Notes

Ring Transformations of 3-(Diethylamino)-5-chloro-2(1*H*)-pyrazinones and the Corresponding 2*H*-1,4-Oxazin-2-ones on Reaction with Acetylenic Compounds

Mayoka G. Tutonda, Stef M. Vandenberghe, Koen J. Van Aken, and Georges J. Hoornaert*

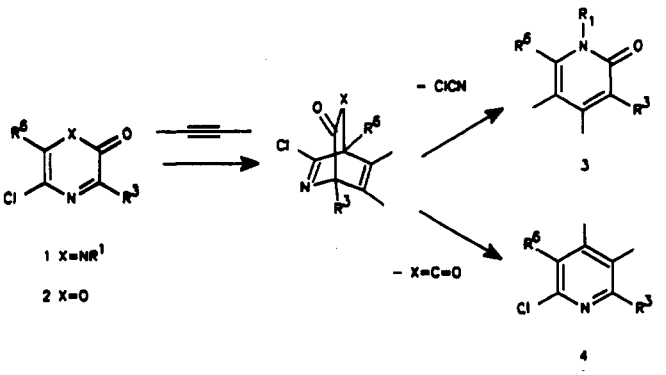
Department of Chemistry, K.U. Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Belgium

Received December 9, 1991

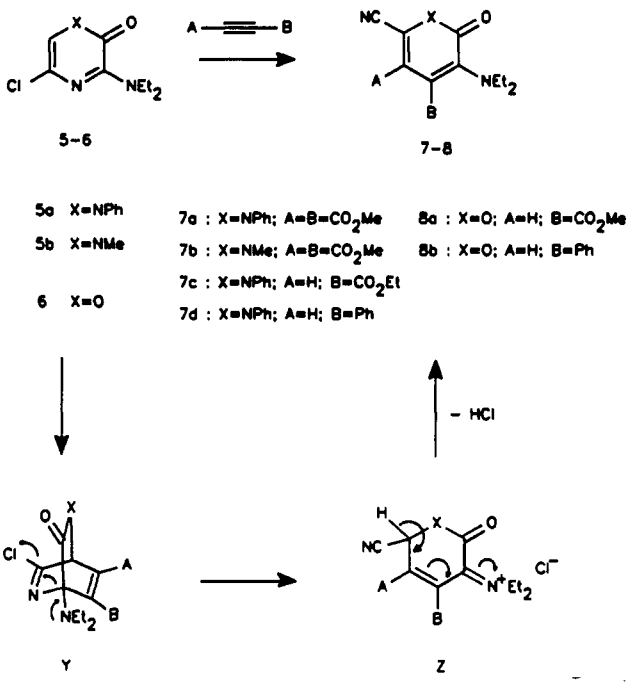
Oxazoles, thiazoles, imidazoles, 1,2,4-triazines and 6*H*-1,3-oxazin-6-ones contain a useful 2-azadiene system. They are known to undergo cycloaddition and subsequent elimination reactions offering interesting routes toward specifically substituted heterocyclic compounds.[1] In recent publications[2,3] we studied cycloaddition–elimination processes in the reaction of acetylenic compounds with the 2-azadiene system of variously substituted 2(1*H*)-pyrazinones 1 and 2*H*-1,4-oxazin-2-ones 2. Depending on the substitution pattern of both the 2(1*H*)-pyrazinone and the dienophile, the initially-formed cycloadducts gave 2-pyridones 3 and/or pyridines 4 (Scheme I). These products resulted from a retro Diels–Alder reaction of the initial cycloadduct with loss of cyanogen chloride and/or isocyanate.[2] However, cycloadducts of 2*H*-1,4-oxazin-2-ones exclusively lose carbon dioxide offering an interesting method for the generation of pyridines 4.[3]

