Reactions on the Dimethylphenylbenzacridinones. VI [1]. Hydrogenation of *ortho*-Nitrophenyl Derivatives

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Received March 22, 1993
Revised January 27, 1994

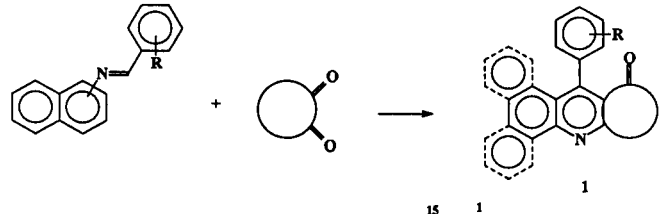
Catalytic hydrogenation of *o*-nitrophenylbenz[*a*], benz[*c*], dibenz[*a,h*] and dibenz[*a,g*]acridinones using Pd/C as catalyst, at 60 psi of pressure, gave the hiterto unknown benzoquinoacridine *N*-oxides and benzopyranonaphthyridine *N*-oxides. The structure of all products was corroborated by ir, ^{1}H- and ^{13}C-nmr and mass spectra data.

J. Heterocyclic Chem., **31**, 1061 (1994).

As a part of a program directed towards the synthesis and spectral properties of heterocyclic derivatives with possible pharmacological activity we have described recently that the cyclic 1,3-dicarbonylic compounds *i.e.* dimedone, addition to 1- or 2-arylidenenaphthylamines affords benzacridinones **1** [4] instead of the benzophenanthridinones [5].

There have been several reports on biological aspects of benzacridines and its analogs. Some of these compounds are known to have activities as carcinogenic [6], enzyme inhibitors [7], antimalarial [8] and other pharmacological properties [9]. In order to explore the unknown reactivity of compounds **2, 3, 4, 5,** and **6** and with the aim to find new compounds with possible biological activity we describe in this report the behavior of these compounds under catalytic hydrogenation using Pd/C as catalyst and ethanol as solvent.

Compounds **2-6** have been prepared following reported procedures [4]. 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.



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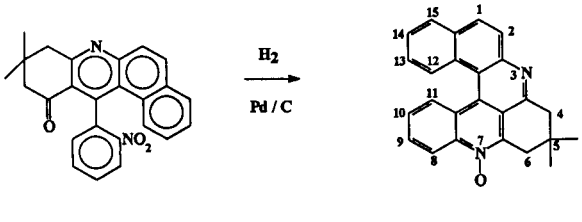

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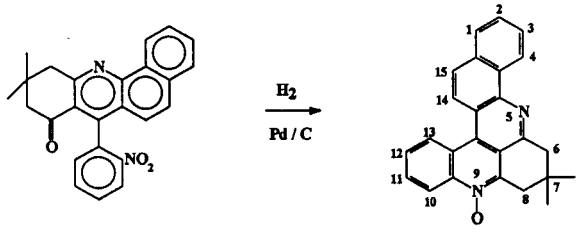

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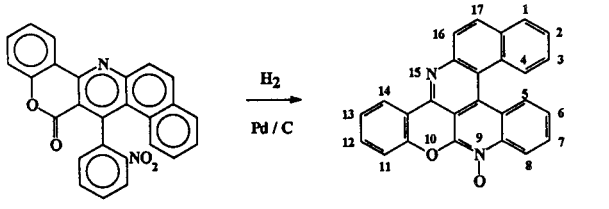
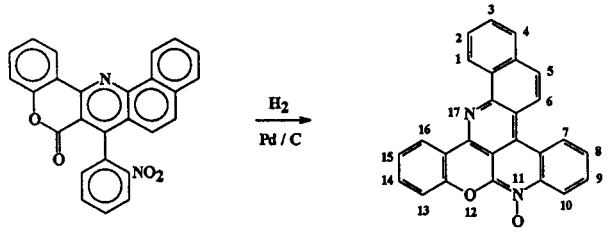
In a typical procedure 12-(*ortho*-nitrophenyl)benz[*a*]acridin-11-one **2** was hydrogenated at 60 psi of pressure in ethanol over Pd/C as catalyst to give **7** as a yellow compound. Structural assignment of **7** was made on spectroscopic grounds. The infrared spectrum of **7** displayed absorption 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 the *N*-oxide moiety in the framework of **7**.

