hydrated anilinium ion over that of the hydrated cyclopropylammonium ion.

In the gas phase, however, anilinium ion is more stabilized than cyclopropylammonium ion by the polarization effect, which tends to offset the "resonance" effect in aniline. Thus there is a substantial increase (~3 kcal) in the gas-phase base strength of aniline compared to cyclopropylamine. In the carbocations, greater polarization stabilization by phenyl than cyclopropyl also presumably occurs (as well as the π electron delocalization, which favors the dicyclopropylethyl cation), but in the absence of the hydrogen-bonding solvation the relative combination of polarization and resonance effects in the carbocations is not changed in solution compared to the gas phase.

Finally, we call attention to the wide variety of sizes, shapes, and carbon content (8–17) of the carbocations involved in Figure 1, as well as the nearly 25-kcal range of structural effects, as evidence supporting the ideas expressed on cation solvation. The methods used for the gas-phase equilibrium constant determinations have been described in detail.[21]

Registry No.—1,2,3,4-Tetramethylbenzene, 488-23-3; hexamethylbenzene, 87-85-4; guaiazulene, 489-84-9; azulene, 275-51-4; 1,1-dicyclopropylethylene, 822-93-5; 1,2-di-*p*-tolylethylene, 2919-20-2; 1,1-diphenylethylene, 530-48-3; (1-methylethenyl)benzene, 98-83-9.

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(1) This work was supported in part by a grant from the Public Health Service.
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(7) This conclusion was first clearly recognized by E. M. Arnett and J. F. Wolf, *J. Am. Chem. Soc.*, **95**, 978 (1973), for alkyl substituent effects in phosphonium and sulfonium ions in fluorosulfuric acid solutions; cf. also E. W. Bittner, E. M. Arnett, and M. Saunders, *ibid.*, **98**, 3734 (1976).
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(9) Cf. E. M. Arnett in ref. 3, Chapter 3.
(10) Similar considerations may prevail for anions. J. E. Bartmess and R. T. McIver, Jr., *J. Am. Chem. Soc.*, in press, have recently presented evidence that alkyl polarizability effects dominate in the relative enthalpies of ionization of alkyl mercaptans in water, but that these effects contribute little to the corresponding quantities for ionization of alcohols in water. The poorer dispersal of charge from mercaptide than alkoxide ions through hydrogen bond acceptor interactions with water appears to be a reasonable interpretation.
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(12) The polarizability and inductive effects of alkyl groups on the gas-phase basicities of amines are correlated by σ_I values, cf. R. W. Taft and L. S. Levitt, *J. Org. Chem.*, **42**, 916 (1977). This consideration makes it difficult to readily dissect their relative contributions, or, in fact, to learn whether these effects are parallel or opposed in a given type of ion.
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(17) Cf. footnote 7 of ref. 11.
(18) E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.*, **88**, 1177 (1966).
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Approaches to the Mitomycins. Photochemistry of Aminoquinones

Kenneth J. Falci, Richard W. Franck,* and Gregory P. Smith

Department of Chemistry, Fordham University, Bronx, New York 10458

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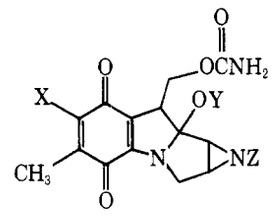
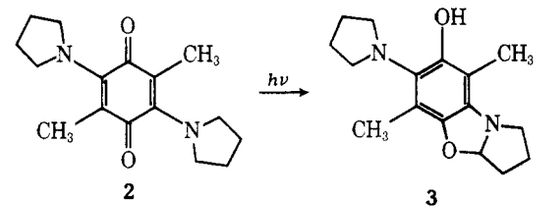
The mitomycin antibiotics (**1**) have been the subject of a wide variety of synthetic endeavors.[1] Very little experimentation has been described that deals with the problem of the introduction of oxygen functionality at the α carbon of the pyrrolidine ring. Toward this goal, we have examined a method for obtaining α-oxygenated aminohydroquinones that was discovered by Cameron and Giles.[2] Readily prepared aminoquinones are photooxidized by an intramolecular oxygen insertion, e.g., **2** → **3**.

