Tetrahedron Vol. 33, pp. 2565 to 2570 Pergamon Press 1977 Printed in Great Britain

FURTHER STUDIES ON THE CHEMISTRY AND STRUCTURE OF N-OXIDES OF SPARTEINE AND ITS DERIVATIVES—V

SYNTHESIS AND STRUCTURE OF 2-PHENYLSPARTEINE-N_{16}-OXIDE, A NEW CASE OF "SPONGE" PROTON†

WŁADYSŁAW BOCZOŃ, GENOWEFA PIECZONKA and MACIEJ WIEWIÓROWSKI*
Institute of Chemistry, Department of Organic Stereochemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

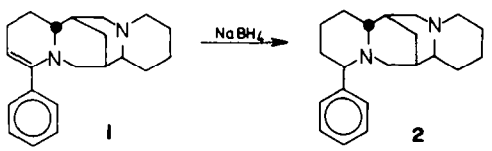
(*Received in the UK* 16 *February* 1977; *accepted for publication* 9 *March* 1977)

Abstract—The synthesis of 2-phenylsparteine-N_{16}-oxide (**7**) and its perchlorate salt (**7**-H^+) was carried out. On the basis of spectral data, and by comparison with appropriate sparteine-N-oxides, the mechanism of formation and the structures of the two new compounds were proposed. It was found, the basicity of the new N-oxide is unexpectedly high and comparable to the basicity of quaternary ammonium hydroxides. The structure and the strength of intramolecular H-bond in **7**-H^+ makes **7** an excellent "catcher" proton or specific "sponge" proton.

During our investigations with sparteine-N-oxide[1-4,14] we attempted the reaction between 2-phenylsparteine (**2**) and H_2O_2.

We obtained 2-phenylsparteine (**2**) by reduction of 2-phenyl-2-dehydrosparteine **1**.[5]

A detailed analysis of the IR and NMR spectra of **2**, its perchlorate salt and specifically deuterated derivatives

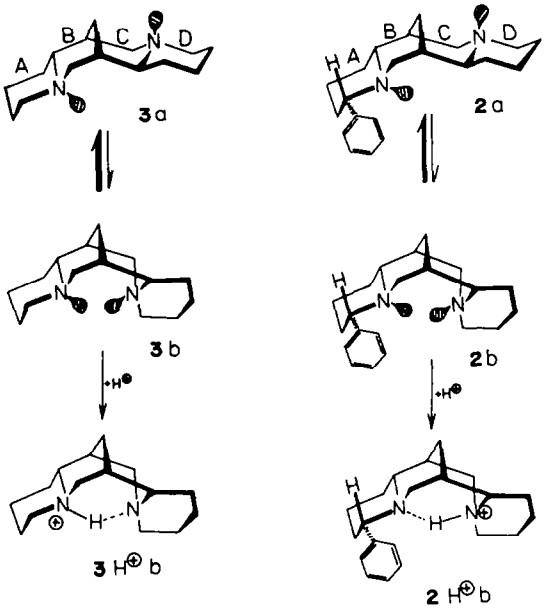


Scheme 1.

made it possible to establish the conformation and the configuration of **2** and its monoprotonated cation (**2**-H^+).[5] Scheme 2 summarizes our knowledge on the structure of **2** and **2**-H^+, in comparison with the structure of sparteine (**3a** and **3b**) and its monocation (**3**-H^+).

As it is evident from Scheme 2, the introduction of a phenyl group into the *trans*-quinolizidine A/B fragment of the sparteine molecule, has no influence on the configuration and conformation of the C/D fragment of **2**, or the free base, or the monocation. Thus, 2-phenylsparteine (**2**), like **3**, persists as the free base in the "transoidal" conformation (one *trans*-quinolizidine chair–chair fragment fused with the second *trans*-quinolizidine boat–chair fragment). After protonation, both amine groups adopt the "cisoidal" form with simultaneous formation of an intramolecular H-bond in monocations **2**-H^+ and **3**-H^+.

