Reaction of Tetrahydrobenz[*a*]acridinones with Hydroxylamine Hydrochloride. VII

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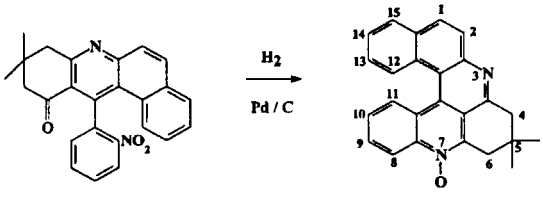
Received June 23, 1994
Revised September 14, 1994

Oximation of *ortho*-substituted phenylbenz[*a*]acridinones using hydroxylamine hydrochloride, sodium hydroxide and ethanol as the solvent gave always the benzoquinacridine *N*-oxide **2**. Oximation of *para*-substituted phenylbenz[*a*]acridinones, however, gave only the corresponding oximes. The structure of all products was corroborated by ir, ^{1}H and ^{13}C-nmr and mass spectral data. Theoretical calculations support the experimental findings.

J. Heterocyclic Chem., **32**, 827 (1995).

There have been several reports on the biological aspects of benzacridines and its analogs. Some of these compounds are known to have activities as carcinogenic [3], enzyme inhibitors [4], antimalarial [5] and other pharmacological properties [6]. As a part of a program directed toward the synthesis and spectral properties of heterocyclic derivatives with possible pharmacological activity we have described recently that catalytic hydrogenation of *ortho*-nitrophenylbenzacridinone **1** using Pd/C as the catalyst afforded benzoquinacridine *N*-oxide **2** (Scheme 1) [7].

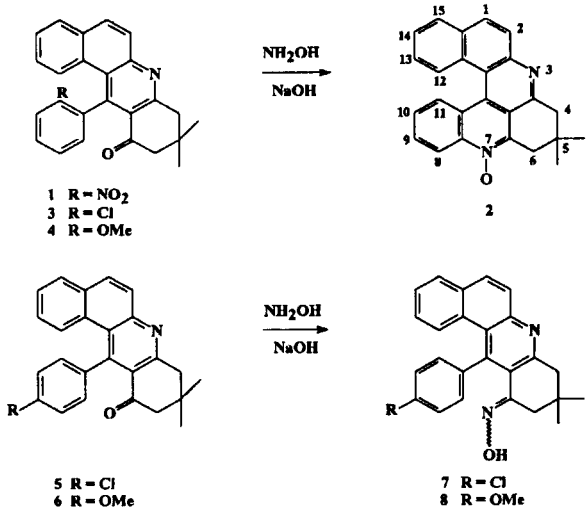
Scheme 1



1 2

To explore the unknown reactivity of benz[*a*]acridinones and with the aim to find new compounds with possible biological activity we describe in this report the behavior of compounds **1** and **3** to **6** under oximation conditions (Scheme 2) using hydroxylamine hydrochloride and ethanol as solvent [8]. *Ortho* and *para*-substituted tetrahydrobenz[*a*]acridinones **3-6** have been prepared following reported procedures. The structures of these compounds were supported by ir, ^{1}H and ^{13}C-nmr and mass spectral data that were similar to those reported [9].

Scheme 2



In a typical procedure 12-(*ortho*-nitrophenyl)benz[*a*]-acridin-11-one **1**, hydroxylamine hydrochloride and sodium hydroxide were refluxed in ethanol on a steam bath to give **2** as a yellow compound. Structural assignment of **2** was made on spectroscopic grounds. The infrared spectrum of **2** displayed absorptions at 1564 and 1320 cm^{-1} that were assigned to C=N and N-O stretching, respectively. The presence of ions at m/z 364 (M$^+$), 348 and 347 in its mass spectrum was consistent with the existence of an *N*-oxide moiety in the framework of **2**. The ^{1}H-nmr spectrum of **2** showed typical signals for the acridine skeleton: two singlets (3H each) at δ 1.22 and δ 1.25 for the methyl protons joined to C-5; two two-proton signals at δ 3.19 (AB, J = 13 Hz) and δ 3.45 (singlet) for methylene protons joined to C-

6 and C-4 and ten signals, one proton each, among δ 9.01-δ 7.40 in the aromatic region. All the above data agree with the structure of 5,5-dimethyl-4*H*-benzo[*a*]quin[2,3,4-*kl*]-acridine 7-oxide **2** [7]. The general run of this reaction was tested with the 12-*ortho*-chlorophenylbenz[*a*]acridinone **3** and the 12-*ortho*-methoxyphenylbenz[*a*]acridinone **4** that were treated as was compound **1** and they also afforded **2** as the only product.

