Acknowledgment. This work was supported by grants from the Ministero della Pubblica Istruzione and from Consiglio Nazionale delle Ricerche. We thank Dr. C. Rosini for CD, Dr. D. Catalano for NMR, and Dr. M. Benetti for MS measurements.

Registry No. **1a**, 122922-40-1; **1b**, 67210-45-1; **1c**, 123052-35-7; **1d**, 62137-90-0; **2g**, 84994-66-1; (+)-**2c**, 123052-36-8; **2d**, 31612-63-2; (±)-**2c**, 123122-61-2; MeH, 9048-63-9.

Notes

Reactivity of *N,N*-Dialkylamide Enolate Ions. Arylation of 1-Methyl-2-pyrrolidinone Enolate Ions by the $S_{RN}1$ Mechanism

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The radical nucleophilic substitution or $S_{RN}1$ mechanism is well-known.[3] The main steps of the propagation cycle are outlined in Scheme I.

Scheme I

$$(RX)^{\bullet-} \rightarrow R^{\bullet} + X^- \quad (1)$$

$$R^{\bullet} + Nu^- \rightarrow (RNu)^{\bullet-} \quad (2)$$

$$(RNu)^{\bullet-} + RX \rightarrow RNu + (RX)^{\bullet-} \quad (3)$$

$$RX + Nu^- \rightarrow RNu + X^- \quad (4)$$

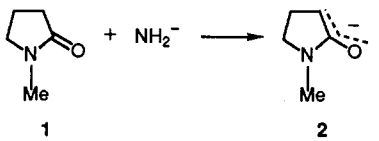
Summation of these steps 1–3 leads to eq 4, which is a nucleophilic substitution, but with radical and radical anions as intermediates. When no spontaneous formation of the radical anion of the substrate takes place to initiate the reaction, it can be catalyzed with solvated electrons in liquid ammonia[4] or with electrons from an electrode,[5] but the most common initiation step is photostimulation.[3,6]

Many aromatic substrates react by this mechanism with different types of nucleophiles, such as the carbanions derived from ketone,[3,7] ester,[3,8] and nitrile enolates ions.[3,9]

We have reported that *N,N*-dialkylamide enolate ions are suitable nucleophiles to react with haloarenes by this mechanism. For instance, the photostimulated reaction in liquid ammonia of several *N,N*-dialkylacetamide enolate ion with haloarenes, such as halobenzenes (chloro, bromo, and iodo), 1-chloronaphthalene, and 9-bromophenanthrene gave good yields of substitution products, together with a low amount of the disubstitution products.[10]

It is known that α,α-diaryl-*N,N*-dialkylamide derivatives constitute an important class of herbicides, such as *N,N*-dimethyldiphenylacetamide (Diphenamid).[11] Therefore we are using this mechanism because it offers the possibility to synthesize different α,α-diaryl-*N,N*-dialkylamide compounds, in order to test their biological activity. We have already synthesized several of these substrates by the $S_{RN}1$ mechanism to study their biological activity.[12] We now attempt to extend this study to *N*-alkyl lactams.

It was reported that the 1-methyl-2-pyrrolidinone enolate ion **2** formed by the acid–base reaction of 1-methyl-2-pyrrolidinone **1** with sodium amide in liquid ammonia gave no reaction with bromobenzene (eq 5 and 6).[13] There



(5)

1 **2**

$$PhBr + \mathbf{2} \xrightarrow{dark} \text{no reaction} \quad (6)$$

were other attempts to form the enolate ion **2** using different bases, such as $NaNH_2$–KH or $NaNH_2$–$KOC(CH_3)_3$; however neither photostimulation nor solvated electrons were used to stimulate the reactions.[13] In general, there are few examples of thermal or spontaneous $S_{RN}1$ reactions, and most of the carbanions derived from enolate ions need solvated electrons or photostimulation to occur in liquid ammonia, and they react slowly, or fail to react in the dark.[3] Therefore, we decided to reinvestigate the reaction of 1-methyl-2-pyrrolidinone enolate ion **2** with

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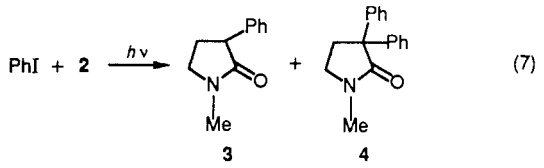
haloarenes in liquid ammonia with light to catalyze the reaction.

