1,3-Dipolar Cycloaddition Reaction of Phenanthridinium *N*-Imines and *N*-Benzoylimine with Acetylenic Compounds

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N-Aminophenanthridinium salt reacted with dimethyl acetylenedicarboxylate in the presence of potassium carbonate to give a 3,3a-dihydropyrazolo[1,5-*f*]phenanthridine but with mono-substituted acetylenes (ethyl propiolate and benzoylacetylene) it produced aromatized pyrazolo-[1,5-*f*]phenanthridines (XII and XIII). The reaction of the *N*-benzoylimine with di-substituted acetylenes (dimethyl acetylenedicarboxylate and methyl phenylpropiolate) and mono-substituted acetylenes (ethyl propiolate and benzoylacetylene) yielded 1,3a-dihydropyrazolo[1,5-*f*]phen-anthridines and the aromatized products (XII and XIII), respectively.

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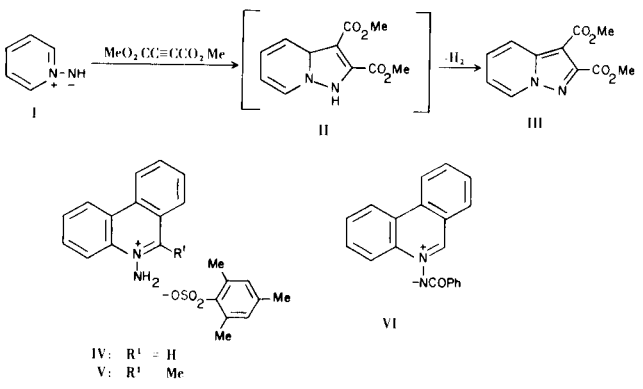
It is well known that *N*-imines (I, R = H) (1) and *N*-acylimines (I, R = CO_2Et or COPh) (2) of pyridines undergo 1,3-dipolar cycloaddition reactions with acetylenic compounds to give fully aromatized pyrazolo[1,5-*a*]-pyridines III. This reaction is believed to proceed *via* dihydropyridine intermediates II, but usually it is difficult to isolate the primary cycloadducts II (3). A possible explanation for this is that loss of resonance energy due to destruction of the aromaticity of the pyridine ring is too large compared with the gain of energy by the formation of two sigma bonds in II, so that the intermediates II readily undergo rearomatization to get stabilization. We have now examined the 1,3-dipolar cycloaddition reaction of phenanthridine system with several activated acetylenes, because the loss of resonance energy in this system by passing from the *N*-imine or *N*-acylimine to the dihydro intermediates is expected to be small enough for the primary cycloadducts to be isolated.