The oximation of the 12-(*p*-chlorophenyl)benz[*a*]-acridin-11-one **5** under similar conditions as for **1**, however, gave a mixture of oximes **7** (*syn/anti*). In the infrared spectra of **7** the appearance of bands at 3590-3200 and 1645 cm^{-1} was consistent with the presence of an oxime group. In agreement with the suggested structure the ^{1}H-nmr spectra of compound **7** exhibited two down-field one proton broad signals at δ 7.26 and δ 8.1 which exchange upon introduction of deuterium oxide. One three proton signal at δ 1.1 was assigned to the methyl protons of C-9. Two-proton signals at δ 3.0 and δ 2.7 were assigned to the methylene protons joined to C-8 and C-10 and ten signals, one proton each, among δ 8.1-δ 7.1 in the aromatic region. The mass spectrum of the compound showed the molecular ion at m/z 400 (10% relative abundance) and its fragmentation is according to the assigned structure. When the 12-(*p*-methoxyphenyl)benz[*a*]acridin-11-one **6** was treated as was compound **5** gave also a mixture of oximes **8** (*syn/anti*). The infrared and ^{1}H-nmr spectra of compound **8** were consistent with the assigned structure therefore it is not discussed in detail.

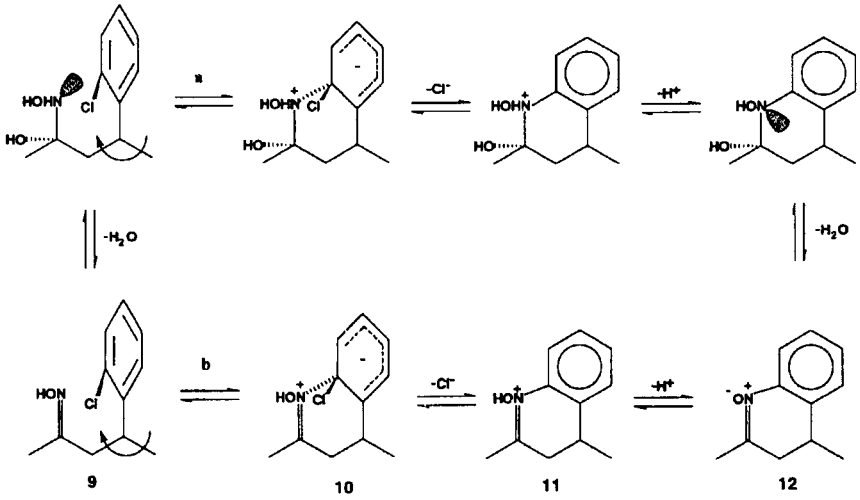
The reaction was also theoretically investigated by AM1 semiempirical method included in the MOPAC 6.0 package [9]. The aim of this investigation was to determine the influence of structure on the reaction course. For the realization of a theoretical model of the ring closure reaction, an initial choice of a hypothetical mechanism is required. In agreement with the literature [10] the reaction can be schematized in at least two different pathways (Scheme 3): a) ring closure without formation of oxime and b) ring closure with formation of an oxime.

The barriers of rotation of the phenyl group on the ketone and oximes derivatives showed it possesses free rotation on an interval of 120° since there exists a steric interaction between the *ortho*-R substituent with the ketone oxygen, the oxime nitrogen and the hydrogen of C-1, respectively. Also the phenyl group is almost perpendicular (104° or 76°) with respect to the ring B. In spite of the fact that the system has three aromatic rings it is not planar; the D ring has a deviation of 22° with respect to the B ring. The barrier of rotation between the N-O bond of the hydroxylamine was also analyzed because the formation of the oxime was carried out approaching the hydroxylamine by the two faces of the ketone. A local minimum was found at 180°, thus the interaction between the ketone and the hydroxylamine will be only of electronic character [11].

The anti approach of the hydroxylamine with respect to the *ortho*-chlorine atom gave a curve that did not show a minimum in the bond region, although when an asymptotic zone was totally optimized gave a bond distance of 1.55 Å. The next step was the deprotonation and departure of a molecule of water. In this case the energy did not decline uniformly, on the contrary, there was a local minimum at 1.6 Å. This presumably was due to electronic interactions of the hydrogen of the water with the *ortho* chlorine atom.

