniline nitrogen atom. In the case of a p-nitrophenyl-hydrazide, O-alkylation is observed.

We have shown previously [1] that reaction of N-methyl-N-phenylamino-2-pyrrolidone with phosphoryl chloride is accompanied by a Kost rearrangement with the formation of 3-(2-arylamino)-2-pyrrolidones. The present work is concerned with the development of a method for the preparation of the difficultly accessible N-arylamino-2-pyrrolidones. 2-Pyrrolidones substituted on the nitrogen atom are generally prepared by the reaction of primary amine salts with γ-butyrolactone [2] or by intramolecular alkylation of amides of γ-halogen-substituted fatty acids [3, 4].

Experiments on the preparation of N-arylaminopyrrolidones by the reaction of arylhydrazine hydrochlorides with γ-butyrolactone were not successful because under these conditions tar formation occurred and the product was a complex mixture from which only the N-arylpyrrolidone could be separated.

The most acceptable method for the preparation of the N-arylamino-pyrrolidones III was the intramolecular alkylation of the arylhydrazides II.

The arylhydrazides IIa-k were prepared by acylation of arylhydrazines Ia-k by means of acid chloride of γ-chlorobutyric acid [5]. In the acylation of arylhydrazines Ia-g which have no substituent on the aniline nitrogen the isomeric arylhydrazide was also obtained together

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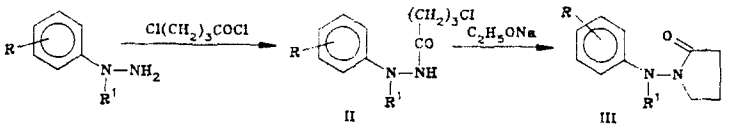


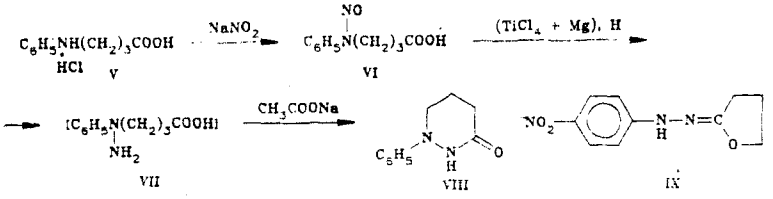
I—III a–d R=H, e, f R=2-CH_3, g—i R=4-CH_3, j, k R=4-NO_2, l,n R=4-Br; a, e, g, j R^1=H, b f, h, l R^1=CH_3, c R^1=C_6H_5, d, i, n R^1=$C_6H_5CH_2$, k R^1=$CH_3C_6H_4$, m R^1=$C_2H_5CH_2$

with a diacyl derivative. Separation was effected by chromatography on a column of silica gel with chloroform or benzene. We note that in the acylation of the hydrazines Ie and Ij, secondary products were not formed in any great quantity, probably as a result of steric factors (Ie) and the presence of the electron-acceptor nitro group in Ij which reduces the basicity of the aniline nitrogen.

The arylhydrazides IIb-d, f, and h-k with no substituent on the aniline nitrogen were subjected to intramolecular alkylation in an alkaline medium without further purification. In an alkaline water–alcohol solution, and in the presence of a phase-transfer catalyst (tetrabutylammonium hydroxide), partial resinification of the reaction products occurred and this made their separation and purification difficult. The best results were obtained when alkylation was carried out under mild conditions at 60°C in alcohol with a small excess of sodium ethoxide, the yields of N-arylamino-2-pyrrolidones then being 70-80% (Table 1).

The N-arylaminopyrrolidones are crystalline substances, freely soluble in organic solvents and insoluble in water. There is an intense band in the infrared spectrum of the compounds due to the carbonyl group at 1700 cm^{-1}, which is characteristic for pyrrolidones [6]. In the proton NMR spectra of the compounds, the triplet of the protons of the methylene group adjacent to the nitrogen atom of the pyrrolidone ring is shifted downfield (3.13-3.53 ppm) relative to the multiplet of the protons of the other methylene groups of the pyrrolidone ring (1.7-2.7 ppm).