The only substantial difference between **2**-H^+ and **3**-H^+ is the location of the "acidic" proton. In the crystalline **3**-$H^+ClO_4^-$ this proton is located exclusively on nitrogen N_1—(*trans*-quinolizidine system),[6,10] and in the crystalline **2**-$H^+ClO_4^-$—on nitrogen N_{16} (*cis*-quinolizidine system).[5] The distinct differences in protonation site, which appear in crystalline forms of both salts are



Scheme 2

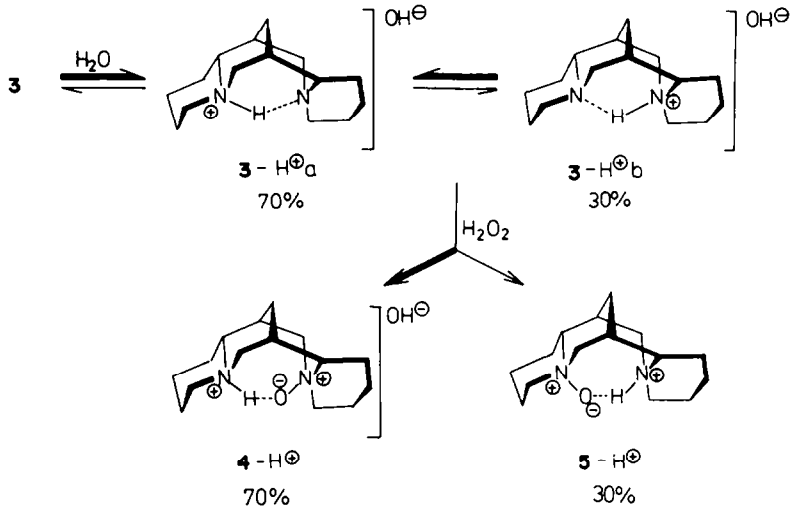
slightly diminished in chloroform solution, because in both cases a tautomeric equilibrium exists, in which the predominant tautomers are **3**-H^+(70%) or **2**-H^+(>90%). It appears from the above, that the introduction of a phenyl group into the α-position with reference to N_1 makes this nitrogen less basic than the N_{16} one. The decrease in basicity of **2** with reference to **3** is about 0.7 pK^*_{MCS} units (Table 1).

In a previous paper,[4] discussing the difficulties in obtaining N-oxide from conformer **3a** of sparteine, we tried to explain the very fast reaction of sparteine (**3**) with H_2O_2, which results in two isomeric sparteine-mono-N-oxides in the constant ratio 70% of **4** to 30% of **5**. We have assumed, that in aqueous solutions in which the oxidation is carried out, sparteine molecules exist partly in protonated form, as tautomeric cations **3**-H^+a and **3**-H^+b. The tautomeric equilibrium is shifted to form **3**-H^+a, and therefore we have assumed that the sparteine

†This study has been supported by the Polish Academy of Sciences in the framework of the problem No. MR-I.9.2.2.

Table 1. pK^{*}_{MCS}-values of sparteine and its derivatives

Compound	pK^{*}_{MCS}	$pK^{*}_{MCS}(1)$	$pK^{*}_{MCS}(2)$	ΔpK^{*}_{MCS}	Ref.
sparteine (3)		3.05	10.26	7.05	9
lupanine (=2-oxosparteine)	7.47				9
2-phenylsparteine (2)		3.75	10.10	6.35	5
2-phenylsparteine-N_{16}-oxide (7)		1.90	12.85	10.95	
sparteine-N_{16}-oxide (4)		2.56	11.94	9.38	4



Scheme 3.

delivers about 70% of N_{16}-oxide (**4**) and about 30% of N_1-oxide (**5**) (Scheme 3).[1]

If the presented hypothesis is correct, compound **2** also should partly exist in aqueous solution in the protonated form, and the equilibrium between tautomers **2**-H^{+}b and **2**-H^{+}a should at least be shifted 90% toward **2**-H^{+}b. Consequently, the reaction of **2** with H_2O_2 should lead mainly to N_1-oxide (**6**), which may be accompanied by about 10% of N_{16}-oxide (**7**).

RESULTS AND DISCUSSION

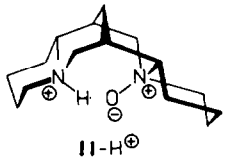
According to the above hypothesis, the reaction of **2** with H_2O_2 results in one dominant product which proved to be not the N_1-oxide (**6**), but the N_{16}-oxide (**7**) (Scheme 4). The evidence, that the product from the reaction between **2** and H_2O_2 is **7**, and not **6** and **8**, is as follows:

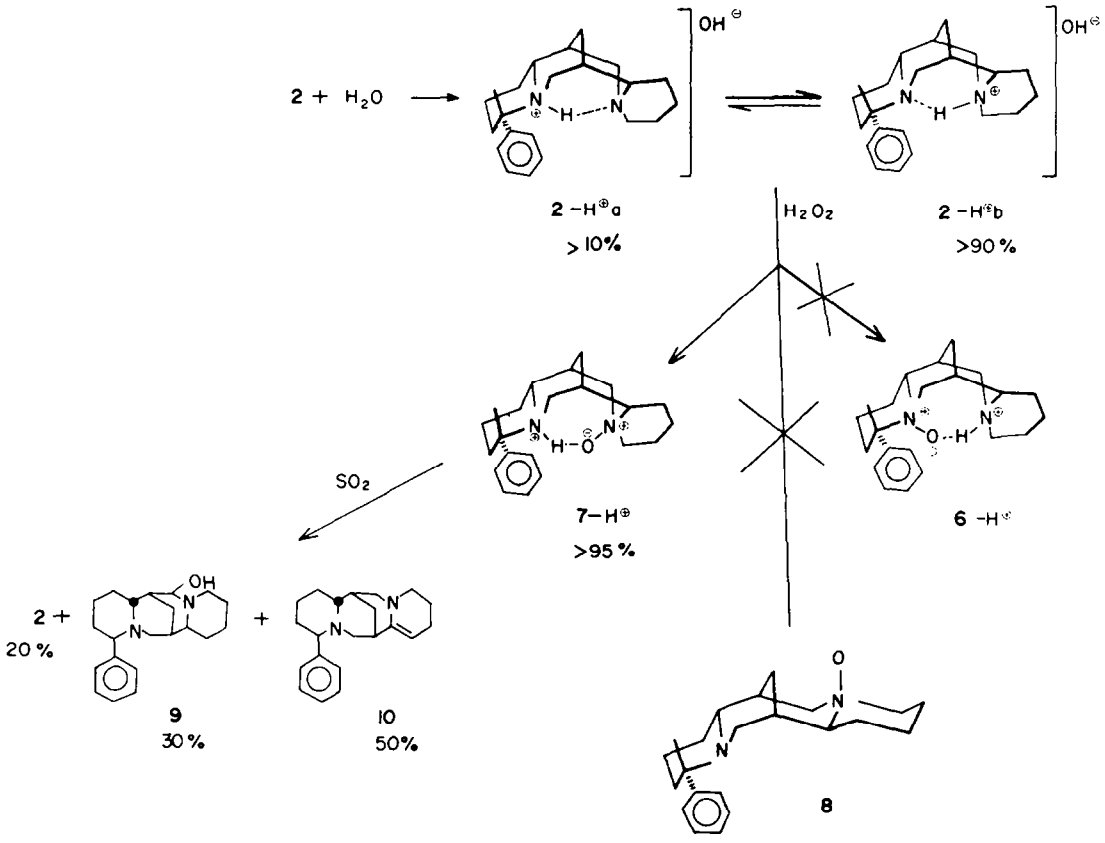
(a) IR and NMR spectra of the monocation of 2-phenylsparteine-N-oxide show a strong intramolecular H-bond, which excludes the "transoidal" structure **8** and indicate the presence of structure **6** or **7**. In the IR spectrum of **7**-$H^{+}ClO_4^{-}$, there is no absorption band $\nu_{N^{+}-H}$, but the continuous absorption with distinct minima in the 1100–650 cm^{-1} region is present, as in the spectrum of **4**-$H^{+}ClO_4^{-}$[4,14] (Fig. 1). In the NMR spectra of these compounds, the signal of the "acidic" proton is shifted very strongly downfield.[4]

(b) A comparison of the "*trans*"-bands (2880–2600 cm^{-1})[10] of **7** with the same bands in the spectra of isomeric sparteine-N-oxides (**4** and **5**) indicates that in the N-oxide investigated, the "*trans*"-band characteristic for a *trans*-quinolizidine system is indeed present (Fig. 2). The "*trans*"-band of **7** is properly modified by the substituent in position **2**. Instead of a doublet, which exists in **4**, in the spectrum of **7** an intense singlet is observed (Fig. 2).[4,14] If the N-oxide obtained has the structure **6**, its "*trans*"-band should be very similar to "*trans*"-band of **5**.[4] As this is not the case, we assume, that the structure **7** is correct.