Herein, we report the peculiar ring transformation and mechanistic features in the reaction of 5-chloro-3-(diethylamino)-2(1*H*)-pyrazinones and the corresponding 2*H*-1,4-oxazin-2-ones with acetylenic compounds. The model 2(1*H*)-pyrazinones **5a** (X = NPh) and **5b** (X = NMe), easily obtained by the reaction of diethylamine and the corresponding 3,5-dichloro-2(1*H*)-pyrazinones,[4] were treated with 3 equiv of dimethylacetylene dicarboxylate (DMAD). This reaction did not yield the expected pyridine derivatives resulting from a retro Diels–Alder reaction of the primarily-formed cycloadducts. However, the 2-cyano-5-(diethylamino)-1,6-dihydro-6-oxo-3,4-pyridinedicarboxylates **7a** and **7b** were isolated as the sole reaction products in yields of 95 and 93%, respectively. Infrared spectra of these solid compounds show typical nitrile bands at 2220–2230 cm^{-1} and carbonyl absorptions at 1720–1740 cm^{-1} (ester) and 1665 cm^{-1} (lactam). ^1H NMR data are in agreement with the presence of both ester and diethylamino functionalities, and the products are characterized by correct mass spectral and combustion analytical data. A plausible mechanism is proposed in Scheme II. The Diels–Alder adduct Y is assumed to rearrange into

Scheme I



Scheme II



intermediate Z by lone pair-assisted cleavage of the C–N bond at the bridgehead. The loss of a proton will lead to the formation of the isolated products **7a** and **7b**. A comparable reaction sequence is suggested for the formation of substituted 2,4-bis(dimethylamino)benzonitriles from the reaction of 6-chloro-3-cyano-2,4-bis(dimethylamino)-pyridines with electrophilic acetylenes.[5]

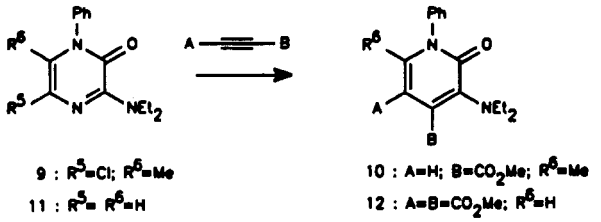
Some further experiments were performed to support this mechanism and to get more information about the scope of this ring transformation. The proposed mechanism requires three essential factors to be present in the 2(1*H*)-pyrazinone: (1) a hydrogen atom in position 6; (2) a good leaving group in position 5 (here Cl); and (3) a substituent with high donating capacity in position 3 (here NEt_2).

The latter requirement is induced by results from previous work[2b] showing that the cycloadducts of 5-chloro-

(1) (a) Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; Vol. 47, pp 300–357 and references cited therein.
(2) (a) Tutonda, M.; Vanderzande, D.; Vekemans, J.; Toppet, S.; Hoornaert, G. *Tetrahedron Lett.* **1986**, *27*, 2509. (b) Tutonda, M.; Vanderzande, D.; Hendrickx, M.; Hoornaert, G. *Tetrahedron* **1990**, *46*, 5715.
(3) (a) Meerpoel, L.; Hoornaert, G. *Tetrahedron Lett.* **1989**, *30*, 3183. (b) Meerpoel, L.; Deroover, G.; Van Aken, K.; Lux, G.; Hoornaert, G. *Synthesis* **1991**, 765.
(4) Vekemans, G.; Pollers-Wieërs, C.; Hoornaert, G. *J. Heterocycl. Chem.* **1983**, *20*, 919.
(5) Sasaki, T.; Kojima, A. *Tetrahedron Lett.* **1971**, 4593.
(6) Van Aken, K., unpublished results.

0022-3263/92/1957-2935$03.00/0

Scheme III



3-methoxy-1-phenyl-2(1*H*)-pyrazinone in comparable conditions do not yield a rearranged product, but simply undergo retro Diels–Alder reaction. In any event, cycloadducts of 5-chloro-3-(diethylamino)-2*H*-1,4-oxazin-2-ones which fulfill the three above-mentioned requirements undergo a comparable ring transformation. Indeed, reactions of 2(1*H*)-pyrazinone **5a** and 2*H*-1,4-oxazin-2-one **6** with (m)ethyl propynoate and phenylacetylene resulted in the regioselective formation of cyano- and diethylamino-substituted pyridone and pyranone derivatives **7c,d** (85%, 89%) and **8a,b** (75%, 34%) with characteristic IR absorptions for nitrile, lactam, or lactone functions (~2225, ~1665, and ~1730 cm^{-1}). Reactions with 2(1*H*)-pyrazinones were carried out at 60 °C in toluene, whereas compound **6** reacted at room temperature in neat acetylenic compounds to give **8a** and **8b** after 1 and 40 h, respectively. As can be expected, the reaction occurs more slowly with less electrophilic dienophiles. Structures **7c,d** and **8a,b** were proven by proton coupled ^{13}C NMR spectra where the nitrile carbon (δ = 112.5–113.5 ppm) appeared as a doublet with a ^3J coupling constant of 4 or 5 Hz. The formation of only one regioisomer is in agreement with the regioselectivity of the Diels–Alder cycloaddition as observed in previous work for 2(1*H*)-pyrazinones[2b] and 2*H*-1,4-oxazin-2-ones[6] with electron-donating substituents in position 3.