The absence of a substituent on the aniline nitrogen atom does not change the direction of the reaction and hydrazides IIa, e, and g are also alkylated exclusively on the amide nitrogen with the formation of the corresponding pyrrolidones IIIa, e, and g. Chromatography shows not even a trace of the possible 3-pyridazinones of type VIII in the reaction product after alkylation. To show conclusively the direction of the alkylation of the hydrazides, we prepared the N-phenyltetrahydro-3-pyridazinine of known structure (VIII) which is isomeric with the hydrazide IIa by the route



Nitrosation of the N-phenyl-γ-amino butyric acid V yielded the N-nitroso compound VI. Reduction of the latter under mild conditions with $TiCl_4$ + Mg in dry ether/methylene chloride [7] yielded the unstable hydrazine VII which, by intramolecular cyclization under the influence of sodium acetate, gave N-phenyltetrahydro-3-pyridazinone (VIII) essentially free from compound IIIa according to melting point, chromatographic retention time and infrared spectra in the "fingerprint" region, 1200-800 cm^{-1}.

Intramolecular alkylation of the 4-nitrophenylhydrazide IIj led to the formation of two products differing in chromatographic retention time but having the same elemental composition $C_{10}H_{11}N_3O_3$ (IIIj, IX). In the IR spectrum of the more mobile compound IIIj [R_f = 0.25 (A)], intense absorption bands were observed at 3240 cm^{-1} (NH) and 1700 cm^{-1} (CO). The proton NMR spectrum showed a methylene triplet at 3.43 ppm which is characteristic for pyrrolidones. In the mass spectrum, a peak due to a molecular ion with m/z = 221 was noted. From this we conclude that IIIj is an N-4-nitrophenylaminopyrrolidone. In the IR spectrum of compound IX with R_f = 0.75 (A) there were bands at 3350 cm^{-1} (NH) and 1690 cm^{-1}; the latter can be assigned to either C=O or C=N. In the proton NMR spectrum of compound IX, one of the methylene group triplets was shifted downfield (4.3 ppm) in comparison with compound IIIj which is typical of signals from methylene groups adjacent to an oxygen atom in cyclic ethers [8]. In addition, on boiling with acetic acid this compound is rapidly converted to N-4-nitrophenyl-N'-acetylhydrazine, and on boiling in o-dichlorobenzene in the presence of an acidic catalyst it

TABLE 1. N-Arylamino-2-pyrrolidones (IIIa-n)