(c) The reaction with SO_2 does not lead exclusively to the parent amine **2**, which should happen if the N-oxide group was included in the all-chair *trans*-quinolizidine system of **6**.[7,8] Instead, the reaction leads to a tri-component mixture (**2** + **9** + **10**; Scheme 4), which could be formed if the N-oxide function occurs in the *cis*-quinolizidine system of **7**.[7,8]

The exclusive formation of **7** in the reaction of **2** with H_2O_2 was a surprise. We supposed, that by introducing an N-oxide group into the compound **2** (i.e. into the base considerably weaker than **3**; Table 1) we should obtain an N-oxide (**6** or **7**), which would be also a weaker base than N-oxide **4** (or **5**). This assumption was additionally supported by the abnormal high basicity of **4** (and also **5**), whose $pK^{*}_{MCS}(2)$-value is 11.94. It was found, that **7** is a stronger base than **4**, as displayed by an unusually high $pK^{*}_{MCS}(2)$-value = 12.85, as well as by the ΔpK^{*}_{MCS} = 10.95 (ΔpK^{*}_{MCS} for **4** is 9.38) (Table 1). Compound **7** is also more basic than alpha-iso-sparteine-oxide (**11**), which was assumed to be the most basic compound in this series due to the rigid bis-*trans*-quinolizidine skeleton and the strength of the intramolecular H-bond[14] (which appears in **11**-H^{+}).





Scheme 4.

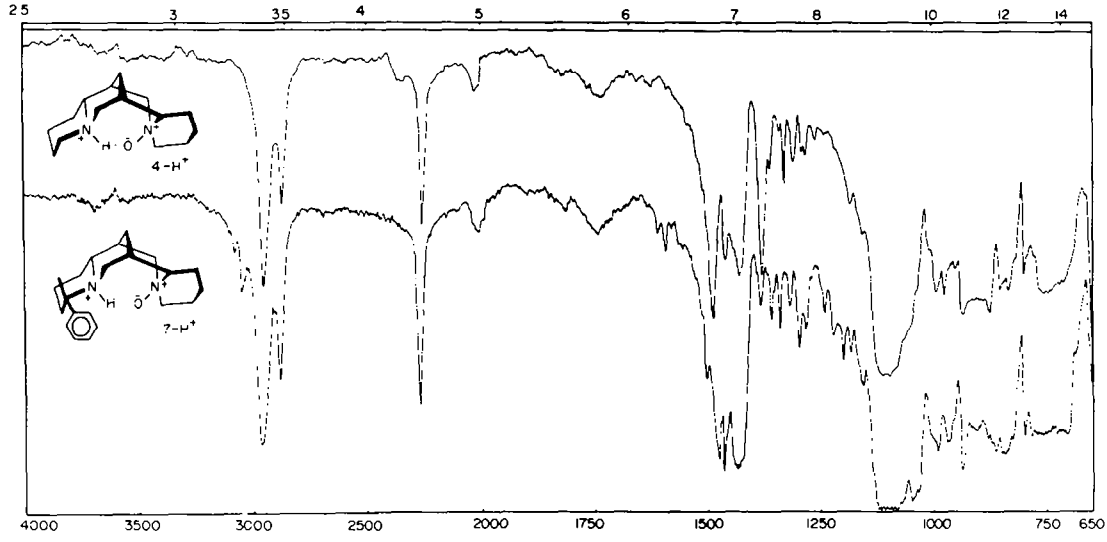


Fig. 1. IR spectra of 4-H^+ and 7-H^+ in $CDCl_3$ solutions.

Spectroscopic and physico-chemical properties of 7 and 7-H^+ forced us to disregard this opinion and to try to find the correct answers to the two essential problems: (a) which factors are responsible for the reaction of H_2O_2 with 2 and with 3 taking place only—or predominantly—on nitrogen atom N_{16}, and (b) which factors are responsible for the increased basicity (proton-acceptor properties) of 7 with reference to 4 and 11?

(1) The behaviour of 2 in the reaction with H_2O_2 shows, that our hitherto view on the mechanism of the reaction 3 with H_2O_2 is erroneous. Observations show, that the site of protonation has no influence on the direction, but only on the rate of reaction. The decisive factor for the site of an efficient attack of the H_2O_2 molecule on one of the two N atoms is the spatial structure of a given diamine. From the observation of a model of the 3-H^+ cation, it is evident, that the N atom N_{16} is more accessible for the attacking H_2O_2 molecule than the N atom N_1. In addition, steric hindrance in 2-H^+, caused by the equatorially situated phenyl group