The syn attack of the hydroxylamine to the ketone showed a local minimum at 1.6 Å. When the positively charged species was deprotonated the two functional groups of interest for ring closure were on the same side. If the reaction mechanism, however, followed pathway 3a, there was a distance of 2.1 Å between C-2' and the oxime nitrogen and a bond order of 0.3; this means it was

Scheme 3



not a completely formed bond. The mechanism of formation of the oxime was completed with the elimination of one molecule of water. In the two cases analogous curves were found with the difference that the second approach was more energetic than the first because there were many functional groups on the same side of the molecule [11].

In accord with the Scheme 3b, the new intermediates were calculated by rotating the phenyl group with minor increments on the angle of rotation ϕ (the torsion angle ϕ:C11a-C12-C1'-C2') which achieved the corresponding optimization at the vicinity of the site of reaction. The initial portion of the curve was as the barriers of rotation obtained above, but upon arriving at an angle of 55°, we began to observe electronic interactions of the molecule. This was reflected in a reduction of IP and the LUMO energy. Furthermore, the drastic change of the dipole moment anticipated the presence of a dipole; this was reflected in the molecular orbital contributions at an angle of 60° (the angle where a minimum was observed) which was found at the HOMO of the *ortho*-chlorine atom and at the LUMO of C-11. The distance of the C-2' and the oxime-nitrogen, with an angle of rotation of 60°, was 1.93 Å with an order of union of 0.9275. In addition the chlorine atom was 90° with respect to the plane of the phenyl group, with a distance of 2.0 Å and an order of union of 0.6257, which indicated that the chloride ion could depart. On the other hand at a rotation angle of 50°, the negative charge began to delocalize on the phenyl group due to the electronic interactions of the oxime nitrogen with C-2'; this was reflected in the contribution of the HOMO (Table 1).

Table 1

Torsional Angle and Physicochemical Properties

ϕ degrees	ΔH_f kcal/mol	IP eV	$-\varepsilon_{LUMO}$ eV	HOMO		LUMO	
0	98.03	8.61	0.783	0.34348 C5 pz	0.32510 C11a pz	0.35253 C5 pz	0.32430 C7a pz
10	99.93	8.62	0.815	0.34242 C5 pz	0.33547 C11a pz	0.34426 C5 pz	0.32721 C12 pz
20	105.84	8.62	0.854	0.34624 C11a pz	0.33889 C5 pz	0.33817 C12 pz	0.33295 C5 pz
30	117.15	8.62	0.897	0.35665 C11a pz	0.33393 C5 pz	0.34360 C12 pz	0.32090 C5 pz
40	134.17	8.63	0.945	0.36651 C11a pz	0.31960 C5 pz	0.34565 C12 pz	0.30730 C5 pz
45	144.53	8.62	0.967	0.34755 C11a pz	0.29302 C6 pz	0.34657 C12 pz	0.29769 C5 pz
50	155.89	8.55	0.985	0.35752 C2' pz	0.32884 C1' pz	0.34644 C12 pz	0.28789 C5 pz
55	167.56	8.24	1.020	0.36419 C2' px	0.35164 C1' pz	0.33937 C11a pz	0.28551 C5 pz
60	148.99	7.57	1.591	0.39532 Cl pz	0.35172 C1' pz	0.27893 C7a pz	0.26866 NOH pz
65	155.28	7.56	1.647	0.46972 Cl pz	0.31797 C1' pz	0.27503 C7a pz	0.27282 NOH pz

Table 2

Physicochemical Properties for the Ring Closure

Entry	ΔH_f kcal/mol	IP eV	$-\varepsilon_{LUMO}$ eV	HOMO		LUMO	
9	98.29	8.62	0.779	0.34452 C5 pz	0.32451 C4 pz	0.36481 C11a pz	0.35407 C5 pz
10	148.90	7.57	1.591	0.39532 Cl pz	0.35172 C1' pz	0.49287 C11 pz	0.27893 C7a pz
11	259.03	11.71	5.308	0.43043 C1 pz	041987 C4 pz	0.46659 C11 pz	0.31402 C12 pz
12	120.44	8.24	1.147	0.38133 C=O pz	0.35267 C11 pz	0.31953 C7a pz	0.27087 C12a pz

The total optimization of the system gave a distance C(2')-NOH of 1.41 Å with an order of union of 0.9989. The loss of a chloride ion caused a positive charge that was eliminated by the deprotonation of the oxime oxygen. The last step was the energy barrier that would be surmounted (Table 2) to get the additional ring.

