Reactions of Halogenoquinolizinium Bromides with Diethylamine

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Received August 25, 1981

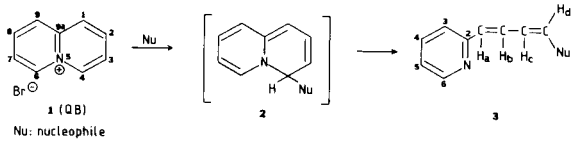
The reactions of quinolizinium bromide (QB) and its four monobromo derivatives with diethylamine have been investigated. For Br in position 2 or 4, substitution is the main process, whereas for Br in positions 1 and 3 quantitative ring opening is found. The substituted pyridylbutadienes formed by ring opening, are *cis-trans*-butadienes, which isomerize into the all-*trans* forms. The steric cours of the ring opening is explained.

J. Heterocyclic Chem., **19**, 797 (1982).

Introduction.

The current interest in our laboratory on the reactivity of halogenoazines with weak and strong nucleophiles has induced us to study the reactions of several isomeric bromoquinolizinium bromides with *N*-nucleophiles. In a previous publication (1) the synthesis of these bromoquinolizinium bromides has been described. In the literature it has been reported that the parent substance quinolizinium bromide **1** (from here on abbreviated as QB) undergoes a ring opening reaction with Grignard reagents (2a,b,c), lithiumaluminiumhydride and sodium borohydride (3), aniline (4) and aliphatic amines (5a,b), leading to substituted 4-(2-pyridyl)-1,3-butadienes (**3**, Scheme 1).

Scheme 1



The expected intermediary 4*H*-quinolizines **2** have never been isolated in these reactions, probably because they undergo a rapid ring opening reaction to the more stable aromatic pyridine system (2a). A few nucleophilic substitution reactions have been reported for halogenoquinolizinium salts, *viz.* 2-bromoQB and 2-bromo-1-hydroxyQB with several aliphatic and aromatic amines (6), 2-bromoQB and 3-hydroxy-4-bromoQB with silver acetate in acetic acid (7), 4-chloroquinolizinium perchlorate with piperidine in ethanol (8) and with several carbanions (9). In order to obtain more information about the structural features deciding whether in the reaction of bromoQB's with nucleophiles substitution or ring opening proceeds, we investigated the reactions of QB and the 1-, 2-, 3- and 4-bromo derivatives with diethylamine. In this paper the results of these reactions are given.

Results.

1. Quinolizinium Bromide (QB) (**1**).

Compound **1** was reacted with an excess of diethylamine in hexadeuteriodimethyl sulfoxide at about 35° in an nmr tube and the reaction was followed by measuring the ^{1}H-nmr spectrum at regular intervals until no further change was observed. It is apparent from the spectra that first the H_aH_b-*cis*, H_cH_d-*trans* isomer of 1-diethylamino-4-(2-pyridyl)-1,3-butadiene (**4a**) is formed, which subsequently isomerizes into the all-*trans* isomer **4b** (Scheme 2).