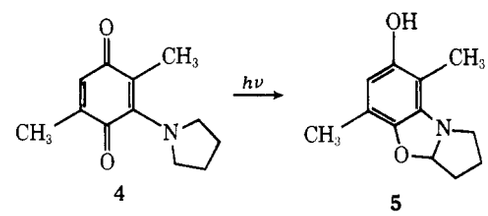


1

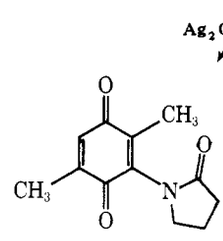


2 **3**

In our work, a model aminoquinone **4** was prepared by using a tenfold dilution of the conventional conditions for the condensation of pyrrolidine and xyloquinone to form a bis adduct. The photolysis of **4** with a sunlamp to produce **5** proceeded cleanly, although isolation of **5** in high yield was not possible.



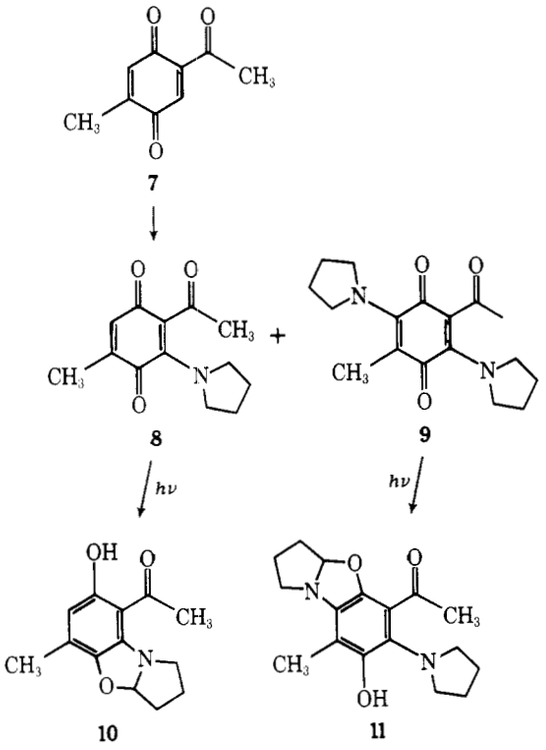
4 **5**



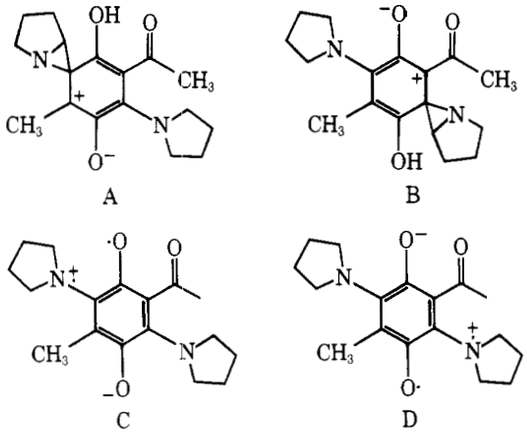
6

These insertion products are characterized by the appearance of a downfield methine hydrogen in their NMR spectra and the disappearance of quinone carbonyls in their IR spectra. Oxidation of photoproduct **5** with silver oxide yielded pyrrolidone–quinone **6**, a derivative with the heterocyclic α carbon in the desired oxidation state. Lactam **6** was characterized by its unambiguous NMR, by its carbonyl band at 5.78 μm, and by its UV λ_{max} 273 nm. This maximum is shifted almost 30 nm to longer wavelength compared to **4**, presumably because of lesser stabilization of the ground state of the chromophore.

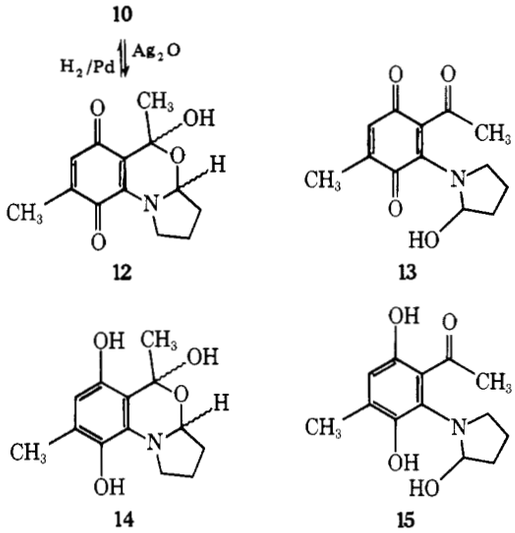
We chose to study next the amine adducts **8** and **9**, either of which was available from the known quinone **7**, depending on the conditions of pyrrolidine addition. If a lactam could be