The photostimulated reaction of iodobenzene with **2**, prepared as shown in eq 5 in liquid ammonia, gave 85% yield of iodide ions after 60 min of irradiation and the monosubstitution product **3** being isolated in 60% yield, together with 7% yield of the disubstitution product **4** (expt 1, Table I; eq 7).



(7)

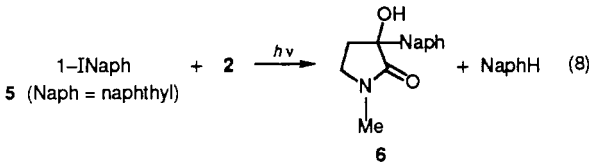
3 **4**

To have minor amounts of the disubstitution product **4**, we had to use an excess of nucleophile **2**, since with a nucleophile/iodobenzene ratio of only 2, we obtained 40% yield of the disubstitution product **4** (expt 3, Table I).

There was not an increased yield with longer irradiation time, and we obtained almost the same results with bromo- and chlorobenzene. Bromobenzene did not react in darkness during the same period of time.

The photostimulated reaction of *p*-iodoanisole with **2** in 60 min of irradiation gave an 80% yield of iodide ion and 58% yield of the monosubstitution product 1-methyl-3-(*p*-anisyl)-2-pyrrolidinone.

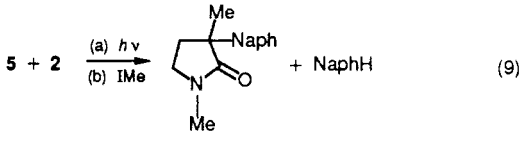
The photostimulated reaction of 1-iodonaphthalene **5** with **2** gave about 90% yield of iodide ion. The product isolated was 1-methyl-3-hydroxy-3-(1-naphthyl)-2-pyrrolidinone (**6**) in 37% yield, together with 40% yield of the reduction product naphthalene (eq 8).



(8)

6

Under the same experimental conditions, but quenching the reaction with methyl iodide, the substitution product 1-methyl-3-methyl-3-(1-naphthyl)-2-pyrrolidinone (**7**) was obtained in 40% yield (eq 9), together with a 45% yield of the reduction product naphthalene (expt 8, Table I).



(9)

7

These results suggest that the oxidation occurs during the workup.[14] We tried to isolate pure unoxidized substitution product working under nitrogen, but we could isolate it only together with some of product **6** (see Experimental Section).[14]

According to these results we can conclude that 1-alkyl-2-pyrrolidinone enolate ions are suitable nucleophiles to react with haloarenes under irradiation by the $S_{RN}1$ mechanism, to give 1-alkyl-3-aryl- and 1-alkyl-3,3-diaryl 2-pyrrolidinones. This method is better than the benzyne mechanism, which gives less overall yields of substitution products. With *p*-bromoanisole as substrate, the benzyne mechanism gave a mixture of both isomers with similar yields, while the present reaction with *p*-iodoanisole gave only para substitution.

Experimental Section

General Methods. ^1H NMR spectra were recorded on a Varian T-60 nuclear magnetic resonance spectrophotometer and also the ^1H NMR and ^{13}C NMR spectra on a Bruker FT 80-MHz nuclear magnetic resonance spectrophotometer through the courtesy of Professor E. Rûveda (Universidad Nacional de Rosario). Infrared spectra were recorded on a 5 SXC Nicolet FTIR spectrophotometer. Mass spectral measurements were obtained with a Finnigan Model 3300 mass spectrometer, and gas chromatographic analyses were performed on a Varian Aerograph series 1400 instrument with a flame ionization detector by using a column packed with 3% SE 30 on Chromosorb P (0.5 m × 3 mm) or 5% OV 17 on Chromosorb P (1.5 m × 3 mm). Column chromatography was performed on silica gel (7–230 mesh, ASTM, Merck). Irradiation was conducted in a reactor equipped with four 250-W UV lamps emitting maximally at 350 nm (Philips Model HPT, water refrigerated). The melting points are not corrected. Potentiometrical tritation of halide ions was performed with a pH meter (Seybold) using a Ag/Ag^+ electrode (Metrohm). Microanalyses were performed in UMYMFOR (Universidad de Buenos Aires), through the courtesy of Professor E. Gros.