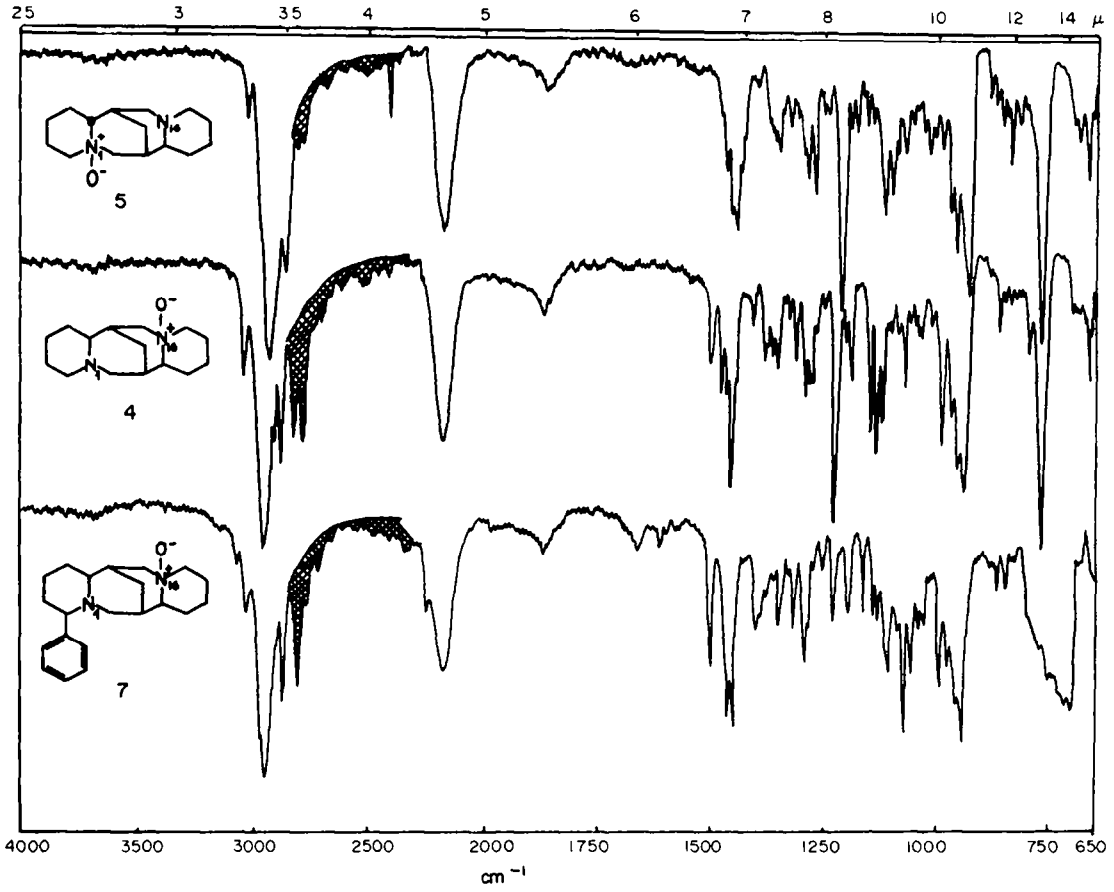


Fig. 2. IR spectra of **5**, **4** and **7** in $CDCl_3$ solutions (circumscribed regions of spectra show the "trans"-band region 2840–2600 cm^{-1}).

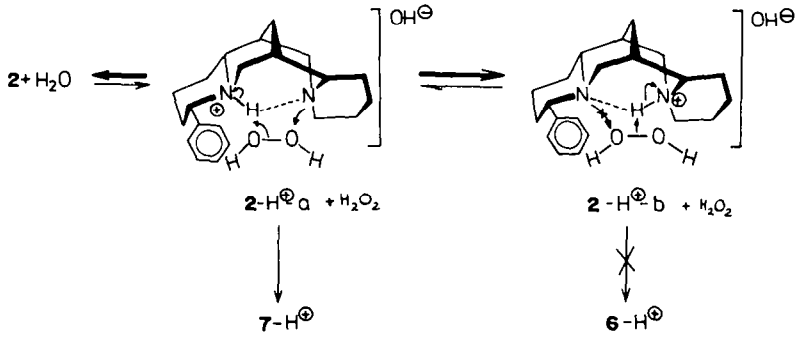
makes the N atom N_1 still less accessible for the reaction with H_2O_2. As a result the attack of the H_2O_2 molecule is directed exclusively to nitrogen N_{16}, and since, it is about 90% protonated, the reaction is about 10-fold retarded against the rate of the reaction of **3** with H_2O_2.