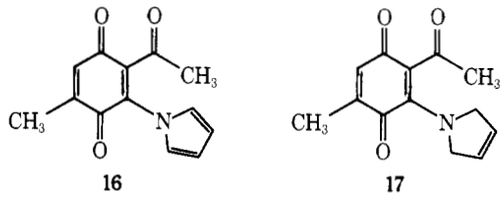
formed, one could plan carbon–carbon forming reactions where the oxygen could remain at the desired angular position. Photolysis of **8** afforded **10** in a clean process, whereas **9** yielded **11**. That dissimilar pyrrolidines had photocyclized was established by the absence of a strongly H-bonded acetyl band at 1625 cm^{-1} in the IR of **11** which was present in **10**. In both products the characteristic methine protons were observed in the NMR. The positional selectivity in the photolysis of **9** can be rationalized by invoking a mechanism for the reaction suggested by Orlando and Bose.[3] The suggestion was made that polar, spirocyclic intermediates such as A or B are involved. It is clear that a polar transition state leading to the latter would be destabilized by having a carbon with carbonium ion character adjacent to a carbonyl. Or, if a charge transfer initiates the reaction, a species such as C would be more stable than D. Furthermore, the intermediate in the photolysis of **8** would require an unfavorable juxtaposition of carbonium ion character and the acetyl group. Thus, the qualitative observation that its photolysis was slower by at least a factor of 4 compared to **9** is also interpretable.



To convert the pyrrolidine α carbon from the masked aldehyde oxidation state to the lactam level, photoproduct **10** was treated with Ag_2O. The structure assigned to the product is that of oxazine **12**. The assignment rests on the reappearance of quinone characteristics in the NMR (allylic coupling of CH_3 and vinyl H) along with the maintenance of the characteristic downfield methine of the oxypyrroldine ring. Further, the side-chain acetyl has been masked as shown by disappearance of its carbonyl peak in the IR and a shift of its CH_3 resonance in the NMR to δ 1.76. Although one would not expect a single epimer to form in this hemiacetal, there is no definitive evidence to suggest that a mixture was obtained. In NMR spectra of the crude oxidation product, the peaks for the methine H and the acetal CH_3 were not as sharp as in purified material. Clearly, the desired intermediate **13** had attacked the reactive acetyl faster than carbinolamine could be oxidized, and the equilibrium concentration of **13** must be too low for an oxidation to lactam at a usable rate. Other oxidants were no more useful at producing uncyclized products. In an effort to prepare **14**, which could have been expected to be in equilibrium with **15**, the oxazine **12** was subjected to catalytic hydrogenation. A clean conversion back to **10** was accomplished.



In a further variation, the condensation of Δ^3-pyrroline with quinone **7** was attempted. In previous work with quinones of lower oxidation potential, Lown had reported the addition to be uneventful.[4] However, in our hands. a spontaneous dehydrogenation of the initial adduct took place, affording pyrrole–quinone **16**. This is the first example of a pyrrole with *N*-quinone substitution. The normal event in the reaction of pyrroles and quinones is α-pyrrole substitution.[5] Thus, we rule out an explanation for the formation of **16**, where there is a prior conversion of Δ^3-pyrroline to pyrrole followed by addition. Instead, we hypothesize that **17** must undergo an intramolecular dehydrogenation–hydrogenation reaction. Photolysis of this pyrroloquinone did not yield an oxygen insertion product.



Experimental Section[6]

3-*N*-Pyrrolidine-2,5-xyloquinone (4). To a stirred solution of 0.200 g (1.469 mmol) of xyloquinone in 40 mL of ethanol was added 0.238 g (3.346 mmol) of pyrrolidine. The mixture, protected from light but not air, immediately darkened and after 6 h, excess amine was

removed by vacuum distillation. Preparative silica plate workup ($CHCl_3$) resulted in the isolation of 0.150 g (50%) of paste-like product **4**: UV (ethanol) λ_{max} 245 nm (log ϵ 4.4); IR ($CHCl_3$) 6.08, 6.40 (br) μm; NMR ($CDCl_3$) δ −1.88 (br s, pyrrolidino CCH_2C), 1.95 (d, J = 1.5 Hz, CH_3), 2.03 (s, CH_3), 2.8–3.2 (br, pyrrolidino NCH_2).

5,8-Dimethyl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]benzoxazol-7-ol (5). A solution of 0.150 g (0.73 mmol) of aminated quinone **4** in oxygen-free benzene was exposed to a sunlamp under a stream of nitrogen. The dark solution rapidly became colorless, the benzene was removed by vacuum distillation, and this gave the yellow photoproduct (80%): NMR ($CDCl_3$) δ 1.95 (br s, pyrrolidino CCH_2C), 2.05 (s, CH_3), 2.14 (s, ArMe), 2.8–3.5 (m, NCH_2), 5.85 (q, NCHOAr), 6.20 (s, ArH).