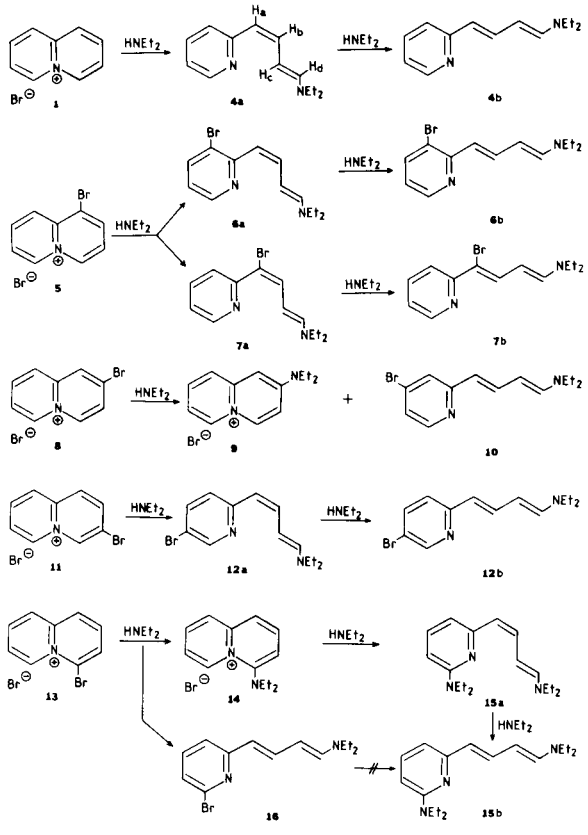
The assignment of the structures of **4a** and **4b** was based on the chemical shifts of the protons H_a, H_b, H_c and H_d in the butadienyl moiety (see Table I) and on the magnitude of the coupling constants which is in accordance with data in the literature (2c,5b,10) ($J_{a,b[cis]}$ = 11 Hz, $J_{a,b[trans]}$ = 15 Hz, $J_{b,c}$ = 11 Hz, $J_{c,d[trans]}$ = 13 Hz). For supporting the chemical shift assignments in the complicated nmr spectra, we prepared 4,6-dideuterioQB and reacted it with diethylamine. For further identification we prepared **4b** by reacting **1** with diethylamine in refluxing ethanolic solution on a preparative scale. Uv and ir spectroscopy, mass spectrometry and, moreover, oxidation with potassium permanganate and subsequent esterification with methanol, yielding methyl picolinate, confirmed the identity of **4b**. In the literature it has been reported that an all-*trans* pyridylbutadiene is formed in the reaction of QB with piperidine and morpholine (5b) and that a *cis-trans* pyridylbutadiene results from the reaction of QB with phenylmagnesium bromide (2c). Probably in the first mentioned reaction the all-*trans* compound has been formed *via* a *cis-trans* pyridylbutadiene.

2. 1-Bromoquinolizinium Bromide (**5**).

Treatment of **5** with diethylamine in hexadeuteriodimethyl sulfoxide gave quantitative ring opening, yielding first H_aH_b-*cis*, H_cH_d-*trans*-4-(3-bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**6a**) as indicated by ^{1}H-nmr spectroscopy (Table I), which then isomerized into the all-*trans* compound **6b** (Scheme 2).

From the spectra we also obtained indications for the formation of about 30% of H_aH_b-*cis*, H_cH_d-*trans*-4-bromo-1-diethylamino-4-(2-pyridyl)-1,3-butadiene (**7a**), isomerizing into **7b**. We supported the nmr assignments by reacting 4,6-dideuterio-1-bromoQB (1) with diethylamine in hexadeuteriodimethyl sulfoxide. Compound **6b** was isolated by carrying out the reaction of **5** with diethyl-

Scheme 2



amine in refluxing ethanolic solution on a preparative scale. The uv, ir and mass spectra and the results of oxidation/esterification reactions (see above) confirm the structure of **6b**. However, the oxidation/esterification reaction gave in addition to methyl 3-bromopicolinate, resulting from **6b**, a small amount of methyl picolinate, which might result from oxidation/esterification of **7b**.

Our results indicate that in compound **5** both position 4 and 6 are vulnerable to a nucleophilic addition by diethylamine; diethylaminodebromination at position 1 does not occur.

3. 2-Bromoquinolizinium Bromide (**8**).

Reaction of **8** with diethylamine in boiling ethanol gave 2-diethylaminoQB (**9**) and a small amount (~10%) of all-*trans*-4-(4-bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**10**) (Scheme 2). When carrying out the reaction in hexadeuteriodimethyl sulfoxide, **10** was not detected by ^{1}H-nmr. The structure of **10** was proved by uv, ir, ^{1}H-nmr and mass spectra and oxidation/esterification, yielding methyl 4-chloropicolinate and a trace of methyl 4-bromopicolinate. The presence of the former compound may be attributed to the treatment with thionylchloride, included in the reaction sequence (see Experimental).

4. 3-Bromoquinolizinium Bromide (**11**).