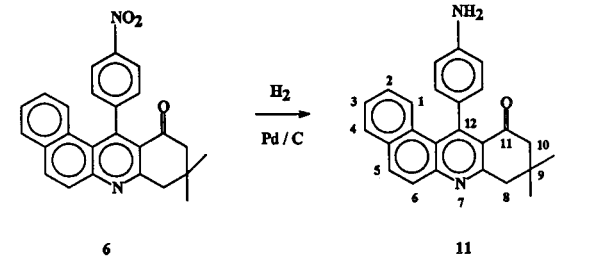
The ^{1}H-nmr spectrum of **7** showed two singlets (3H each) at δ 1.22 and δ 1.25 for the methyl protons joined to C-5. Two two-proton signals at δ 3.19 (ABq, J = 13 Hz) and δ 3.45 (singlet) were assigned to the methylene protons joined to C-6 and C-4, respectively. The identification of ten signals, one proton each, in the aromatic region was carried out through decoupling experiments. The irradiation of the signal at δ 9.01 (d, J = 8 Hz, H-8) simplified the signal centered at δ 7.88 (ddd, J = 8, 7.8, 1.4 Hz, H-9). The irradiation of the last signal simplified the signals at δ 9.01 (H-8) and δ 7.49 (ddd, J = 8, 7.8, 1.3 Hz, H-10). Similarly the irradiation of the signal at δ 8.52 (d, J = 8 Hz, H-12) allowed identification of the signal of H-13 at δ 7.40 (ddd, J = 7.5, 7.5, 1.4 Hz) and H-14 at δ 7.61 (ddd, J = 7.5, 7.5, 1.2 Hz). Irradiation of signal at δ 7.95 assigned to H-15 (d, J = 7.5 Hz) also simplified the signal at δ 7.61 (H-14). The

clear ABq (J_{AB} = 8.8 Hz) at δ 8.04 and δ 8.13 was assigned to H-2 and H-1, respectively. Finally, the signal at δ 8.68 (d, J = 8 Hz) was assigned to H-11. The ^{13}C-nmr spectrum of **7** and ^{1}H-^{13}C correlation (HETCOR) confirmed the structure proposed.

The general run of this reaction was tested with the *o*-nitrophenylbenzacridinones **3, 4** and **5** that were hydrogenated as was compound **2**. The hydrogenation of compounds **3, 4** and **5** afforded compounds **8, 9** and **10**. All of them exhibited characteristic absorption in the infrared spectra (nujol) at 1564 and 1320 cm^{-1} of -C=N- and -N-O- stretching in agreement with theirs suggested structures. Further information of the structure of **8, 9** and **10** was derived from their mass spectral data. All the compounds showed the molecular ion and the characteristic peaks at m/z (M-16) and m/z (M-17) for the *N*-oxide moiety [10]. Unfortunately, the ^{1}H-nmr data of these compounds ar not given due to their insolubility in solvents normally used in this analysis.







The hydrogenation of the 12-(*p*-nitrophenyl)benz[*a*]acridin-11-one **6** under similar conditions as for **2** gave compound **11**. The infrared spectra (chloroform) showed very strong bands at 3300-3200 cm^{-1} (amine) and 1690 cm^{-1} (ketone carbonyl). The signal at δ 198 in the ^{13}C-nmr spectrum of **11** supported the existence of a ketone carbonyl moiety in its framework. The ^{1}H-nmr spectrum of **11** showed one singlet (6H) at δ 1.1 for the methyl protons joined to C-9. Two two-proton singlets at δ 2.45 and δ 3.27 were assigned to the methylene protons joined to C-10 and C-8, respectively. Likewise, it showed a series of eight signals in the aromatic region as follow: a doublet at δ 7.84 (J = 8.8 Hz) for H-5, a doublet at δ 7.73 (J = 8.8 Hz) for H-6, a partially split doublet at δ 7.66 (J = 7.8, 1.0 Hz) for H-4 and other doublet at δ 7.36 (J = 7.8 Hz) for H-1. In addition there are two doublets of doublets at δ 7.29 (dd, J = 7.8, 7.8 Hz) and δ 7.01 (dd, J = 7.8, 7.8 Hz) for H-3 and H-2. The AA'BB' system for the protons of 12-phenylamine substituent appeared at δ 6.80 (J = 8.4 Hz) and δ 6.67 (J = 8.4 Hz). The ^{1}H-^{1}H COSY experiment provides definitive assignments for all protons.

These results suggested that the spatial disposition of the *o*-nitrophenyl and the ketone carbonyl group is the driving force for this intramolecular reaction to occur. Similar ring closure of γ-nitroketones [11,12] have been reported, however they have been accomplished with zinc and acetic acid. Further investigation of the general run of this reaction is presently being carried out with cyclic γ-nitroketones.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H-, COSY and decoupling nmr spectra were determined on a Varian FT-200 instrument; the ^{13}C- and ^{1}H-^{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.

Synthesis of 5,6-Dihydro-5,5-dimethyl-4*H*-benzo[*a*]quino[2,3,4-*kl*]-acridine 7-Oxide, **7**.

General Procedure.