Scheme 5 shows our proposed mechanism of formation of **7** from **2** in an aqueous solution of H_2O_2.

(2) The basicity of **7** and **4** depends on the same proton-acceptor centers: t-amine groups $\rangle N_1$ and N-oxide groups $\rangle N^+_{16}—O^-$ mutually "cisoidally" oriented at such a distance, that in monoprotonated cations short and strong H-bonds are formed.

Of the two centers, the amine groups surely have stronger basic properties. It can be deduced from the higher pK^*_{MCS}-values of these groups in comparison with those of N-oxide groups,† and in the case of **4**-H^+ and **7**-H^+, also from the X-rays evidence,[16] that the "acidic" proton is located on N_1 and not on the N_{16}-oxide oxygen.

†E.g. pK^*_{MCS} of lupanine[9] = 7.47, and its N-oxide[9] = 5.91, so pK^*_{MCS} "NR_3" − pK^*_{MCS}"N^+R_3" = 1.56.



Scheme 5.

The $\rangle N_1$ group of **2** is surely less basic than that of **3**. This is caused by the inductive effect of the phenyl group. In spite of lowered basicity of $\rangle N_1$ in **7**, the nitrogen atom N_1 is a stronger proton-acceptor than the $\rangle N^+_{16}—O^-$ group. The smaller difference in proton-acceptor properties between these centers enables the proton located on N_1 in **7**-H^+ to be more effectively H-bonded by $\rangle N^+_{16}—O$ than in **4**-H^+. Consequently, the intramolecular H-bond in **7**-H^+ should be stronger than in **4**-H^+.

A measure of the strength of the intramolecular H-bond may be the chemical shifts of the bridge proton. In both monocations, these signals are very strongly shifted downfield and appear at 18.2 and 18.8 ppm (δ) for **4**-H^+ and **7**-H^+, respectively.[2] Thus, in **7**-H^+ this proton is more shielded than that of **4**-H^+ ($\Delta\delta = 0.6$ ppm), therefore, the intramolecular H-bond in **7**-H^+ is stronger than that in **4**-H^+.

In this connection, the question arises, whether the decrease in proton-acceptor properties of both closely situated basic centers in **7** is the only one factor, responsible for the higher basicity of **7** as compared with **4**.

An additional factor, which has to be considered is the geometry of the H-bond in **7**-H^+ and **4**-H^+. We assume, that this bond in **7**-H^+ may be not only slightly shorter, but its angle may be closer to 180°, in comparison with the same bond in **4**-H^+. This problem can be resolved by X-rays analysis, which is in progress for[16] both **4**-H^+ and **7**-H^+.

Another difference between **4** and **7** is the monoperchlorate salt of **4** which undergoes further protonation, and, from the aqueous solutions the sesquiperchlorate (2,**4**-3$HClO_4$) can be isolated easily, while it is very difficult to obtain the diperchlorate salt (**4**-2$HClO_4$). The X-rays analysis of 2, **4**-3$HClO_4$[12] confirmed our earlier assumption based on the IR spectra,[13] that the sesquication of **4** is composed of the two monocations (**4**-H^+), which are connected by a symmetrical, very short H-bond between the O atoms of the two N-oxide groups. Favourable spatial factors, which exist within this sesquication, particularly the geometry of the two intramolecular H-bonds and one intermolecular H-bond cause, that this cation (as a perchlorate salt) is very easily isolated from aqueous solutions of **4** in a crystalline form, even in the presence of a large excess of $HClO_4$.

In this respect, **7** is different from **4**. Beside the monoperchlorate, which is formed very easily, we did not obtain any other salt of **7** in crystalline form. We suppose, that there are two factors, which decide that the monocations **7**-H^+ are not ready to be connected by proton in the strong symmetrical intermolecular H-bonds leading to the sesquication (as in 2,**4**-3$HClO_4$):—steric hindrance created by the equatorially situated phenyl substituent, and—very large decrease of the basicity of N-oxide oxygen involved in the very strong intermolecular H-bond in **7**-H^+.