Compound	mp, °C	IR spectrum, cm^{-1}	Proton NMR spectrum, ppm*	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N(Br)		C	H	N(Br)	
IIIa	96	1695, 3210	1,7—2,6 (m, CH_2—CH_2); 3,47 (t, —CH_2—N); 6,3—7,4 (m, CH arom.)	67,9	6,6	15,8	$C_{10}H_{12}N_2O$	68,2	6,8	15,9	22
IIIb	Oil	1700	1,7—2,37 (m, CH_8—CH_2); 3,37 (t, —CH_2—N); 3,03 (s, CH_3); 6,4—7,3 (m, CH arom.)	69,6	7,4	14,4	$C_{11}H_{14}N_2O$	69,5	7,4	14,7	47
IIIc	123—124	1700	1,87—2,6 (m, CH_2—CH_2); 3,53 (t, —CH_2—N); 6,83—7,6 (m, CH arom.)	76,1	6,3	11,1	$C_{16}H_{16}N_2O$	76,2	6,4	11,1	84
IIId	84—85	1700	1,67—2,46 (m, —CH_2—CH_2); 3,27 (t, —CH_2—N); 4,7 (s, CH_2); 6,54—7,6 (m, CH arom.)	76,9	7,1	10,4	$C_{17}H_{12}N_2O$	76,7	6,8	10,5	87
IIIe	120—125	1680, 3240	1,83—2,5 (m, CH_2—CH_2); 3,53 (t, —CH_2—N; 2,17 (s, CH_3); 6,43—7,23 (m, CH arom.); 5,93 (NH)	69,7	7,3	14,6	$C_{11}H_{14}N_2O$	69,5	7,4	14,7	81
IIIf	Oil	1700	1,7—2,4 (m, CH_2—CH_2); 3,13 (t, —CH_2—N); 2,17 (s, CH_3); 3,07 (s, CH_3); 6,9—7,33 (m, CH arom.)	70,6	7,9	13,5	$C_{12}H_{14}N_2O$	70,6	7,9	13,7	80
IIIg	133—135	1700, 3200	1,67—2,6 (m, CH_2—CH_2); 3,47 (t, —CH_2—N); 2,2 (s, CH_3); 6,53 and 6,7 (d, CH arom.); 6,1 (NH)	69,5	7,5	14,7	$C_{11}H_{14}N_2O$	69,5	7,4	14,7	23
IIIh	Oil	1700	1,7—2,57 (m, CH_2—CH_2); 3,4 (t, —CH_2—N); 2,23 (s, CH_3); 3,07 (s, CH_3); 6,63 and 7,03 (2 d, CH arom.)	68,9	8,0	13,6	$C_{12}H_{16}N_2O$	70,6	7,9	13,7	71
IIIi	118—119	1700	1,5—2,4 (m, CH_2—CH_2); 3,27 (t, —CH_2—N); 2,13 (s, CH_3); 4,67 (s, CH_2); 6,5—7,63 (m, CH arom.)	77,3	7,4	9,7	$C_{18}H_{20}N_2O$	77,1	7,2	10,0	87
IIIj	188—189	1700, 3240	1,67—2,7 (m, CH_2—CH_2); 3,43 (t, —CH_2—N); 6,4 (d) and 7,8 (CH arom.)	54,7	5,1	18,6	$C_{10}H_{11}N_3O_3$	54,3	5,0	19,0	60
IIIk	205—206	1700	1,87—2,53 (m, CH_2—CH_2); 3,17—3,7 (m, —CH_2—N); 6,7 and 8.0 (2d, CH arom.); 7,07 (s, CH arom.)	65,5	5,6	13,4	$C_{17}H_{17}N_3O_3$	65,6	5,5	13,5	83
IIIl	89—90	1700	1,63—2,67 (m, CH_2—CH_2); 3,4 (t, —CH_2—N); 3,1 (s, CH_3); 6,53 and 7,3 (2d, CH arom.)	49,1	5,2	10,2 (30,1)	$C_{18}H_{13}BrN_2O$	49,1	4,9	10,4 (29,7)	90
IIIm	184—185	1695	1,6—2,53 (m, CH_2—CH_2); 3,3 (t, —CH_2—N); 6,47 and 7,03 (2d, CH arom.)	46,6	3,4	6,6 (39,1)	$C_{16}H_{14}Br_2N_2O$	46,7	3,4	6,8 (39,0)	81
IIIn	150—151	1700	1,63—2,5 (m, CH_2—CH_2); 3,27 (t, —CH_2—N); 4,67 (s, CH_2); 6,57 and 7,23 (2d, CH arom.); 7,23 (s, CH arom.)	59,2	5,2	8,4 (23,2)	$C_{17}H_{17}BrN_2O$	59,1	5,0	8,1 (23,1)	83

*Solvent for IIIa, e-i, m, n = $CDCl_3$; IIIb = CCl_4; IIIc, k = DMSO-D_6; IIIj = CF_3COOH.

rearranges to the pyrrolidone IIIj. Compound IX is apparently the product of O-alkylation of the initial hydrazide IIj to 2-(4-nitrophenyl)hydrazonotetrahydrofuran IX.

For the preparation of N-(4-bromoalkyl)amino-2-pyrrolidones (IIIℓ-n), the most convenient method was the direct bromination of N-arylamino-2-pyrrolidones (IIIb-d) with the appropriate quantity of bromine in dry chloroform.