Compound **2** (0.5 g, 1.26 x 10^{-3} mole) dissolved in ethanol (25 ml) was hydrogenated over 10% Pd/C (5 x 10^{-2} g) at 60 psi of pressure. The reaction was followed by tlc (hexane-ethyl acetate, 8:2) and after 5 hours the substrate disappeared. The solution was filtered through celite, the solvent was removed under reduced pressure and the residue was recrystallized from dichloromethane-hexane to yield 0.38 g (82%) of **7**, mp 240°; ir (neat): ν cm^{-1} 2960, 1564, 1320; ^{1}H-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), 7.4 (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); ^{13}C-nmr (deuteriochloroform): δ 28.5 (q, CH_3), 28.7 (q, CH_3), 31.1 (s, C-5), 39.3 (t, C-4), 46.6 (t, C-6), 120.0 (d, C-8), 124.5 (s, C-15a), 125.3 (d, C-13), 126.5 (d, C-10), 127.3 (d, C-2), 127.3 (d, C-14),

128.0 (d, C-12), 128.2 (d, C-15), 128.5 (d, C-11), 128.6 (s, C-11d), 129.4 (s, C-11b), 131.5 (d, C-1), 131.6 (d, C-9), 132.7 (s, C-11c), 140 (s, C-6b), 143.3 (s, C-11a), 146.7 (s, C-6a, 7a), 157.0 (s, C-2a, 3a); ms: m/z 364 (M+), 349, 348, 347.

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.38; H, 5.54. Found: C, 82.32; H, 5.50.

Synthesis of 7,8-Dihydro-7,7-dimethyl-6*H*-benzo[*c*]quino[2,3,4-*kl*]-acridine 9-Oxide, **8**.

Compound **3** (0.5 g, 1.26 x 10^{-3} mole), ethanol (50 ml) and 10% Pd/C (5 x 10^{-2} g) was allowed to react according to the procedure described above. The desired product was formed in 77% yield (0.35 g), mp 186-188°; ir (neat): ν cm^{-1} 2960, 1564, 1320; ms: m/z 364 (M+), 349, 348, 347.

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.38; H, 5.54. Found: C, 82.33; H, 5.50.

Synthesis of Benzo[*c*][1]benzopyrano[4,3,2-*ij*]naphtho[1,2-*f*][2,7]-naphthyridine 9-Oxide, **9**.

Compound **4** (0.5 g, 1.2 x 10^{-3} mole), ethanol (50 ml) and 10% Pd/C (5 x 10^{-2} g) was allowed to react according to the procedure described above. The desired product was formed in 69% yield (0.296 g), mp >300°; ir (neat): ν cm^{-1} 2960, 1564, 1320; ms: m/z 386 (M+), 370, 369.

Anal. Calcd. for $C_{26}H_{14}N_2O_2$: C, 80.81; H, 3.65. Found: C, 80.77; H, 3.62.

Synthesis of Benzo[*c*][1]benzopyrano[4,3,2-*ij*]naphtho[2,1-*f*][2,7]-naphthyridine 11-Oxide, **10**.

Compound **5** (0.5 g, 1.2 x 10^{-3} mole), ethanol (50 ml) and 10% Pd/C (5 x 10^{-2} g) was allowed to react according to the procedure described above. The desired product was formed in 41% yield (0.189 g), mp 265°; ir (neat): ν cm^{-1} 2960, 1564, 1320; ms: m/z 386 (M+), 370, 369.

Anal. Calcd. for $C_{26}H_{14}N_2O_2$: C, 80.81; H, 3.65. Found: C, 80.78; H, 3.61.

Synthesis of 12-(*p*-Aminophenyl)-9,9-dimethyl-8,9,10,11-tetrahydrobenz[*a*]acridin-11-one **11**.

Compound **6** (0.5 g, 1.26 x 10^{-3} mole), ethanol (50 ml) and 10% Pd/C (5 x 10^{-2} g) was allowed to react according to the procedure described above. The desired product was formed in 69% yield (0.319 g), mp 236°; ir (chloroform): ν cm^{-1} 3350, 1680; ^{1}H-nmr (deuteriochloroform): δ 1.1 (s, 6H, 2 x CH_3-), 2.45 (s, 2H, H-10), 3.27 (s, 2H, H-8), 6.67 (d, 2H, H-3', 5'), 6.80 (d, 2H, H-2', 6'), 7.01 (dd, 1H, H-2), 7.29 (dd, 1H, H-3), 7.36 (d, 1H, H-1), 7.66 (dd, 1H, H-4), 7.73 (d, 1H, H-6), 7.84 (d, 1H, H-5); ^{13}C-nmr (deuteriochloroform): δ 27.0 (2 x CH_3), 32.0 (C-9), 47.3 (C-8), 54.3 (C-10), 123.4, (C-4a), 124.1 (C-11a), 125.4 (C-2), 125.9 (C-3), 127.0 (C-1), 127.8 (C-6), 128.1 (C-4), 130.4 (C-12b), 132.3 (C-5), 133.4 (C-12a), 146.3 (C-12), 150.0 (C-6a), 159.6 (C-7a), 198.0 (C-11); ms: m/z 366 (M+), 351.

Anal. Calcd. for $C_{25}H_{22}N_2O$: C, 81.93; H, 6.06. Found: C, 81.90; H, 5.96.

Acknowledgements.

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

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