The 3-bromo compound **11** reacted with diethylamine in hexadeuteriodimethyl sulfoxide by quantitative ring opening, yielding **12a** and subsequently **12b** (Scheme 2). Only the unsubstituted ring was attacked by the nucleophile, contrary to the behaviour of 1-bromoQB. The structure of **12b**, isolated from the preparative reaction of **11** with diethylamine in ethanol, was proved in the way described above for **6b** and **10**, the oxidation/esterification reaction leading to methyl 5-bromopicolinate. Moreover, a reaction with 4,6-dideuterio-3-bromoQB (1) was carried out for sup-

Table I

^{1}H-NMR and UV Spectral Data of Pyridylbutadienes, Obtained From Quinolizinium Bromides and Diethylamine

	δ								UV
	H(3)	H(4)	H(5)	H(6)	H(a)	H(b)	H(c)	H(d)	λ max (nm)
				a,b-*cis*, c,d-*trans*-pyridylbutadienes (a)					
4a	7.10	7.56	6.91	(b)	5.60	6.23	6.61	6.55	
6a	-	7.74	6.79	8.33	5.85	6.32	6.68	6.67	
12a	7.00	7.68	-	8.43	5.53	6.24	6.58	6.56	
15a	6.22	7.22	6.17	-	5.42	5.88	6.53	6.64	
				a,b-*trans*, c,d-*trans*-pyridylbutadienes (a)					
4b	7.09	7.50	6.88	8.31	6.00	7.24	5.12	6.65	375
6b	-	7.76	6.80	8.27	6.31	7.48	5.22	6.79	395
10	7.33	-	7.12	8.18	5.94	7.33	5.15	6.73	391
12b	7.07	7.69	-	8.38	5.98	7.29	5.14	6.71	390
15b	6.25	7.23	6.17	-	5.88	7.15	5.10	6.52	386

(a) See for numbering system formula **3** (Scheme 1). (b) The signal for H-6 is hidden under the signals of the starting material.

porting the interpretation of the ^{1}H-nmr spectra.

5. 4-Bromoquinolizinium Bromide (**13**).

4-BromoQB (**13**) with diethylamine in hexadeuteriodimethyl sulfoxide showed fast conversion into 4-diethylaminoQB (**14**), as indicated by nmr spectroscopy, followed by a much slower ring opening process, leading *via* **15a** to **15b** (Scheme 2). That the nucleophilic displacement takes place in **13** and not in a possible precursor 4-(6-bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**16**) is supported by the fact that 2-bromopyridine does not react with diethylamine in dimethyl sulfoxide under the conditions used for the reaction of **13**.

Compound **15b** was isolated by refluxing **13** with pure diethylamine. The structure of the product thus obtained, was established by uv, ir, ^{1}H-nmr and mass spectra; furthermore, gc/ms analysis showed that **15b** is indeed the main constituent but that it is contaminated with a minor amount of **16**. Evidently, under these preparative conditions ring opening in **13** competes with nucleophilic displacement, whereas in dimethyl sulfoxide solution such a process does not occur according to the nmr spectra.

Discussion.

From our results it is evident that the bromine atom in the 1- and 3-position, thus β to the hetero atom, is not easily substituted by diethylamine, in contrast with the bromine atom in positions 2 and 4. This fact is in agreement with what is known about the reactivity of halogen atoms in six-membered aza heterocycles.

The formation of the open-chain products is thought to proceed by attack of the nucleophile at C-4 or C-6, followed by a ring opening which restores aromaticity (*cf.* Scheme 1). As expected, H_a and H_b of the pyridyl-1,3-butadiene initially formed are in the *cis*-configuration. The fact that H_c and H_d are always situated *trans* towards each other, can be explained by assuming that in the initially formed adduct **2** the nucleophile is in the *trans* position towards the lone electron pair of nitrogen. A disrotatory ring opening will then lead to the H_c, H_d*trans* configuration. That *cis-trans* isomerization around the C(a)-C(b) double bond occurs so easily in dimethyl sulfoxide is not surprising: the double bond character in the butadiene system of these compounds is considerably decreased due to the important mesomeric interaction of the diethylamino group with the pyridine ring.

EXPERIMENTAL

1. General.

Melting points are uncorrected. The ir spectra were measured on a Perkin Elmer 237 spectrophotometer, uv spectra on a Beckman spectrophotometer Acta C III, mass spectra on an Ae MS-902 mass spectrometer and gc/ms analyses were performed on a Micromass 7070 F apparatus. ^{1}H-nmr spectra were recorded on a 60 MHz Hitachi Perkin Elmer R-24B spectrometer and on a 90 MHz Varian EM 390 spectrometer, using tetramethylsilane (TMS) as internal standard and hexadeuteriodimethyl sulfoxide as solvent, unless stated otherwise.