EXPERIMENTAL

Infrared spectra were run on a Perkin-Elmer 577 instrument as nujol mulls, NMR spectra on a Tesla-467 (60 MHz) with HMDS as internal standard. The progress of the reactions and the purity of the products were monitored by TLC on plates of Silufol UV-254 in 10:1 benzene/acetone (A), 2:1 benzene/acetone (B) or 20:1 chloroform/methanol (C).

Reaction of N-Methyl-N-phenylhydrazine Hydrochloride with γ-Butyrolactone. A mixture of 4.75 g (0.03 mole) N-methyl-N-phenylhydrazine hydrochloride and 3.42 g (0.04 mole) γ-butyrolactone was heated for 20 h at 190°C until TLC showed all the initial hydrazine to have disappeared. The cold reaction mass was washed with chloroform and the precipitate filtered off. This was ammonium chloride (1.3 g, 81%), identical with a known sample. The filtrate was evaporated in vacuum and the residue chromatographed on a column of 200 cm^3 silica gel, elutin with 20:1 benzene/chloroform. The eluate was evaporated to yield 2.3 g (48%) N-phenylpyrrolidone identical with a known sample obtained by the method of [2].

N-Arylamino-2-pyrrolidones (IIIa-i, k). To a mixture of 0.05 mole of the appropriate hydrazine I and 0.05 mole triethylamine in 50 ml dry chloroform at 5°C was added, dropwise with stirring, 0.05 mole of the acid chloride of γ-chlorobutyric acid. The reaction mixture was stirred at 20°C until the TLC showed that all the initial hydrazine had reacted (4 h), diluted to 150 ml with chloroform, washed with 2 × 100 ml water, dried over sodium sulfate and the chloroform distilled off under reduced pressure. The oily residue of II was triturated with hexane (2 × 30 ml) and subjected to intramolecular alkylation. To a solution of 0.0105 mole sodium ethoxide in 30 ml absolute ethanol was added 0.01 mole of the appropriate γ-chlorobutyric acid hydrazide II and the mixture stirred at 60°C until TLC showed that the initial reactant had disappeared (4-5 h). The reaction mixture was acidified with acetic acid to pH 6, diluted to 100 ml with water and extracted with 3 × 50 ml chloroform. The chloroform extract was dried over sodium sulfate and the solvent removed under vacuum. The oily residue was triturated with hexane (3 × 20 ml) and dried. Yields and physicochemical characteristics of the N-arylamino-2-pyrrolidones (IIIa-k) are shown in Table 1.

N-Phenyl-γ-aminobutyric Acid Hydrochloride (V). A mixture of 4.83 g (0.03 mole) N-phenylpyrrolidone and 10 ml HCl (d = 1.17) was heated to boiling for 20 h. The acid was distilled off in vacuum and residue washed with ether, dried, and crystallized from a mixture of 1:1 ethanol/ether. Yield 79%, mp 137-138°C. IR spectrum (cm^{-1}): 3000-2300 (broad, NH^+), 1730 (CO), 1600 (C=C). Found, %: C 56.2, H 6.7, N 6.6. $C_{10}H_{13}NO_2 \cdot HCl$. Calculated, %: C 55.8, H 6.5, N 6.5.

N-Nitroso-N-phenyl-γ-aminobutyric Acid (VI). To a solution of 4.31 g (0.02 mole) N-phenyl-γ-aminobutyric acid hydrochloride in 20 ml HCl (d = 1.17) cooled to −5°C was added, dropwise with stirring, a solution of 2 g (0.03 mole) $NaNO_2$ in 10 ml water. The reaction mixture was stirred for 30 min and the precipitate filtered off, washed with water, dried, and recrystallized from hexane. Yield 80%, mp 83-85°C. IR spectrum (cm^{-1}): 1700 (CO), 1600 (C=C). Mass spectrum: M^+ 208. Found, %: C 57.2, H 5.4, N 13.3. $C_{10}H_{12}N_2O_3$. Calculated, %: C 57.7, H 5.8, N 13.5.

