BENZYLATION OF γ-N-(ARYLAMINO)PIPERIDINES VIA THE WALLACH REACTION

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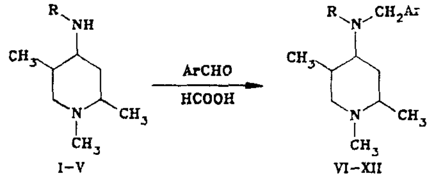
N-Aryl(aralkyl)-N-(4-piperidinyl)benzylamines have been prepared from γ-N-(arylamino)piperidines using the Wallach reaction. Carbonyl-containing compounds have been detected as impurities in these products using mass spectrometry. A possible mechanism is discussed for the Wallach reaction, based on the structures of the secondary amine starting materials used in this study.

Among the antihistamine agents which have been described in the literature and employed clinically are compounds which contain, as might be expected, an N-benzyl fragment [1]. In continuation of our studies of the synthesis and properties of γ-aminopiperidines, we have synthesized γ-(N-benzyl)piperidinyl compounds, starting from the previously described N-benzyl- (I) [cyclohexyl-(II), phenyl- (III), o-anisyl- (IV), p-anisyl- (V)]-N-(1,2,5-trimethyl-4-piperidinyl)amines [2-4]. These compounds were subjected to Wallach benzylation using benzaldehyde and anisaldehyde.



I, VI $R=C_6H_5CH_2$; II, VII $R=C_6H_{11}$; III, VIII, XI $R=C_6H_5$; IV, IX $R=o\text{-}CH_3OC_6H_4$; V, X, XII $R=p\text{-}CH_3OC_6H_4$; IV—X $Ar=C_6H_5$; XI, XII $Ar=p\text{-}CH_3OC_6H_4$

N-Benzyl(VI) [cyclohexyl(VII)]-N-(1,2,5-trimethyl-4-piperidinyl)benzylamines were obtained as colorless oils from the secondary amines I and II and benzaldehyde, in 50% yields. These compounds were isolated in the form of mixtures of geometric isomers (based on TEC data; the amine precursors I and II also consist of mixtures of stereoisomers [3,4]). The composition and structures of compounds VI and VII were established based on elemental and IR spectral analysis; their mass spectra, however, contain, in addition to peaks for their corresponding molecular ions (M^+), M^+ peaks corresponding to the secondary amines I and II, which were not detected in their IR spectra (Tables 1 and 2). The dihydrochlorides of these tertiary diamines were isolated as colorless crystalline substances.

The N-phenyl(V) [o-anisyl(IX), p-anisyl(X)]-N-(1,2,5-trimethyl-4-piperidinyl)benzylamines and N-phenyl(XI) [p-anisyl(XII)]-N-(1,2,5-trimethyl-4-piperidinyl)-p-methoxybenzylamines were prepared from the secondary amines III-V via the same procedure. The synthesis of the compounds proceeds uneventfully.

In the case of the synthesis of amines VIII-XI, these compounds were isolated as colorless crystalline substances which melted over a wide temperature range; this may be attributed to the formation of mixtures of isomers differing in the position of the substituents in the piperidine ring, as well as to the presence of impurities which could not be removed either chromatographically or via crystallization. Amine XII was isolated as an oil. The results of elemental analysis (Table 1) for these compounds did not differ greatly from the calculated data for diamines VIII-XII, which indicates that the concentration of impurities in these compounds is insignificant. The structures of the diamines were confirmed based on their IR spectral data, as well as on their electron impact (EI) and chemical ionization (CI) mass

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TABLE 1. Characteristics of the Isolated Wallach Reaction Products

Compound	T_{mp}, °C	R_f	IR spectrum, ν, cm^{-1}		Found N, %	Molecular formula	Calculated N, %	Yield, %
			NH	CO				
VI	Oil	0,72; 0,60; 0,50	—	—	9,3	$C_{22}H_{30}N_2$	8,9	50
VII	Oil	0,82; 0,78	—	—	8,6	$C_{21}H_{34}N_2$	8,7	52
VIII	90...106	0,78; 0,51; 0,22	3410	1685	7,7	$C_{21}H_{28}N_2 \cdot C_2H_5OH$	7,9	80
IX*	48...54	0,26; 0,14	3410	—	8,4	$C_{22}H_{30}N_2O$	8,2	70
X	80...89	0,69; 0,46; 0,16	3430	1685	8,3	$C_{22}H_{30}N_2O$	8,2	62
XI	75...83	0,28; 0,14	3430	1690	8,1	$C_{22}H_{30}N_2O$	8,2	40
XII	Oil	0,45; 0,20	3350	1670	7,9	$C_{23}H_{33}N_2O_2$	7,6	23

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*The data presented here correspond to compound IX, which was isolated after acidic hydrolysis.