Materials. 1-Methyl-2-pyrrolidinone (Fluka), chlorobenzene (Baker), bromobenzene (Carlo Erba), iodobenzene (Aldrich), *p*-iodoanisole (Fluka), and 1-iodonaphthalene (Fluka) were commerically available and used as received.

Photostimulated Reactions of 1-Methyl-2-pyrrolidinone Enolate Ion 2 with Iodobenzene. The following procedure is representative of these reactions: into a three-necked 500-mL round-bottomed flask, equipped with a coldfinger condenser charged with dry ice–ethanol, a nitrogen inlet, and a magnetic stirrer, was condensed 300 mL of ammonia previously dried with sodium metal under nitrogen. Potassium metal (15 mmol) and a small amount of $FeCl_3$ was added to the ammonia to catalyze the formation of potassium amide. 1-Methyl-2-pyrrolidinone (15 mmole) was added and after 15 min 1 mmol of iodobenzene was also added and the solution was irradiated for 60 min. The reaction was quenched by the addition of excess ammonium nitrate, and the ammonia was then allowed to evaporate. The residue was washed with dichloromethane (1-methyl-2-pyrrolidinone is insoluble in this solvent, while the substitution products were soluble). The residue was dissolved with water. In the aqueous solution iodide ions were determined potentiometrically. The dichloromethane solution was analyzed by GLC using the internal standard method (standard 9-bromophenanthrene). (In the reaction with p-iodoanisole the internal standard was diphenyldisulfide). In other experiments, removal of the dichloromethane by distillation gave a residue from which after column chromatography (flash) on silica gel (elution with benzene:acetone 80:20) gave 1-methyl-3-phenyl-2-pyrrolidinone (60% yield); white solid mp: 59–61 °C (lit mp. 58–59 °C;[15a] 60–61 °C[15b]); ^1H NMR (CCl_4) δ 1.80–2.60 (m, 2 H), 2.82 (s, 3 H), 3.11–3.60 (m, 3 H), 7.21 (s, 5 H); *MS*, *m/e* (rel intensity) 175 (M^+, 17), 117 (97), 103 (18), 42 (100); IR (NaCl, cm^{-1}) 3009, 1687, 1494, 1274, 1239, 1070, 755, 705, 539. Also isolated was a white solid whose spectral analyses and mp probably indicated the disubstitution product 1-methyl-3,3-diphenyl-2-pyrrolidinone (7%), mp = 142–144 °C (lit. mp 145,[16a] 146–148 °C[16b]); ^1H NMR (CCl_4) δ 2.58–2.82 (m, 2 H), 2.90 (s, 3 H), 3.10–3.52 (m, 2 H), 7.21 (s, 10 H); MS, *m/e* (rel intensity) 251 (M^+, 40), 193 (25), 165 (16), 115 (75), 103 (22), 42 (100); IR (NaCl, cm^{-1}) 2921, 2851, 1666, 1489, 1396, 1272, 1091, 702.

Photostimulated Reactions of 1-Methyl-2-pyrrolidinone Enolate Ion 2 with Bromobenzene in the Dark. The procedure was similar to the previous reaction, except that the reaction

(14) The easy oxidation reaction of 1-methyl-3-(1-naphthyl)-2-pyrrolidinone to give 1-methyl-3-hydroxy-3-(1-naphthyl)-2-pyrrolidinone quantitatively by dioxygen comes up quite unexpectedly. It is known that the oxidation of related structures (carbanions) occurs in presence of oxygen peroxide (Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576. Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299) or dioxygen (Russell, G. A.; Benis, A. G. *J. Am. Chem. Soc.* **1966**, *88*, 5491). We will study this reaction in the further.