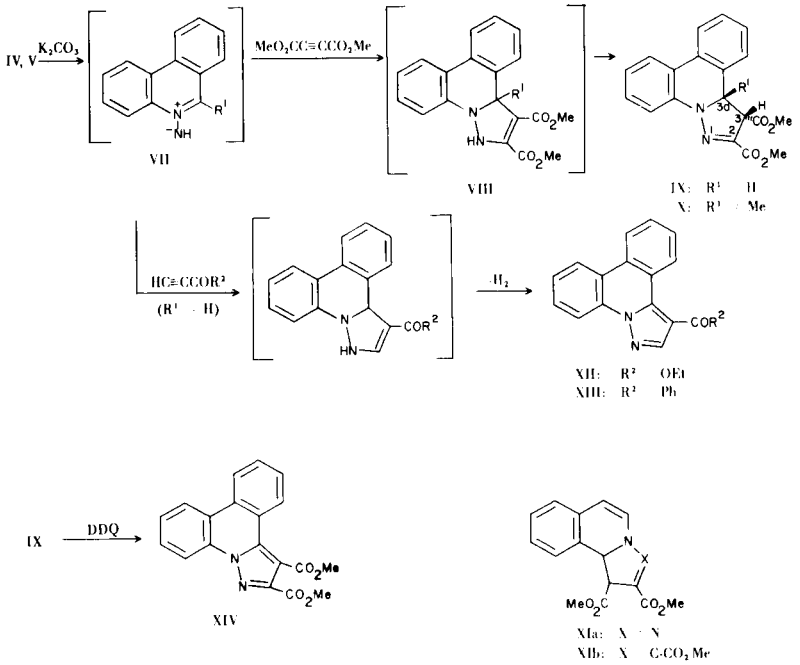
Scheme I



Starting *N*-amine salts of phenanthridine and 6-methyl-phenanthridine (IV and V) were synthesized by the reaction of the parent heterocycles and *O*-mesitylene-sulfonylhydroxylamine (MSH) (4) in 86 and 87% yields, respectively. Benzoylation of IV was effected by heating at 90-95° with benzoyl chloride without solvent to give *N*-benzoylimine VI in 81% yield.

N-Aminophenanthridinium salt (IV), when treated with base, is known to form a yellow high-melting dimeric substance which is inert to 1,3-dipolarophiles (1a). However, the formation of the dimer was found to be markedly suppressed when the reaction was carried out in the presence of strong dipolarophiles. Thus, when IV was treated with potassium carbonate in the presence of excess dimethyl acetylenedicarboxylate in dimethylformamide at room temperature, 1:1-adduct IX was obtained in 57% yield. The dimer was formed only in a small amount. The structure and stereochemistry of the adduct was assigned on the basis of spectral and chemical evidence; its ir spectrum shows a strong carbonyl band at 1730 cm^{-1} and its nmr spectrum reveals the presence of two methoxy-carbonyl singlets at δ 3.93 and 4.07 and two doublets due to H_3 and H_{3a} at δ4.50 and 5.42, respectively, with a coupling constant 14.5 Hz, and a multiplet (8H) in the aromatic region. The observed large coupling of 14.5 Hz is in agreement with a reported value for *cis* vicinal coupling (13.5 Hz) in 1,10b-dihydropyrrolo[2,1-*a*]iso-quinoline (XIb) (5). Compound IX is stable in refluxing toluene, but in the presence of 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) it was converted to aromatized product XIV. (It is interesting to note that both IX and

Scheme 2



XIV have essentially identical melting points and the uv and ir spectra.)

In a similar manner, compound V reacted with dimethyl acetylenedicarboxylate to give adduct X in 32% yield. The stereochemistry of 3a-methyl group and H_3 was tentatively assigned *cis* by a comparison of the chemical shift (δ 3.89) of the methoxycarbonyl groups at C_2 and C_3 in X with those (δ 3.93 and 4.07) of IX, showing no significant difference between them.

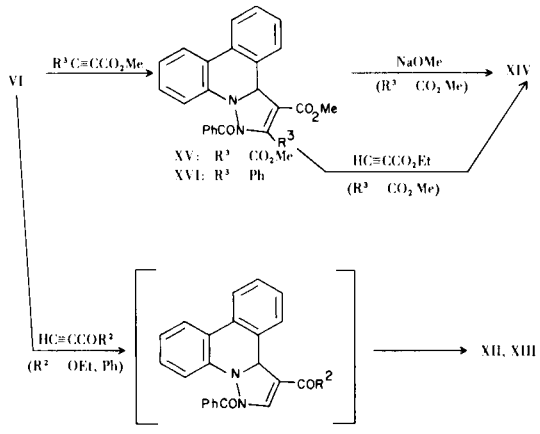
Compounds IX and X are presumed to arise by tautomerization of the unisolable primary cycloadducts VIII which in turn are formed by a 1,3-dipolar cycloaddition reaction between *N*-imines VII derived from IV and V, and dimethyl acetylenedicarboxylate. This behavior closely resembles the cases of isoquinolinium *N*-imine (1a) and carbethoxymethylide (5,6) which form XI with dimethyl acetylenedicarboxylate.

On the other hand, the reaction of IV with ethyl propiolate and benzoylacetylene at room temperature or 50° gave only dimer of VII, but at 80° it afforded aromatized pyrazolo[1,5-*f*]phenanthridines XII and XIII in 21 and 24% yields, respectively. The structures of these adducts followed from their spectral data (see Experimental).