From the inspection of spatial models of **7**-H^+ it is seen, that two cations can be arranged in such a way, as to reach the connection through an intermolecular H bond. This bond would be longer, however, than it is observed in 2,**4**-3$HClO_4$, and also its geometry would be less favourable. May be that in spite of steric hindrance, the sesquication of **7** would be formed, if the oxygen of $N_{16}—O$ group in **7**-H^+ was more basic. But this is not the case as its pK^*_{MCS}-value is equal to only 1.90 (Table 1). In consequence, **7** is—in spite of two formal proton-acceptor centers—a monoproton "sponge", excellent *intra*molecularly stabilised and shielded by the phenyl group from the competitive solvatation by the external molecules.

The structure and the strength of the intramolecular H bond in **7**-H^+ makes **7** an excellent "catcher" of protons, especially in an aprotic medium, and **7**-H^- an interesting cationic part of the salt, created from **7** and weak organic acids.

Investigations on application of **7** as a specific proton "sponge" for the organic synthesis are in progress.

EXPERIMENTAL

General procedure. The IR spectra were recorded by means of a Unicam SP-200G spectrophotometer using 0.4 M solns in $CDCl_3$ and 0.1 mm cells with NaCl windows. The ^1H NMR spectra were recorded by means of an 80MC Tesla BC 487A spectrometer and a 100MC Varian spectrometer using 10% solns in $CDCl_3$ and TMS as the internal standard. The solns in $CDCl_3$ were dried by means of 4Å molecular sieves for 2–3 hr immediately before the recording of the IR or ^1H NMR spectra. The pK^*_{MCS}-values were determined by potentiometric titrations in a mixture of 2-methoxyethanol (MCS) and water 80:20 wt/wt using an automatic device for electrometric titrations (Radiometer SA, Copenhagen). The details of pK^*_{MCS} measurements were described earlier.[9] The elemental analysis were carried out in the Analytical Laboratory of the Institute of Chemistry of the A. Mickiewicz University by means of a Perkin Elmer 240 automatic device. M.p. (uncorrected) were determined with a Tottoli mp. apparatus (Büchi Co. Ltd.).

2-*Phenylsparteine*-N-*oxide perchlorate* (7-$H^+ClO_4^-$). To a soln of **2**[5] (200 mg) in 5 ml MeOH, 0.8 ml 30% H_2O_2 was added, and the mixture kept during 7–8 hr at the room temp. (this reaction can be accomplished in about 2 hr at 40–50°C). The progress of the reaction was controlled by: (a) paper chromatography (disc technique) on Whatman No. 3 ($\phi = 20$ cm), with saturated, aqueous ammonium sulphate as the developing phase; (b) TLC on plastic plates (2.5 × 2.5 cm) covered with silica gel type N-HR/UV_{254} with the mixture of methanol–water–ammonium hydroxide (7:1:2, v/v) as the developing phase. In the first case, the chromatographic spots were made visible by means of iodine vapour, in the second—by means of Dragendorff reagent. Compound **7** formed about fifteen times slower than **4** and **5** from **3**. The excess of H_2O_2 was decomposed with 10% Pd—C(5-10 mg). The mixture was allowed to stand overnight, then, filtered through asbestos and the soln neutralized by means of a mixture of $HClO_4$/MeOH (1:4, v/v). After addition of ethyl ether until the soln became cloudy, it was allowed to stand yielding 260 mg of white crystals, m.p.: 216°, yield: 90%. These crystals were dissolved in about 12 ml EtOH and ethyl ether was added. The resulting crystals (210 mg) of **7**-$H^+ClO_4^-$ were filtered off, washed with 5 ml ethyl ether, yield: 80%, m.p. 216°. (Found: C, 57.08; N, 6.26; H, 7.54. Calc. for $C_{21}H_{30}ON_2 \cdot HClO_4 \cdot H_2O$ (m.w. 444): C, 56.75; N, 6.30; H, 7.43%). IR spectrum ($CDCl_3$): no evidence of ν_{N^+-H} (free and bonded), 3040 (w, ν_{C-H} aromatic), 2960 (s, ν_{C-H}), 2840–2600—no "*trans*"-band,[15] 2260 (s, ν_{C-D} from $CDCl_3$ associated with proton acceptor centers of **7**-H^+), minima at 950, 810, 665, connected with the very strong H-bond, cm^{-1}. NMR ($CDCl_3$): δ 7.55 (5H, aromatic), 18.8 (1H, $N^+—H$).