TABLE 2. Mass Spectral Data for Amines VI-XII, Which Were Isolated after Hydrolysis

Compound	m/z (relative intensity, %)							
	M^+	Φ_1*	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	$Ar\overset{+}{C}H_2$
VI	322 (2)	307 (1)	126 (15)	110 (100)	231 (47)	197 (50)	70 (16)	91 (19)
VII	314 (10)	299 (4)	126 (57)	110 (56)	223 (17)	188 (100)	70 (15)	91 (44)
VIII	308 (6)	293 (2)	126 (55)	110 (20)	217 (1)	183 (3)	70 (100)	91 (7)
IX	338 (10)	323 (0,5)	126 (37)	110 (100)	247 (1)	213 (23)	70 (82)	91 (53)
X	338 (5)	323 (0,5)	126 (43)	110 (100)	247 (2)	213 (7)	70 (61)	91 (12)
XI	338 (10)	323 (0,5)	126 (20)	110 (100)	217 (9)	213 (5)	70 (22)	121 (34)
XII	368 (9)	353 (0,5)	126 (37)	110 (100)	247 (2)	243 (9)	70 (60)	121 (26)

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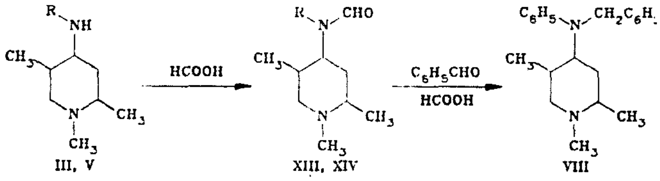
*Consult the text for the designations of the Φ_1-Φ_6 fragments.

spectra. The EI decomposition of the M^+ molecular ions for tertiary amines VI-XII occurs via elimination of a methyl radical from the 2-position of the piperidine ring. The resulting $[M - CH_3]^+$ (Φ_1) ion undergoes further cleavage via a retrodiene mechanism to form a $CH_2{=}N^+(CH_3){-}CH{=}CH_2$ fragment (Φ_6) a diamine molecule is displaced in a parallel reaction, and its formation explains the appearance of a highly intense peak corresponding to the $[M - CH_3, -RNHCH_2Ar]^+$ fragment at m/z 110 (Φ_3). The formation of the following characteristic ions: $[M - CH_2Ar]^+$ (Φ_4), $[M - RNCH_2Ar]^+$ (Φ_2), and $[RNHCH_2Ar]^+$ (Φ_5) establishes the nature of the amine substituent in the γ-position of the piperidine ring (Table 2).

The IR and mass spectral data for these compounds also provide evidence concerning the presence of impurities and their chemical (functional) nature. In particular, the IR spectra contain bands in the 3350-3430 cm^{-1} region, which are assigned to NH group vibrations in the secondary amine starting materials III-V, while the mass spectra contain their corresponding molecular ion peaks. The IR spectra of compounds VIII, X, and XI also contain carbonyl group bands in the 1660-1690 cm^{-1} region. Our conclusions concerning the nature of these carbonyl-containing impurities are based on both the EI and CI mass spectral data of the compounds. In addition to M^+ peaks for the tertiary amine products and their secondary amine precursors, the mass spectra of these compounds also contain M^+ peaks for compounds with molecular weights 28 amu greater than the molecular weights of the secondary and tertiary amines mentioned previously. For instance, the mass spectra of the reaction product from the synthesis of compound VIII contain four M^+ peaks: m/z 218 (EI), 219 (CI), M_1^+ for amine III; 308 (EI), 309 (CI), M_2^+ for amine VIII; 246 (EI), 247 (CI), $[M_1 + CO]^+$; and 336 (EI), 337 (CI), $[M_2 + CO]^+$. We assume that the first carbonyl-containing compound is N-phenyl-N-(1,2,5-trimethyl-4-piperidinyl)-formamide (XIII), and that the second carbonyl compound is the N-phenyl-N-(1,2,5-trimethyl-4-piperidinyl) amide of phenylacetic acid. The M^+ peaks for the analogous amides of formic and arylacetic acids are also present in the mass spectra of compound X (366 (EI), 367 (CI)) and compound XI (246 (EI), 366 (EI), and 367 (CI)). It was not possible to detect the Wallach reaction product (for instance, for substance VIII) in pure form using chromatography-mass spectrometry, since the substance was adsorbed very strongly on the support.