These results provide evidence that the spatial arrangement of the *ortho*-substituted phenyl group and the oxime nitrogen is the driving force for this intramolecular reaction to occur. Similar aromatic nucleophilic denitrocyclization reactions, which involve displacement of the nitro group by a nitrogen nucleophile has been described [12] under different conditions. Further investigation of the general course of this reaction is presently being carried out with cyclic nitroketones.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^1H, COSY and decoupled nmr spectra were determined on a Varian FT-200 instrument; the ^{13}C and ^1H-^{13}C nmr spectra were determined on a Varian FT-300 instrument. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Hewlett-Packard 59854-A quadropole mass spectrometer.

Reaction of 12-(*ortho*- and *para*-R-Phenyl)-9,9-dimethyl-,8,9,10,11-tetrahydrobenz[*a*]acridin-11-ones with Hydroxylamine Hydrochloride.

General Procedure (R = *ortho*-NO_2).

To a solution of **1** (0.5 g, 1.26 x 10^{-3} mole) dissolved in 15 ml of ethanol was added a solution of 1.95 g (2.8 x 10^{-3} mole) of hydroxylamine hydrochloride dissolved in 15 ml of 5 *M* sodium hydroxide and the mixture was stirred on a steam-bath for three hours. Removal of the solvent under reduced pressure gave an amorphous solid that was separated by column chromatography (silica gel: hexane-ethyl acetate 6:4) to give 0.335 g (78%) of **2**, mp 238° (lit [7] 240°); ir (neat): ν cm^{-1} 2960, 1564, 1320; ^1H-

nmr (deuteriochloroform): δ 1.22 (s, 3H, CH_3-), 1.25 (s, 3H, CH_3-), 3.19 (dd, 2H, H-6), 3.45 (s, 2H, H-4), 7.40 (ddd, 1H, H-13), 7.49 (ddd, 1H, H-10), 7.61 (ddd, 1H, H-14), 7.88 (ddd, 1H, H-9), 7.95 (d, 1H, H-15), 8.04 (d, 1H, H-2), 8.13 (d, 1H, H-1), 8.52 (d, 1H, H-12), 8.68 (d, 1H, H-11), 9.01 (d, 1H, H-8); ms: m/z 364 (M^+), 349, 348, 347.

Compound **3** (R = *o*-Cl; 0.5 g, 1.3 x 10^{-3} mole) and compound **4** (R = *o*-OMe; 0.5 g, 1.4 x 10^{-3} mole) were allowed to react according to the procedure described above. They gave also compound **2** in 67% (0.31 g) and 65% (0.32 g) yield, respectively.

Compound **5** (R = *p*-Cl; 0.5 g, 1.3 x 10^{-3} mole) was allowed to react according to the procedure described above. Removal of the solvent under reduced pressure followed by recrystallization from methylene chloride-hexane gave 0.39 g (75%) of **7** mp 253°; ir (neat): ν 3590-3200 (N-OH), 1645 (C=N) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.1 (s, 6H, 2 x CH_3), 2.7 (s, 2H, H-10), 3.0 (s, 2H, H-8), 7.26 (NOH, deuterium oxide-exchangeable), 7.1-8.0 (m, 10H); ms: m/z 400 (M^+), 399 (100).

Compound **6** (R = *p*-OMe; 0.5 g, 1.3 x 10^{-3} mole) was allowed to react according to the procedure described above. Removal of the solvent under reduced pressure followed by recrystallization from methylene chloride-hexane gave 0.43 g (82%) of **8** mp 240°; ir (neat): ν 3300-3200 (N-OH), 1645 (C=N) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.1 (s, 6H, 2 x CH_3), 2.7 (s, 2H, H-10), 3.0 (s, 2H, H-8), 3.9 (3H, OCH_3), 10.0 (NOH, deuterium oxide-exchangeable), 6.95-8.0 (m, 10H); ms: m/z 396 (M^+), 395 (100).

Acknowledgements.

We wish to thank R. Patiño, R. Gaviño, A. Gutiérrez, J. Pérez and L. Velasco for their assistance in the acquisition of the ir, ^{1}H- and ^{13}C-nmr and mass spectral data.

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