In addition, some Diels–Alder experiments were carried out on 2(1*H*)-pyrazinones with a substitution pattern that does not fulfill the requirements mentioned above. The reaction of the 6-methyl derivative **9** with methyl propynoate under the same reaction conditions as for compounds **5a** and **5b** yielded unreacted starting material, tarry products and a small amount (15%) of 3-(diethylamino)-1,2-dihydro-6-methyl-2-oxo-1-phenyl-4-pyridinecarboxylate **10**. The latter product presumably originates from the loss of cyanogen chloride from the Diels–Alder adduct. The regiochemistry of **10** was confirmed by its proton-coupled ^{13}C NMR spectrum with C-5 absorbing at 103.4 ppm (dxq) and the methyl group in position 6 at 20.1 ppm. In the ^1H NMR spectrum H-5 appears as a singlet at 6.1 ppm. The large amount of tarry products may be connected with the mentioned rearrangement: because of the presence of a 6-methyl substituent instead of a 6-H atom in the starting material, proton loss out of an intermediate of type Z cannot occur; this leads to unidentified side products.

Reaction at 60 °C of the 2(1*H*)-pyrazin-2-one **11** (obtained by reduction[2b] of the corresponding 5-chloro derivative) with DMAD yielded after 3 h only one product (85%). It was identified as the dimethyl 5-(diethylamino)-1,6-dihydro-6-oxo-1-phenyl-3,4-pyridinedicarboxylate (**12**). It has characteristic IR absorptions at 1730 (ester) and 1665 (lactam) cm^{-1} and a singlet absorption for H-2 at 8.2 ppm. This compound probably results from the normal retro Diels–Alder reaction with loss of hydrogen cyanide out of the adduct.

We can conclude that this rearrangement yielding 5-(diethylamino)-1,6-dihydro-6-oxo-2-pyridinecarbonitriles and 3-(diethylamino)-2-oxo-2*H*-pyran-6-carbonitriles predominates over the normal retro Diels–Alder reaction when a specific substitution pattern is present. The behavior of related cycloadducts with substituents different from dialkylamino groups, e.g., $-NH_2$, –NHR, or 3-indolyl, and the influence of solvent polarity and temperature on the competition between both processes are under current investigation.

Experimental Section

Melting points were taken using a Reichert-Jung Thermovar apparatus and are uncorrected. All NMR spectra were recorded on a Bruker Cryospec FT-250 spectrometer using $CDCl_3$ as solvent. ^1H and ^{13}C NMR spectra were measured at 250 and 63 MHz, respectively, and their shifts are expressed in parts per million (ppm) downfield from TMS; the coupling constants are expressed as $^nJ_{CH}$, where n is the number of bonds between carbon and hydrogen, and are in Hz. IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR-spectrophotometer. Mass spectra were run using a Kratos MS 50 instrument and DS 90 data system. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyzer type 1106. Silica gel (Macherey Nagel Type 60) and chloroform stabilized with amylene were used for chromatographic separations. All solvents and reagents were dried and purified according to standard procedures. All cycloaddition reactions were performed under nitrogen atmosphere.

The 3,5-dichloro-2(1*H*)-pyrazinones and the corresponding 2*H*-1,4-oxazin-2-ones used for the preparation of compounds **5a**, **5b**, and **6** were synthesized according to the procedures described in the literature.[4,3a]

5-Chloro-3-(diethylamino)-2(1*H*)-pyrazinones 5a, 5b. General procedure: To a solution of 3,5-dichloro-1-phenyl- or -1-methyl-2(1*H*)-pyrazinone (40 mmol) in dry 1,4-dioxane (100 mL) was added freshly dried diethylamine (80 mmol). The reaction mixture was stirred for 2 h at 50 °C. After complete substitution, the solvent and excess of diethylamine were removed under reduced pressure, and the residue was then dissolved in chloroform and washed two times with water (10 mL). Drying of the organic layer on $MgSO_4$, evaporation, and chromatography (10% ethyl acetate–chloroform) on a silica gel column yielded compounds **5a** and **5b**. They were recrystallized from hexane–chloroform.