2. Open-Chain Compounds.

Chemical shifts for the protons of the open-chain compounds formed by reaction of QB and its bromo derivatives with diethylamine, are given in Table I. The data for **7a** and **7b** have been omitted from the table; the spectrum of the mixture of **6a, 6b, 7a** and **7b** was too complicated to allow complete assignment for the minor components **7a** and **7b**. J values of the open-chain compounds were rather constant; average values are $J_{3,4}$ = 8 Hz, $J_{4,5}$ = 7.5 Hz, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz, $J_{3,5}$ = 1-2 Hz, $J_{a,b[cis]}$ = 11 Hz, $J_{a,b[trans]}$ = 15 Hz, $J_{b,c}$ = 11 Hz, $J_{c,d}$ = 13 Hz. The uv maxima of the open-chain compounds were measured in methanol (Table I); ϵ max values were not determined except for **4b**, ϵ max = 20000. Mass spectra gave the expected m/e values. The ir spectra agree with the structures assigned. All open-chain compounds were prepared in the way described in the experimental section **3b**; they were found to be rather unstable, colored oils.

1-Diethylamino-4-(2-pyridyl)-1,3-butadiene (**4b**).

Compound **4b** was obtained in a yield of 65% from QB (**1**).
Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97. Found: C, 77.6; H, 9.1.

4-(3-Bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**6b**) and 4-Bromo-1-diethylamino-4-(2-pyridyl)-1,3-butadiene (**7b**).

A mixture of compounds **6b** and **7b** was obtained in a yield of 65% from 1-bromoQB (**5**). This mixture could not be separated and was analysed as such.
Anal. Calcd. for $C_{13}H_{17}BrN_2$: C, 55.52; H, 6.09. Found: C, 55.7; H, 6.1.

4-(4-Bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**10**).

Compound **10** was obtained in 10% yield from 2-bromoQB (**8**).
Anal. Calcd. for $C_{13}H_{17}BrN_2$: C, 55.52; H, 6.09. Found: C, 55.4; H, 6.0.

4-(5-Bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**12b**).

Compound **12b** was obtained in a yield of 55% from 3-bromoQB (**11**).
Anal. Calcd. for $C_{13}H_{17}BrN_2$: C, 55.52; H, 6.09. Found: C, 55.8; H, 5.8.

1-Diethylamino-4-(6-diethylamino-2-pyridyl)-1,3-butadiene (**15b**).

Compound **15b** was obtained in a yield of 70% from 4-bromoQB (**13**) by refluxing in pure diethylamine (see experimental section **3b**). The product was contaminated with some 4-(6-bromo-2-pyridyl)-1-diethylamino-1,3-butadiene (**16**), which could not be removed by column chromatography. Accurate mass determination of both compounds gave for **15b** the value 273.221 (Calcd. 273.2205) and for **16** 280.060 and 282.054 (Calcd. 280.0576 and 282.0556).
Anal. Calcd. for a mixture of 77.1% of **15b** ($C_{17}H_{27}N_3$) and 22.9% of **16** ($C_{13}H_{17}BrN_2$): C, 70.29; H, 9.07. Found: C, 70.3; H, 9.0.

Oxidation/Esterification of Open-Chain Compounds.

Fifty ml of water and the open-chain compound resulting from 1.7 mmoles of quinolizinium compound were stirred together at 70°. During six hours, 2.5 g of potassium permanganate was added in small portions, until decolorisation no longer occurred. Excess of potassium permanganate was then destroyed by adding sodium sulfite and the precipitate of manganese dioxide was filtered and washed with water. The filtrate was evaporated and the residue was refluxed with 25 ml of thionyl chloride for 1 hour. Excess of thionyl chloride was removed by distillation *in vacuo*; 25 ml of methanol and 25 ml of benzene were then added to the residue. After refluxing for 1 hour, the mixture was cooled and stirred for a few minutes with saturated sodium hydrogencarbonate solution. The aqueous layer was extracted with ether, the ether extract and the organic layer were dried together over magnesium sulfate and evaporated. The residue of (bromo)pyridinecarboxylic ester was investigated by glc, tlc, nmr, mass spectrometry and gc/ms analysis.