N-Phenyltetrahydro-3-pyridazinone (VIII). Following the method of [8], to a mixture of dry ether and methylene chloride (250 ml, 1:4) was added with stirring 6.6 ml (0.06 mole) titanium tetrachloride followed by 1.5 g (0.06 mole) magnesium powder in a current of nitrogen, and the mixture was stirred for 2.5 h at 20°C. A solution of 3.12 g (0.015 mole) N-nitroso-N-phenyl-γ-aminobutyric acid (VI) in ether was then added and after 1 h a saturated solution of sodium acetate was added up to pH 5.0-5.5 and the mixture boiled for 6 h. The inorganic deposit was filtered off and washed with methylene chloride. The filtrate was washed with sodium carbonate solution and water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue recrystallized from a 1:1 mixture of benzene and hexane Yield 65%, mp 153-154°C. IR spectrum (cm^{-1}): 3180 (NH), 1680 (CO). Proton NMR spectrum ($CDCl_3$, ppm): 1.7-2.53 (m, $-CH_2-CH_2-$); 3.67 (t, $-CH_2-O$); 6.77-7.33 (m, C_6H_5); 7.87 (NH). Mass spectrum: M^+ 176. Found, %: C 68.2, H 7.0, N 15.5. $C_{10}H_{12}N_2O$. Calculated, %: C 68.2, H 6.8, N 15.9.

N-4-Nitrophenylamino-2-pyrrolidone (IIIj) and 2-(4-Nitrophenylhydrazino)tetrahydrofuran (IX). In the preparation of N-4-nitrophenylamino-2-pyrrolidone (IIIj) by an analogous method, after the disappearance of all the initial arylhydrazide (TLC) there were two reaction products present. The suspension formed in the course of the reaction was acidified with acetic acid to pH 6 and the precipitate filtered off and washed with water. It was suspended in 3 ml DMF at 50°C and diluted to 50 ml with ether and the precipitate of IIIj filtered off. R_f = 0.25 (A), R_f = 0.4 (B). The filtrate from the separation of IIIj was evaporated under reduced pressure, diluted with 50 ml water at 100°C, and the precipitated solid filtered off to yield 0.75 g (17%) 2-(4-nitrophenylhydrazino)tetrahydrofuran (IX), R_f = 0.75 (A), R_f = 0.85 (B); mp 169-170°C (from ethanol). IR spectrum (cm^{-1}): 3350 (NH), 1690 (C=H). Proton NMR spectrum ($CDCl_3$, ppm): 1.9-2.87 (m, $-CH_2-CH_2-$), 4.3 (t, $-CH_2-O-$), 6.8 + 8.03 (2 d, CH arom.), 7.6 (s, NH). Found, %: C 54.6, H 5.1, N 18.6. Mass spectrum, M^+ 221. $C_{10}H_{11}N_3O_3$. Calculated, %: C 54.3, H 5.0, N 19.0, M^+ 221.

On boiling 50 mg IX in 2 ml o-dichlorobenzene with 2 mg p-toluenesulfonic acid at 140°C for 6 h followed by purification on a silica gel column in chloroform, IIIj was obtained in 10% yield.

N-4-Nitrophenyl-N'-acetylhydrazine. A solution of 220 mg (0.01 mole) compound IX in 10 ml acetic acid was heated to boiling for 1 h. The mixture was evaporated to dryness and the residue recrystallized from alcohol. Yield 130 mg (67%), mp 210-213°C. The compound had properties identical to those of the known compound [9].

N-4-Bromoarylamino-2-pyrrolidones (IIIl-n). To a solution of 0.01 mole of the corresponding arylaminopyrrolidone (IIIb-d) in 30 ml dry chloroform, cooled to 0°C and stirred, a solution of 0.01 mole bromine in dry chloroform (1:10) was added dropwise over 30 min. After the addition of bromine was complete, the reaction mixture was stirred until TLC showed that all the initial reactant had disappeared (~30 min) and then washed with sodium carbonate solution and water and the chloroform evaporated off under reduced pressure. The oily residue was triturated in hexane (3 × 30 ml). The yields and properties of the products are shown in Table 1.

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