5-Chloro-3-(diethylamino)-1-phenyl-2(1*H*)-pyrazinone (5a). This compound was obtained in a yield of 10.4 g (94%): mp 63–64 °C; IR (KBr) 1665 (lactam) cm^{-1}; ^1H NMR δ 1.3 (t, 6 H, NCH_2CH_3), 3.7 (q, 4 H, NCH_2CH_3), 6.5 (s, 1 H, H-6), 7.3 (m, 5 H, ArH); ^{13}C NMR δ 13.6 (CH_2CH_3), 44.8 (CH_2CH_3), 113.6 (d, C-6, $^1J_{CH}$ = 190), 126.0 (s, C-5), 126.1, 128.5, 129.3 (m, C-Ar), 139.9 (dxd, C-ipso), 149.9 (m, C-3), 150.9 (s, C-2); MS (m/z) 277 (M^+, 100), 262 ($M^+ - CH_3$, 52), 248 ($M^+ - C_2H_5$, 72), 234 (262-CO, 86); HRMS calcd for $C_{14}H_{16}ClN_3O$ (M^+) 277.0982, found 277.0995. Anal. Calcd for $C_{14}H_{16}ClN_3O$: C, 60.54; H, 5.81; N, 15.13. Found: C, 60.25; H, 5.67; N, 14.93.

5-Chloro-3-(diethylamino)-1-methyl-2(1*H*)-pyrazinone (5b). This compound was obtained in a yield of 8.1 g (95%): mp 87–88 °C; IR (KBr) 1665 (lactam) cm^{-1}; ^1H NMR δ 1.22 (t, 6 H, NCH_2CH_3), 3.4 (s, 3 H, NCH_3), 3.75 (q, 4 H, NCH_2CH_3), 6.5 (s, 1 H, H-6); MS (m/z) 215 (M^+, 92), 200 ($M^+ - CH_3$, 76), 186 ($M^+ - C_2H_5$, 88), 172 (100); HRMS calcd for $C_9H_{14}ClN_3O$ (M^+) 215.0825, found 215.0834. Anal. Calcd for $C_9H_{14}ClN_3O$: C, 50.12; H, 6.54; N, 19.48. Found: C, 49.87; H, 6.43; N, 19.36.

5-Chloro-3-(diethylamino)-2*H*-1,4-oxazin-2-one (6). To a solution of 0.64 g of 3,5-dichloro-2*H*-1,4-oxazin-2-one (3.95 mmol) in $CHCl_3$ (50 mL) at reflux was added dropwise 0.83 mL of diethylamine (7.7 mmol) dissolved in $CHCl_3$ (50 mL). Purification of the residue after solvent removal by flash chromatography ($CHCl_3$) gave 0.64 g (81%) of **6** as a dark oil: IR (neat) 1735 (lactone), 1600 (C=N) cm^{-1}; ^1H NMR δ 1.26 (t, 6 H, CH_3), 3.72 (br q, 4 H, CH_2), 6.93 (s, 1 H, H-6); ^{13}C NMR δ 13.3 (CH_3), 45.0 (CH_2), 126.8 (C-6, d, $^1J_{CH}$ = 212), 128.2 (C-5, d, $^2J_{CH}$ = 7), 145.3 (C-3), 150.6 (C-2, d, $^3J_{CH}$ = 4); MS (m/z) 202 (M^+, 44), 174 (M^+ – CO, 58), 159 (M^+ – CO-Me, 100); HRMS calcd for $C_8H_{11}ClN_2O_2$ (M^+) 202.0509, found 202.0512.

Reaction of 3-(Diethylamino)-2(1*H*)-pyrazinones 5a–b, 9, and 11 with Acetylenic Compounds: Generation of Com-

pounds 7, 10, and 12. General procedure: A solution of 3-(diethylamino)-2(1*H*)-pyrazinone (1 mmol) in freshly dried toluene (10 mL) containing 3 equiv of dienophile was heated at 60 °C until all starting material had disappeared. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography (ethyl acetate–chloroform) on a silica gel column. The product was then recrystallized from hexane–chloroform.