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Table I. Photostimulated Reaction of Haloarenes with 1-Methyl-2-pyrrolidinone Enolate Ions 2 in Liquid Ammonia[a]

expt	ArX	hν, min	products,[b] % X⁻	3	4
1	PhI	60	85	60[c]	7
2[d]	PhI	180	90	60	6
3[e]	PhI	180	87	*f*	40[c]
4	PhBr	60	85	51	2
5	PhBr	60[g]	5		
6	PhCl	60	80	52	1
7	*p*-IAn[h]	60	80	58[i]	2[j]
8	1-INaph[k]	60	*l*	40[m]	

[a] 15 mmol of 2 and 1 mmol of ArX were dissolved in 300 mL of liquid ammonia, unless otherwise indicated. [b] Determined by GLC unless otherwise indicated. [c] Isolated yield. [d] 8% yield of iodobenzene remained. [e] 10 mmol of 2 and 5 mmol of PhI. [f] Not determined. [g] Dark reaction. [h] *p*-IAn = *p*-iodoanisole. [i] 1-Methyl-3-(*p*-anisyl)-2-pyrrolidinone. [j] 1-Methyl-3,3-(di-*p*-anisyl)-2-pyrrolidinone. [k] 1-INaph = 1-iodonaphthalene. [l] The reaction was quenched with methyl iodide, and 45% yield of naphthalene was found. [m] 1-Methyl-3-(1-naphthyl)-3-methyl-2-pyrrolidinone.

flask was draped with aluminum foil.

Photostimulated Reactions of 1-Methyl-2-pyrrolidinone Enolate Ion 2 with *p*-Iodoanisole. The procedure was similar to the previous reaction. After flash chromatography 1-methyl-3-(*p*-anisyl)-2-pyrrolidinone was isolated as a yellow oil. ^{1}H NMR, mass, and IR spectra were similar to those reported.[13] Also isolated was a yellow oil whose spectral analyses probably indicate the disubstitution product 1-methyl-3,3-(di-*p*-anisyl)-2-pyrrolidinone (2%): MS, *m/e* (rel intensity) 311 (M^+ 56), 254 (50), 252 (90), 223 (100), 165 (37), 145 (44), 115 (44).

Photostimulated Reactions of 1-Methyl-2-pyrrolidinone Enolate Ion 2 with 1-Iodonaphthalene (5). The procedure was similar to the previous reaction. After flash chromatography naphthalene (40% yield) and 1-methyl-3-hydroxy-3-(1-naphthyl)-2-pyrrolidinone were isolated. The substitution product consisted of white crystals, mp 202–204 °C; ^{1}H NMR δ 1.10–1.41 (m, 1 H), 2.60–2.85 (m, 2 H), 3.08 (s, 3 H), 3.16–3.50 (m, 2 H), 7.10–8.52 (m, 7 H); ^{13}C NMR δ 175.31, 136.74, 134.72, 130.59, 129.06, 128.86, 126.05, 125.76, 125.41, 124.13, 123.64, 79.9, 45.67, 35.52, 30.06; IR (NaCl, cm^{-1}) 3279, 2945, 1878, 1399, 1264, 1113, 780, 708; MS, *m/e* (rel intensity) 241 (M^+ 75), 183 (33), 169 (41), 155 (81), 127 (100), 115 (14), 86 (27), 58 (43), 44 (75). Anal. Calcd for $C_{15}H_{15}O_2N$: C, 74.67; H, 6.27. Found: C, 74.42; H, 6.45. We performed a reaction similar to the previous one, but the ammonia was allowed to evaporate under nitrogen, and the residue was dissolved in dichloromethane and chromatographed on silica gel eluted with diethyl ether by using a Chromatotrom, and 1-methyl-3-(1-naphthyl)-2-pyrrolidinone together with a small amount of the oxidized product 6 were isolated, mp 137–139 °C; MS, *m/e* (rel intensity) 225 (M^+ 89), 168 (54), 167 (68), 153 (100), 139 (12), 58 (18), 42 (18); ^{1}H NMR δ 1.85–2.85 (m, 2 H), 3.05 (s, 3 H), 3.40–4.60 (m, 3 H), 7.25–810 (m, 7 H). We performed a reaction similar to the previous one, except that this was quenched with methyl iodide. After flash chromatography naphthalene (45% yield) and 1-methyl-3-(1-naphthyl)-3-methyl-2-pyrrolidinone were isolated, mp 91–93 °C; ^{1}H NMR (CCl_4) δ 1.65 (s, 3 H), 2.42–2.59 (m, 2 H), 2.85 (s, 3 H), 3.02–3.29 (m, 2 H), 7.18–8.05 (m, 7 H), MS, *m/e* (relative intensity) 239 (M^+ 21), 224 (3), 182 (10), 167 (24), 152 (26), 112 (19), 96 (14), 82 (21), 58 (91), 44 (100); IR (NaCl, cm^{-1}) 3045, 2932, 2875, 1682, 1598, 1503; 1455; 1400, 1273, 780, 700.