3-*N*-(2-Oxypyrrolidino)-2,5-xyloquinone (6). The photoproduct **5** (0.120 g, mmol) was placed in a 100-mL flask with 50 mL of benzene, 0.160 g of silver oxide, and 10 mL of water. The reaction mixture was stirred for 3.5 at 40 °C, after which the silver oxide was removed by suction filtration through a Celite column. Preparative silica plate workup ($CHCl_3$–acetone; 4:1) resulted in the isolation of 0.05 g (42%) of a reddish-purple paste **6.**

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.97; N, 6.39. Found C, 64.60; H, 7.09; N, 5.57.

UV (ethanol) λ_{max} 225, 273 (log ϵ 4.57, 4.44); IR ($CHCl_3$) 5.78, 6.08 μm; NMR ($CDCl_3$) δ 1.83 (pyrrolidino CH_2), 2.0 (br s, pyrrolidino $COCH_2$), 2.07 (d, J = 1.5 Hz, CH_3), 2.16 (s, CH_3), 2.9–3.7 (m, NCH_2), 6.50 (q, J = 1.5 Hz, vinyl H).

2-Acetyl-3-*N*-pyrrolidino-5-methyl-1,4-benzoquinone (8). To 0.36 g (1.8 mmol) of cupric acetate in 30 mL of methanol and 0.168 g (2.4 mmol) of pyrrolidine was added 0.200 g (1.22 mmol) of quinone **7** in 20 mL of methanol.[7] This was allowed to stir at room temperature in an aluminum foil wrapped 100-mL round-bottom flask with the surface well exposed to air for 20 min, at which time the solvent was removed. Workup involved putting the crude residue on preparative silica plates and eluting with chloroform. A dark red band was isolated from the plates (R_f 0.25) and 0.207 g (64%) of **8** was recovered as a paste: IR ($CHCl_3$) 3.38, 6.00, 6.09, 6.32, 6.75, 7.00, 7.35, 7.60, 9.15, 10.10 μm; UV (ethanol) λ_{max} 285 nm (ϵ 8700), (16 600), 480 (3300); NMR ($CDCl_3$) δ 183–2.18 (br, m, 4 H), 2.00 (d, 3 H, J = 1.5 Hz), 2.57 (s, 3 H), 3.37–3.68 (br, m, 4 H), 6.50 (q, 1 H, J = 1.5 Hz).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.90; H, 6.43; N, 6.00. Found: C, 66.60; H, 6.56; N, 5.63.

2-Acetyl-3,5-di-*N*-pyrrolidino-5-methyl-1,4-benzoquinone (9). Only a disubstituted product (25%) could be isolated if the time in the above-described reaction was extended 30 min: IR ($CHCl_3$) 3.45, 6.10, 6.19, 6.68, 6.92, 7.14, 7.64, 9.19 μm; UV (ethanol) λ_{max} 273 nm (ϵ 7200), 325 (7830), 375 sh (2685), 495 (716); NMR ($CDCl_3$) δ 1.80–2.17 (br, m, 8 H), 2.02 (s, 3 H), 2.51 (s, 3 H), 3.55–4.04 (br, m, 8 H).

8-Acetyl-1,2,3-3a-tetrahydro-5-methylpyrrolo[2,1-b]benzoxazol-7-ol (10). A stirred solution of 0.94 g (0.403 mmol) of red aminoquinone **8** in 150 mL of distilled benzene purged with nitrogen was irradiated for 90 min with a GE 250-W sunlamp. Silica preparative plate chromatography of the concentrated residue ($CHCl_3$–EtOAc, 20:80) yielded 0.910 g (96.8%) of yellow phenol as an oil: IR ($CHCl_3$) 2.79, 3.42, 6.13, 6.20, 7.01, 7.91, 8.50, 9.35, 9.80, 10.80 μm; UV (ethanol) λ_{max} 225 nm (ϵ 13 900), 286 (11 700), 398 (4600); NMR ($CDCl_3$) δ 1.73–2.52 (br, m, 4 H), 2.21 (s, 3 H), 2.75 (s, 3 H), 2.90–4.28 (br, m, 2 H), 5.90–6.08 (br, m, 1 H), 6.44 (s, 1 H), 13.30 (s, 1 H, ex).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 67.00; H, 6.45; N, 6.00. Found: C, 67.07; H, 6.61; N, 5.60.