Dimethyl 2-Cyano-5-(diethylamino)-1,6-dihydro-6-oxo-1-phenyl-3,4-pyridinedicarboxylate (7a). After reaction for 3 h followed by chromatography this compound was obtained from **5a** and dimethyl butynedioate in a yield of 363 mg (95%): mp 118–119 °C; IR (KBr) 2230 (CN), 1720 (ester), 1665 (lactam) cm^{-1}; ^1H NMR δ 1.3 (t, 6 H, NCH_2CH_3), 3.45 (q, 4 H, NCH_2CH_3), 4.0 (s, 6 H, CO_2CH_3), 7.4 (m, 5 H, ArH); MS (*m/z*) 383 (M^+, 54), 368 ($M^+ - CH_3$, 100), 351 ($M^+ - CH_3OH$, 65), 322 (91); HRMS calcd for $C_{20}H_{21}N_3O_5$ (M^+), 383.1481, found 383.1490. Anal. Calcd for $C_{20}H_{21}N_3O_5$: C, 62.66; H, 5.52; N, 10.96. Found: C, 62.28; H, 5.43; N, 10.71.

Dimethyl 2-Cyano-5-(diethylamino)-1,6-dihydro-1-methyl-6-oxo-3,4-pyridinedicarboxylate (7b). After reaction for 3 h this compound was obtained from **5b** in a yield of 299 mg (93%): mp 87–88 °C; IR (KBr) 2220 (CN), 1740 (ester), 1720 (ester), 1665 (lactam) cm^{-1}; ^1H NMR δ 1.3 (t, 6 H, NCH_2CH_3), 3.3 (q, 4 H, NCH_2CH_3), 3.8 (s, 3 H, CH_3), 3.9 (s, 3 H, CO_2CH_3), 3.95 (s, 3 H, CO_2CH_3); ^{13}C NMR δ 13.7 (q, NCH_2CH_3), 35.3 (q, NCH_3), 46.3 (t, NCH_2CH_3), 52.6 (q, OCH_3), 53.1 (q, OCH_3), 111.8 (s, CN), 116.8 (q, C-2, ^3J = 4), 118.3 (s, C-3), 132.0 (s, C-4), 143.6 (m, C-5, ^3J = 3), 159.8 (q, C-6, ^3J = 2), 163.0 (q, C=O, ^3J = 5), 165.6 (q, C=O, ^3J = 5); MS (*m/z*) 321 (M^+, 30), 306 ($M^+ - CH_3$, 100), 290 ($M^+ - OCH_3$, 26), 260 (46), 246 (39); HRMS calcd for $C_{15}H_{19}N_3O_5$ (M^+) 321.1325, found 321.1322. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found: C, 55.76; H, 5.87; N, 13.00.

Ethyl 6-Cyano-3-(diethylamino)-1,2-dihydro-2-oxo-1-phenyl-4-pyridinecarboxylate (7c). After reaction for 8 h this compound was obtained from **5a** and ethyl propynoate in a yield of 288 mg (85%): mp 84 °C; IR (KBr) 2230 (CN), 1735 (ester), 1665 (lactam) cm^{-1}; ^1H NMR δ 1.25 (t, 6 H, NCH_2CCH_3), 1.4 (t, 3 H, $CO_2CH_2CH_3$), 3.5 (q, 4 H, NCH_2CH_3), 4.3 (q, 2 H, $CO_2CH_2CH_3$), 7.1 (s, 1 H, H-5), 7.4 (m, 5 H, ArH); ^{13}C NMR δ 13.5 (NCH_2CH_3), 14.1 (OCH_2CH_3), 46.4 (NCH_2CH_3), 61.4 (OCH_2CH_3), 109.4 (d, C-6, ^2J = 3), 113.2 (d, CN, ^3J = 5), 117.8 (d, C-5, ^1J = 174), 120.6 (s, C-4), 127.5, 128.3, 129.5 (C-Ar), 137.8 (C-ipso), 146.3 (m, C-3), 160.1 (C-2), 164.7 (C=O); MS (*m/z*) 339 (M^+, 43), 324 ($M^+ - CH_3$, 56), 310 ($M^+ - C_2H_5$, 100), 264 (73); HRMS calcd for $C_{19}H_{21}N_3O_3$ (M^+) 339.1583, found 339.1586. Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.20; H, 6.22; N, 12.40.