It is essential that the formation of the above-mentioned NH- and CO-containing products be explained and that their connection to the final reaction products be elucidated. The Wallach reaction [5] is an effective method for the alkylation of primary and secondary amines using aldehydes or ketones in formic acid. Although this reaction has been the subject of many research studies, the mechanism of the reaction remains open to discussion. Enamines [6], geminal hydroxyalkylamines, azomethines, and animals [7] have all been considered as possible initial intermediates in this reaction. In [7], the synthesis of N-benzylpiperidine from N-formylpiperidine was described, without any discussion of the possible mechanism. The formylation of amines using formic acid has also been reported previously [8, 9].

We assume that the first step in the Wallach reaction involves N-formylation of the secondary amine, and that subsequently the resulting substituted formamide reacts with an aldehyde to give a tertiary amine. Indeed, N-phenyl(XIII)-[p-anisyl(XIV)]-N-(1,2,5-trimethyl-4-piperidinyl)formamides were obtained from the secondary amine III and V after refluxing in formic acid. Amide XIII is hydrolyzed in acidic media to give amine III, which was isolated in 56% yield. Under conditions of the Wallach reaction (refluxing with benzaldehyde in formic acid), however, amide XIII was further converted to the tertiary amine VIII (85% yield).

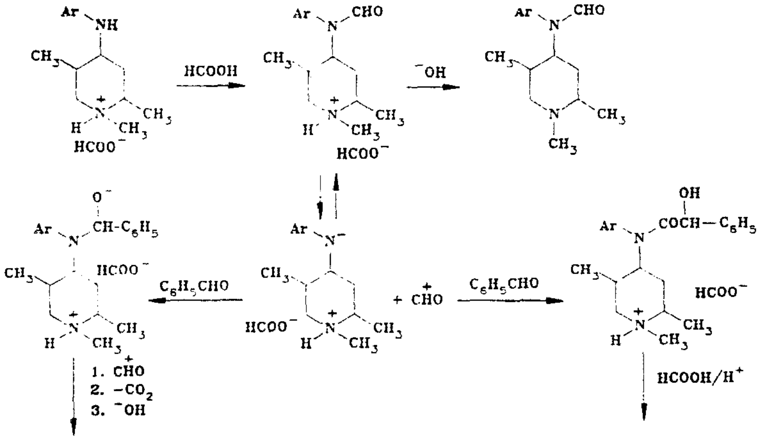


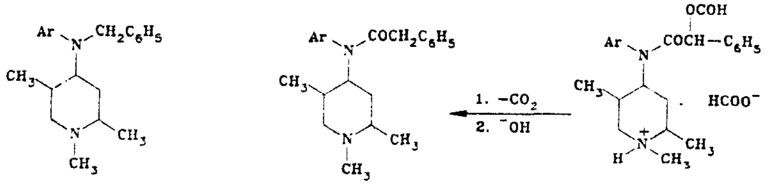
III, XIII R = C_6H_5; V, XIV R = p-$CH_3OC_6H_4$

The presence of formyl derivatives of amines III-V as impurities among the reaction products arising in the preparation of tertiary amines VIII-XI was established based on their acidic hydrolysis. In all cases the IR spectra of the substances isolated after hydrolysis did not contain an amide ν_{CO} band in the 1660-1690 cm^{-1} region, while the intensity of the ν_{NH} band at 3400 cm^{-1} had increased. In addition, the mass spectra of these substances did not contain the M^+ peaks for the formyl derivatives or the M^+ peaks for the corresponding N,N-substituted amide of phenylacetic acid.