3. Reactions with Diethylamine (11).

a. Reactions in Dimethyl Sulfoxide.

Pure dry diethylamine (0.05 ml) was added to 0.03-0.04 g of quinolizinium compound in 0.5 ml of hexadeuteriodimethyl sulfoxide in an nmr tube. The ^{1}H-nmr spectra were measured at reaction times of 5 minutes to several days, until no further change in the spectrum was observed; reaction temperature 35°.

b. Reactions in Ethanol on a Preparative Scale.

One g of the quinolizinium salt, 10 ml of pure dry diethylamine and 10 ml of absolute ethanol were refluxed together with stirring for 10 minutes (under these conditions 4-bromoQB (**13**) gave a mixture of open-chain and substitution product; refluxing 0.5 g of **13** in 30 ml of pure diethylamine gave a better yield of ring opening product). The mixture was poured into 200 ml of ice-water and extracted with dichloromethane. The extract was washed with water, dried over magnesium sulfate, concentrated and purified over a column of 25 g of alumina (basic, act. III, eluent dichloromethane). The swift wandering yellow band of open-chain compound was collected. Substitution products were isolated from the aqueous layer by evaporation and crystallization.

4. Preparations.

2-DiethylaminoQB (**9**) (1).

This compound had mp 122-124°.

4-DiethylaminoQB (**14**).

To a cold suspension of 3.0 g of 4-bromoQB in 120 ml of absolute ethanol, 120 ml of diethylamine was added in an ice-bath. After 5 minutes, the ice-bath was removed and the mixture was stirred for 2.5 hours at room temperature. The mixture was then filtered and poured into 750 ml of distilled water, washed with three portions of diethyl ether and concentrated to a volume of 200 ml. In order to remove any diethylammonium bromide present, the solution was alkalized to *p*H = 13 and continuously extracted with diethyl ether for 4 hours. The aqueous layer was then neutralized with concentrated hydrobromic acid, the water was evaporated *in vacuo* and the residue was stirred with 50 ml of dry acetone. The insoluble inorganic salts were filtered off and the acetone was evaporated *in vacuo*, yielding 1.6 g of **14** (54%) as an oil. ^{1}H-nmr (deuterium oxide): δ 9.54 (br dd, J = 7 Hz, J = 2 Hz, H(6)); δ 8.56 (ddd, J = 8.5 Hz, J = 2 Hz, J = 0.5 Hz, H(9)); δ 8.46 (dd, J = 7.5 Hz, J = 8.5 Hz, H(2)); δ 8.36 (ddd, J = 8.5 Hz, J = 7 Hz, J = 2 Hz, H(8)); δ 8.26 (dd, J = 8.5 Hz, J = 2 Hz, H(1)); δ 8.12 (ddd, J = 7 Hz, J = 7 Hz, J = 2 Hz, H(7)); δ 7.89 (dd, J = 7.5 Hz, J = 2 Hz, H(3)); δ 3.53 (q, J = 7 Hz, CH_2); δ 1.32 (t, J = 7 Hz, CH_3); uv (methanol): λ max (ε) nm 269 (4800), 358 (6000).

All attempts to crystallize **14** failed, therefore we prepared the cyrstalline 4-diethylaminoquinolizinium reineckate for characterization purposes.

4-Diethylaminoquinolizinium Tetrathiocyanato Diammine Chromate (III) (4-Diethylaminoquinolizinium reineckate).

To a solution of 0.50 g of **14** in 10 ml of water a solution of 0.63 g of ammonium reineckate in 25 ml of water was added. After 1 hour the precipitate was filtered off and crystallized from cold acetone-water, mp 119-121°.

Anal. Calcd. for $C_{17}H_{23}CrN_8S_4$ (519.67): C, 39.29; H, 4.46. Found: C, 39.3; H, 4.6.

Acknowledgements.

We are indebted to Mr. A. van Veldhuizen for his assistance with the nmr measurements, to Dr. C. A. Landheer and Mr. W. P. Combé for determination of the mass spectra, to Mr. H. Jongejan for carrying out the microanalyses and to Dr. M. C. Posthumus for the gc/ms analyses.

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