Free base **7** *from perchlorate salt.* Compound **7**-$H^+ClO_4^- \cdot H_2O$ (100 mg) was dissolved in a separatory funnel in 5 ml water, made strongly alkaline with KOH pellets, and exhaustively extracted (Dragendorff's test) with ethyl ether. The combined etheral extracts were dried with KOH pellets and the ether was evaporated under reduced pressure. The residue was dissolved in petroleum ether: at the beginning oil was precipitated, which progressively turned into **7** as crystals. 70 mg, yield 95%; m.p.: 105°. (Found: C, 73.20; N, 8.00; H, 9.26. Calc. for $C_{21}H_{30}ON_2 \cdot H_2O$ (m.w. 344): C,

73.26; N, 8.14; H, 9.30%). IR spectrum of **7** (see Fig. 2). The pK^{*}_{MCS}-values: (1) = 1.90, (2) = 12.85. $[\alpha]^{20}_{D} = -5.7$ (EtOH, c = 1.0). The reaction of **7** with SO_2 was performed in H_2O[8] (in analytical scale). The reaction course was controlled by means of TLC and paper chromatography, and with the parallel reactions of **4** (and **5**) with SO_2.

An attempt of further protonation of 7-$H^{+}ClO_4^{-}\cdot H_2O$. Compound 7-$H^{+}ClO_4^{-}\cdot H_2O$ (50 mg) was dissolved in 2 ml MeOH and the mixture of $HClO_4$/MeOH (1:4, v/v) was added to pH 2. After addition of ethyl ether, the mixture was allowed to stand but yielded 45 mg of unchanged substrate. Other attempts to transform **7** into the 7-$2HClO_4$ or 2,7-$3HClO_4$ were without success.

Acknowledgement—The authors are indebted to Dr. J. Skolik for pK^{*}_{MCS} measurements and discussions.

REFERENCES

[1]Z. Kałuski, A. I. Gusiew, Ju. T. Struczkow, J. Skolik, P. Baranowski and M. Wiewiórowski, *Bull. Acad. Polon. Sci., Ser. sci. chim.* XX, **1**, 1 (1972).
[2]J. Skolik, K. Łangowska and M. Wiewiórowski, *Ibid.* XX, **5**, 383 (1972).
[3]J. Skolik, K. Łangowska and M. Wiewiórowski, *Ibid.* XXIII, **3**, 215 (1975).
[4]M. D. Bratek-Wiewiorówska, J. Skolik, K. Łangowska and M. Wiewiórowski, *Ibid.* XXII, **12**, 1025 (1974).
[5]Wł. F. Boczoń and M. Wiewiórowski, in preparation (1977).
[6a]T. Borowiak, N. G. Bokij and Ju. T. Struczkow, *Ż. Strukturnoj chimii* XIV, **2**, 387 (1973);
[b]T. Borowiak, N. G. Bokij, Ju. T. Struczkow and M. Wiewiórowski, *Bull. Acad. Polon. Sci., Ser. sci. chim.*, in preparation (1977).
[7]M. Wiewiórowski and P. Baranowski, *Bull. Acad. Polon. Sci., Ser. sci. chim.* X, **10**, 549 (1962).
[8]P. Baranowski and M. Wiewiórowski, *Ibid.* XII, **11**, 761 (1964).
[9]M. Wiewiórowski and J. Skolik, *Ibid.* XI, **2**, 69 (1963).
[10]J. Skolik, M. Wiewiórowski and P. J. Krueger, *J. Mol. Structure* **5**, 461 (1970).
[11]H. Małuszyńska and Y. Okaya, *Acta Crystallogr.* B, in press (1977).
[12]S. N. Srivastava and M. Przybylska, *Ibid.* **B25**, 1651 (1969).
[13]M. Wiewiórowski and P. Baranowski, *Bull. Acad. Polon. Sci., Ser. sci. chim.* X, **10**, 537 (1962).
[14]P. Baranowski, J. Skolik and M. Wiewiórowski, *Tetrahedron* **20**, 2383 (1964).
[15]J. Skolik, P. J. Krueger and M. Wiewiórowski, *Ibid.* **24**, 5439 (1968).
[16]According to our suggestion, the X-rays analysis of 4-$H^{+}ClO_4^{-}$ has been performed by Dr. Z. Kałuski, and of 7-$H^{+}ClO_4^{-}$ by Dr. H. Małuszyńska. The structure of 7-$H^{+}ClO_4^{-}$ has been determined and sent to press.[11] It has been shown that the length of N_1–H ... O H-bond is 2.471 Å, and its angle is 161°.