Photo Product 11 from 2-Acetyl-3,6-di-*N*-pyrrolidino-5-methyl-1,4-benzoquinone. A stirred solution of 0.070 g (0.232 mmol) of red bispyrrolidinoquinone **9** in 100 mL of distilled benzene purged with nitrogen was irradiated for 40 min with a GE 250-W sunlamp. Silica preparative plate chromatography ($CHCl_3$–EtOAc, 20:80) yielded 0.051 g (72.9%) of a single yellow phenol **11** as an oil: IR ($CHCl_3$) 2.70 br, 3.24, 3.49, 6.00, 7.00, 7.40, 8.58 9.25 μm; NMR ($CDCl_3$) δ 1.73–2.36 (br, m, 8 H), 2.28 (s, 3 H), 2.61 (s, 3 H), 2.92–3.26 (br, m, 5 M, 1 ex), 3.26–4.26 (br, m, 2 H), 5.83–5.99 (br, t, 1 H).

Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.70; H, 7.20; N, 9.27. Found: C, 67.20; H, 7.03; N, 8.90.

Oxidation of Photoproduct 10. A mixture of 0.083 g (0.36 mmol) of phenol **10**, 25 mL of benzene, 5 mL of water, 0.267 g (1.11 mmol) of Ag_2O, and 5 mg of K_2CO_3 was warmed at 45 °C for 3 h. The reaction mixture was worked up by filtration of the silver and silver oxide. That some organic material was adsorbed on the solid was revealed by the recovery of 73% of the organic product. Preparative TLC using 90:10 $CHCl_3$–EtOAc gave a major red band which was characterized as follows: IR ($CHCl_3$) 2.70, 3.42, 6.50 μm; NMR ($CDCl_3$) δ 1.78 (s, CH_3), 1.89 (m, CH_2CH_2), 2.02 (d, J = 1.5 Hz, CH_3), 3.67–4.33 (br m, NCH_2 and OH, exchangeable), 5.15 (m, OCHN), 6.52 (g, J = 1.5 Hz, vinyl H). We were not able to obtain a satisfactory combustion analysis, but its conversion back to **10** as described below allows us to assign its structure as **12.**

Conversion of 12 to 10. A sample of **12** (0.069 g, 0.277 mmol) was hydrogenated in EtOAc using 0.01 g of 10% Pd/C catalyst. Upon removal of the catalyst (again some organic material was adsorbed) and the solvent, 0.050 g (79% yield) of phenol **10** was isolated.

2-Acetyl-5-methyl-3-(1*H*-pyrrol-1-yl)benzoquinone (16). To a stirred solution of excess 3-pyrroline and 0.300 g (1.5 mmol) of cupric acetate in 40 mL of methanol was added 0.130 g (0.793 mmol) of quinone **7** in 15 mL of methanol. After 25 min the reaction was complete and silica chromatography on a preparative plate ($CHCl_3$) yielded 0.048 g (26.4%) of **16** from an orange-yellow band, R_f 0.06, as a paste: IR ($CHCl_3$) 5.81, 5.93, 6.02, 6.21, 6.83, 7.31, 7.53, 7.62, 8.82, 9.14, 9.95, 10.70, 11.23 μm; NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.14 (d, 3 H, J = 1.5 Hz), 6.38 (t, 2 H, J = 2.5 Hz), 6.67 (q, 1 H, J = 1.Hz), 6.77 (t, 2 H, J = 2.5 Hz).

Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.20; H, 4.80; N, 6.12. Found: C, 68.30; H, 4.96; N, 5.82.

Registry No.—**4,** 63076,91-5; **5,** 63076-92-6; **6,** 63076-93-7; **7,** 63076-94-8; **8,** 63076-95-9; **9,** 43140-86-9; **10,** 63076-96-0; **11,** 63076-97-1; **12,** 63076-98-2; **16,** 63076-99-3; xyloquinone, 137-18-8; pyrrolidine, 123-75-1; 3-pyrroline, 109-96-6.

References and Notes

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(6) Analyses were performed by Spang Laboratories, Ann Arbor, Mich. NMR spectra were determined with Varian A-60A, XL 100, and Perkin-Elmer R12B spectrometers with chemical shifts expressed in δ units. For funds used to purchase the Perkin-Elmer R12B, we acknowledge Biomedical Sciences Support Grant RR 07150 from DHEW. Further we acknowledge the National Cancer Institute for grant CA 11421. We thank Dr. Ian Baxter for pertinent suggestions concerning quinone chemistry.

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