5-(Diethylamino)-1,6-dihydro-6-oxo-1,4-diphenyl-2-pyridinecarbonitrile (7d). After reaction for 12 h this compound was obtained from **5a** and phenylacetylene in a yield of 305 mg (89%): mp 140–141 °C; IR (KBr) 2220 (CN), 1660 (lactam) cm^{-1}; ^1H NMR δ 1.0 (t, 6 H, NCH_2CH_3), 3.05 (q, 4 H, NCH_2CH_3), 6.85 (s, 1 H, H-3), 7.6–7.15 (m, 10 H, ArH); ^{13}C NMR δ 13.6 (q, NCH_2CH_3), 45.9 (t, NCH_2CH_3), 112.4 (d, C-2, ^2J = 2.6), 113.5 (d, CN, ^3J = 5), 120.3 (d, C-3, ^1J = 171), 127.7, 127.8, 128.6, 129.3, 129.5, 129.6 (m, CAr), 136.7 (m, C-4), 138.0, 138.3 (2 × C-ipso), 143.1 (m, C-5), 161.1 (s, C-6); MS (*m/z*) 343 (M^+, 55), 328 ($M^+ - CH_3$, 59), 314 ($M^+ - C_2H_5$, 100), 299 (73); HRMS calcd for $C_{22}H_{21}N_3O$ (M^+) 343.1685, found 343.1686. Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 76.64; H, 6.02; N, 11.93.

Methyl 3-(Diethylamino)-1,2-dihydro-6-methyl-2-oxo-1-phenyl-4-pyridinecarboxylate (10). After reaction of compound **9** with methyl propynoate for 8 h, this compound was isolated in a yield of 47 mg (15%): mp 85–86 °C; IR (KBr) 1740 (ester), 1665 (lactam) cm^{-1}; ^1H NMR δ 1.05 (t, 6 H, NCH_2CH_3), 1.95 (s, 3 H, CH_3), 3.15 (q, 4 H, NCH_2CH_3), 3.9 (s, 2 H, CO_2CH_3), 6.1 (s, 1 H, H-5), 7.4 (m, 5 H, ArH); ^{13}C NMR 21.2 (qd, 6-CH_3), 103.5 (dq, C-5, ^1J = 168) MS (*m/z*) 314 (M^+, 100), 299 ($M^+ - CH_3$, 97), 285 ($M^+ - C_2H_5$, 85), 271 (35); HRMS calcd for $C_{18}H_{22}N_2O_3$ (M^+) 314.1630, found 314.1627.

Dimethyl 5-(Diethylamino)-1,6-dihydro-6-oxo-1-phenyl-3,4-pyridinedicarboxylate (12). After reaction of **11** with dimethyl butynedioate for 3 h, this compound was isolated in a yield of 305 mg (85%): mp 89–90 °C; IR (KBr) 1730 (ester), 1665 (lactam) cm^{-1}; ^1H NMR δ 1.0 (t, 6 H, NCH_2CH_3), 3.1 (q, 4 H, NCH_2CH_3), 3.75 (s, 3 H, CO_2CH_3), 3.9 (s, 3 H, CO_2CH_3), 7.4 (m, 5 H, ArH), 8.2 (s, 1 H, H-2); MS (*m/z*) 358 (M^+, 89), 329 ($M^+ - C_2H_5$, 21), 327 ($M^+ - OCH_3$, 47), 299 ($M^+ - CO_2CH_3$, 100); HRMS calcd for $C_{19}H_{22}N_2O_5$ (M^+) 358.1529, found 358.1533. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.19; N, 7.82. Found: C, 63.54; H, 6.15; N, 7.75.

Reactions of 5-Chloro-3-(diethylamino)-2*H*-1,4-oxazin-2-one 6 with Acetylenic Compounds: Generation of Compounds 8. General procedure: A solution of compound **6** (1 mmol) in neat acetylenic compound (3 mL) was stirred at room temperature until compound **6** had disappeared. Workup and purification of compounds **8** was done as for compound **7** using silica gel plates and chloroform as eluent.