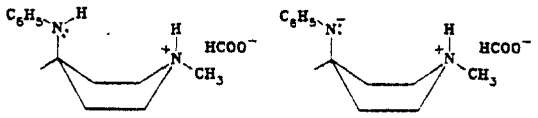
The experimental data obtained herein can be applied to elucidate the mechanism of the Wallach reaction, in particular, to understand the fact that the reaction proceeds via an intermediate formylation stage of the secondary amine. With respect to the substrates examined in this study, it should be mentioned that the reactions were carried out in highly acidic (formic) acid medium.

In the scheme below we have illustated possible steps in the formation of the compounds which were detected experimentally among the reaction products of γ-N-aryl(1,2,5-trimethyl-4-piperidinyl)amines with benzaldehyde and formic acid.





In considering the individual reaction steps in these processes, it is apparently necessary to take into account the conformation of the piperidine ring containing a quaternized nitrogen atom. In the "tub" configuration of N-aryl-N-(1,2,5-trimethyl-4-piperidinyl)amine formate, there is an angular interaction of the unshared electron pair on the nitrogen atom of the γ-amino group with the positively charged nitrogen atom in the piperidine ring, which would be expected to facilitate cleavage of a proton from the exocyclic nitrogen atom at the condensation stage with formic acid. In an analogous manner, strong interaction between the negatively charged exocyclic nitrogen atom and the quaternized nitrogen atom in the piperidine ring, which occurs in the zwitterion formed via dissociation of the corresponding N-formyl derivative, should facilitate dissociation and stabilization of the zwitterion. In both cases the methyl group attached to the nitrogen atom in the piperidine ring does not shield the exocyclic nitrogen atom, based on examination of Dreiding molecular models.



We have thus investigated in the present paper a special example of the Wallach reaction. Factors responsible for the color of various dihydrochlorides of these newly synthesized tertiary amines will be discussed in a separate publication.

EXPERIMENTAL

IR spectra were recorded on UR-20 (for KBr pellets) and Specord IR-75 (for thin films) spectrophotometers. Electron impact and chemical ionization mass spectra (with ammonia as the reagent gas) were obtained on an LKV-2091 mass spectrometer at an ionizing electron energy of 70 eV and anionization chamber temperature of 250°C. Combined chromatography—mass spectrometry of substance VIII wasperformed using a capillary column (ℓ = 25 m, d = 0.3 mm) in a programmed temperature mode from 50 to 250°C. Column chromatography was carried out on grade II activity aluminum oxide. Alufol plates and an ethyl acetate—heptane eluting system, with the following component ratios: 1:1 (compounds VIII, IX, XI); 1:2 (VII); 1:3 (VI); 2:1 (X, XII), were used for TLC.

N-Benzyl(VI)[Cyclohexyl (VII), Phenyl (VIII), o-Anisyl (IX), p-Anisyl (X)]-N-(1,2,5-trimethyl-4-piperidinyl)benzylamines and N-Phenyl(XI)[p-Anisyl (XII)]-N-(1,2,5-trimethyl-4-piperidinyl)p-methoxybenzylamines. To 1 mole of freshly distilled secondary amine I-V was added 1.2-1.8 moles of freshly distilled benzaldehyde (anisaldehyde). At a temperature of 5-0°C 5-6 moles of formic acid were also added to the reaction mixture. The mixture was heated at mild reflux. Gas evolution occurred within 30 min to 2 h. After gas evolution had ceased the mixture was heated for an additional 6-8 h. After being cooled the mixture was treated with 18% hydrochloric acid to give a pH of 1-2. The mixture was then evaporated to dryness under vacuum. The residue was worked up with a solution of sodium carbonate, extracted with ether, and dried over magnesium sulfate; after ether removal the product was crystallized from heptane (or hexane). In a variational procedure, benzaldehyde was steam distilled out of the initial acidic aqueous solution, and the residue was then worked up in an analogous manner.