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Registry No. 1, 872-50-4; 3, 54520-82-0; 4, 20538-39-0; 5, 90-14-2; 6, 123074-45-3; 7, 123074-44-2; PhI, 591-50-4; PhBr, 108-86-1; PhCl, 108-90-7; *p*-IC_6H_4OMe, 696-62-8; 1-methyl-3-(*p*-anisyl)-2-pyrrolidinone, 107770-12-7; 1-methyl-3,3-(di-*p*-anisyl)-2-pyrrolidinone, 123074-43-1; naphthalene, 91-20-3; 1-methyl-3-(1-naphthyl)-2-pyrrolidine, 123074-46-4.

Synthesis of a Truncated A-Unit Analogue for CC-1065[1]

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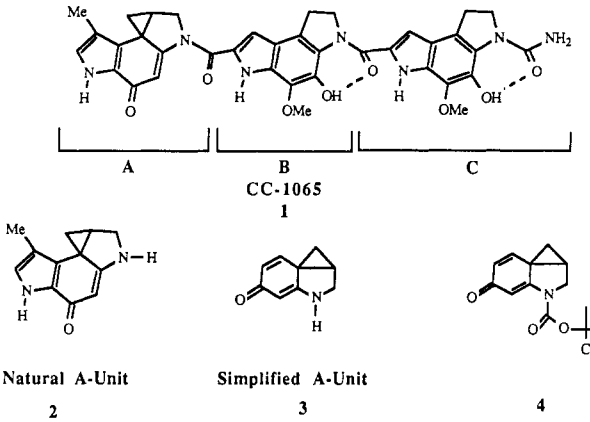
The antibiotic CC-1065 (1) is one of the most active yet toxic antitumor natural products known,[2] and considerable efforts have been directed toward the synthesis of less toxic analogues containing modified B and C units.[3] Since the cyclopropanedienone of the natural A unit 2 is essential for biological activity, our current goal is to synthesize analogues of CC-1065 derived from modified A units. We now report the first synthesis of the parent truncated A-unit dienone 3 from 6-methoxyindole via its acyl derivative 4.[4]



The synthesis of 3 starts from 6-methoxyindole (5),[5] which was converted to 6-methoxygramine (6) by a Mannich reaction with aqueous dimethylamine and formalin in acetic acid (90%) (Scheme I). Methylation of 6 with methyl iodide in benzene gave 6-methoxygramine methiodide (7, 99%),[6] which was converted to nitrile 8 (NaCN, EtOH, reflux, 73%), followed by hydrolysis to acid 9 (NaOH, EtOH, reflux, 80%). The acid 9 was converted to the ester 10 (absolute MeOH, CSA, 99%), which was smoothly reduced with sodium cyanoborohydride in acetic acid,[7] followed by immediate protection with TCBOC-Cl[8] to give the crystalline carbamate 11 (74% yield from indole

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