Methyl 6-Cyano-3-(diethylamino)-2-oxo-2*H*-pyran-4-carboxylate (8a). After reaction for 1 h compound **8a** was obtained as an oil from **6** and methyl propynoate in a yield of 188 mg (75%): IR (KBr) 2225 (CN), 1740 (CO) cm^{-1}; ^1H NMR δ 1.2 (t, 6 H, NCH_2CH_3), 3.5 (q, 4 H, NCH_2CH_3), 3.9 (s, 3 H, CO_2CH_3), 7.2 (s, 1 H, H-5); ^{13}C NMR δ 13.4 (CH_2CH_3), 47.4 (CH_2CH_3), 52.5 (OCH_3), 112.4 (d, CN, ^3J = 4), 116.4 (s, C-4), 118.3 (d, C-5, ^1J = 175), 121.6 (d, C-6, ^2J = 4), 141.8 (m, C-3), 158.1 (C-2), 163.6 (CO_2CH_3); MS (*m/z*) 250 (M^+, 100); HRMS calcd for $C_{12}H_{14}N_2O_4$ (M^+) 250.0954, found 250.0950.

3-(Diethylamino)-4-phenyl-2-oxo-2*H*-pyran-6-carbonitrile (8b). After reaction for 40 h compound **8b** was obtained from compound **6** and phenyl acetylene in a yield of 91 mg (34%): mp 84 °C; IR (KBr) 2218 (CN), 1724 (CO) cm^{-1}; ^1H NMR δ 1.0 (t, 6 H, NCH_2CH_3), 3.0 (q, 4 H, NCH_2CH_3), 6.8 (s, 1 H, H-5), 7.5–7.3 (m, 5 H, ArH); ^{13}C NMR δ 13.4 (q, NCH_2CH_3), 46.0 (t, NCH_2CH_3), 112.6 (d, CN, ^3J = 4), 121.1 (d, C-5, ^1J = 171), 125.0 (d, C-6, ^2J = 4), 127.5, 128.8 (C-Ar), 135.0 (m, C-4), 136.5 (C-ipso), 137.3 (m, C-3), 159.3 (s, C-2); MS (*m/z*) 268 (M^+, 100); HRMS calcd for $C_{16}H_{16}O_2N_2$ (M^+) 268.1212, found 268.1207.

Acknowledgment. The authors are indebted to the F.K.K.O. and the "Ministerie voor Wetenschapsbeleid" for financial support. They wish to thank the K. U. Leuven (M.G.T.) and the IWONL (S.M.V. and K.J.V.A.) for a fellowship and the Janssen Pharmaceutica company for elemental analysis. They are also grateful to Dr. S. Toppet, Dr. F. Compernolle, R. De Boer, and P. Valvekens for technical assistance.

Registry No. 1 (R^1 = Ph, R^3 = Cl), 87486-37-1; 1 (R^1 = Me, R^3 = Cl), 87486-33-7; **2** (R^3 = Cl), 125850-02-4; **5a**, 139706-32-4; **5b**, 139706-33-5; **6**, 139706-34-6; **7a**, 139706-35-7; **7b**, 139706-36-8; **7c**, 139706-37-9; **7d**, 139706-38-0; **8a**, 139706-39-1; **8b**, 139706-40-4; **9**, 139706-43-7; **10**, 139706-41-5; **11**, 139706-44-8; **12**, 139706-42-6; diethylamine, 109-89-7; dimethyl acetylenedicarboxylate, 762-42-5; ethyl propiolate, 623-47-2; phenylacetylene, 536-74-3.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of **8a** and **8b** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

An Asymmetric Synthesis of Crobarbatic Acid

Ming-Yi Chen and Jim-Min Fang*

Department of Chemistry, National Taiwan University, Taipei, Taiwan 10764, Republic of China

Received July 9, 1991

The knowledge that pyrrolizidine alkaloids are highly biologically active[1] has ensured that the synthesis[2] of such

(1) For recent reviews, see: (a) Robins, D. J. In *Fortsch. Chem. Org. Naturstoffe/Progr. Chem. Org. Nat. Prod.*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Spring-Verlag: Vienna, 1982; Vol. 41. (b) Robins, D. J. *Nat. Prod. Rep.* **1989**, 221.

0022-3263/92/1957-2937$03.00/0