N-Phenyl-N-(1,2,5-trimethyl-4-piperidinyl)benzylamine (VIII). The reaction was carried out with 0.87 g (4 mmole) of an isomeric mixture of diamine III, 0.8 g (7.5 mmole) benzaldehyde, and 4 ml (86 mmole) formic acid. The color of the reaction mixture changed from yellow to green, and then emerald green, upon heating and after gas evolution had commenced. After acid workup benzaldehyde was removed by steam distillation. The solution decolorized after treatment with sodium bicarbonate. Yield of isolated substance, 1 g of a mixture of isomers of compound VIII with impurities. Colorless crystals, mp 90-106°C (from heptane). Diamine dihydrochloride VIII, blue green crystals, mp 240-248°C (from alcohol).

The dihydrochloride of diamine VIII (0.97 g, 2.5 mmole) was refluxed in 10 ml 18% hydrochloric acid for 1 h and 30 min. The color of the solution did not change during this procedure. The mixture was then treated with a solution of sodium carbonate, extracted with ether, and 0.54 g (87%) of substnce VIII was isolated, mp 104-108°C(from heptane), R_f 0.75; 0.51; 0.22 (Alufol, 1:1 ethyl acetate–heptane). IR spectrum ($CHCl_3$ film): 3400 (w, NH), 1600, 1500 (C=C) cm^{-1}.

The physical characteristics and mass spectral data for the free bases of compounds VI-XII are given in Tables 1 and 2.

N-Phenyl-N-(1,2,5-trimethyl-4-piperidinyl)formamide (XIII). A mixture of 1.16 g (5.3 mmole) of an isomeric mixture of compound III in 1.2 ml (26 mmole) formic acid was refluxed for 4 h and 30 min. The mixture was treated with 50 ml water, neutralized with sodium carbonate, and extracted with ether. Yield 1.04 g (79%) of compound XIII as a yellow oil, R_f 0.93; 0.73; 0.53 (Alufol, 1:1 ethyl acetate–heptane). Found: N 11.0%; M^+ 246. $C_{15}H_{22}N_2O$. Calculated: N 11.4%; M 246. Hydrochloride of compound XIII exists as a colorless hygroscopic crystalline substance, mp 64-67°C. Found: Cl 12.9; N 9.4%. $C_{15}H_{22}N_2O \cdot HCl$. Calculated: Cl 12.6; N 9.9%.

A mixture of 0.1 g (0.4 mmole) compound XIII in 5 ml 18% hydrochloric acid was refluxed for 1 h. After neutralization with sodium carbonate and extraction with ether 0.05 g (56%) of amine III was isolated as a mixture of isomers, R_f 0.6 and 0.3 (Alufol, ethyl acetate–heptane, 1:2). IR spectrum (thin film): 3390 cm^{-1} (NH). Found: M^+ 218. $C_{14}H_{22}N_2$. Calculated: M 218.

Under Wallach reaction conditions compound XIII was converted further to substance VIII. A solution of 1.87 g (7.6 mmole) compound XIII and 0.8 g (7.5 mmole) benzaldehyde in 1.7 ml (37 mmole) formic acid was refluxed for 7 h. To the emerald green solution was then added 5 ml concentrated hydrochloric acid, and the mixture was refluxed another 1 h and 30 min. The intense color of the solution did not dissipate under these conditions. Excess benzaldehyde was removed by steam distillation. The mixture was neutralized with sodium carbonate, and the solution color was extinguished. The reaction products were extracted with ether. Yield 2.0 g (85%) of substance VIII. Colorless crystals, mp 95-100°C. The IR spectrum was analogous to that of substance VIII prepared directly from diamine III. The dihydrochloride of substance VIII, prepared from the free base, exists as blue-green crystals, mp 246-250°C (from alcohol).

N-(p-Anisyl)-N-(1,2,5-trimethyl-4-piperidinyl)formamide (XIV). This was prepared in an analogous manner in 72% yield in the form of a pale yellow oil, R_f 0.84; 0.65; 0.48 (Alufol, 1:1 ethyl acetate–heptane). IR spectrum (thin film): 1666 cm^{-1} (CO). Found: N 9.7%. M^+ 276. $C_{16}H_{24}N_2O_2$. Calculated: N 10.1%. M 276. The hydrochloride of compound XIV exists as colorless hygroscopic crystals, mp 65-68°C. Found: N 8.5%. $C_{16}H_{24}N_2O_2 \cdot HCl$. Calculated: N 8.9%.

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