N-Benzoylimine VI also reacted with acetylenic compounds. When a solution of VI and dimethyl acetylenedicarboxylate in benzene was stirred at room temperature, 1:1-cycloadduct XV was obtained in 78% yield, whose structure was assigned on the basis of spectral evidence. The ir spectrum shows three carbonyl bands at 1740, 1715, and 1650 cm^{-1}, and the nmr spectrum reveals the presence of two methoxycarbonyl groups at δ 3.60 and 3.90, one methine proton at δ 5.87 and thirteen aromatic protons. Further confirmation was obtained by conversion of XV into XIV with base treatment. The reaction of VI with methyl phenylpropiolate gave adduct XVI in 55% yield.

In sharp contrast, the reaction of VI with monosubstituted acetylenes such as ethyl propiolate and benzoylacetylene at room temperature produced aromatized products XII and XIII in 61 and 65% yields, respectively.

Scheme 3



One possible rationalization for the different behavior of VI toward di- and mono-substituted acetylenes is that the presence of the substituent at the 2-position of the adducts can stabilize the primary adducts by the conjugation with C_2-C_3 double bond. An alternative is that the mono-substituted acetylenes have stronger ability of hydrogen abstraction from dihydro intermediates than the di-substituted acetylenes. To test these possibilities, XV was stirred with ethyl propiolate in benzene at room temperature, and aromatized compound XIV was obtained in 69% yield (7). This result suggests that the latter explanation is more likely.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on an Hitachi EPI-G2 spectrophotometer, uv spectra on an Hitachi 124 spectrophotometer, and nmr spectra on an Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Preparative tlc was carried out on Merck Alumina PF_{254}.

N-Aminophenanthridinium Mesitylenesulfonate (IV).

This salt was obtained in 86% yield form phenanthridine by a procedure described in reference 4, m.p. 204-205° (from methanol-ethyl acetate).

Anal. Calcd. for $C_{22}H_{22}N_2O_3S$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.81; H, 5.42; N, 6.76.

N-Amino-6-methylphenanthridinium Mesitylenesulfonate (V).

Similarly, compound V was obtained from 6-methylphenanthridine in 87% yield as white crystals, m.p. 246-247° (from methanol-ethyl acetate).

Anal. Calcd. for $C_{23}H_{24}N_2O_3S$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.50; H, 5.92; N, 6.89.

N-Benzoyliminophenanthridinium Betaine (VI).

A mixture of IV (1.1 g.) and benzoyl chrolide (3.0 g.) was heated at 90-95° for 3 hours. The excess benzoyl chloride was evaporated off *in vacuo*. The residue was washed with ether, made alkaline with 10% potassium hydroxide solution and extracted with chloroform. The extract was concentrated to give yellow plates of VI, m.p. 217-218° (from methanol), yield, 670 mg. (81%); ir (chloroform): cm^{-1} 1590, 1545, and 1330; nmr (deuterochloroform): δ 7.25-9.1 (m, 13H) and 9.77 (s, 1H, H-6).

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73; N, 9.39. Found: C, 80.24; H, 4.73; N, 9.50.

Dimethyl 3,3a-Dihydropyrazolo[1,5-*f*]phenanthridine-2,3-dicarboxylate (IX).

Potassium carbonate (414 mg.) was added to a stirred solution of IV (788 mg.) and dimethyl acetylenedicarboxylate (428 mg.) in dimethylformamide (15 ml.). The mixture was stirred for 1 day at room temperature and the solvent was evaporated off. The residue was dissolved in water and the aqueous layer was extracted with chloroform. The extract was concentrated to give yellow crystals, which were recrystallized from methanol, m.p. 158-159°, yield, 384 mg. (57%); ir (chloroform): cm^{-1} 1730; nmr (deuterochloroform): δ 3.93 (s, 3H, CO_2CH_3), 4.07 (s, 3H, CO_2CH_3), 4.50 (d, 1H, J = 14.5 Hz, H-3), 5.42 (d, 1H, J = 14.5 Hz, H-3a), 7.0-8.8 (m, 8H).

Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 68.17; H, 4.50; N, 8.40.

Dimethyl 3,3a-Dihydro-3a-methylpyrazolo[1,5-*f*]phenanthridine-2,3-dicarboxylate (X).

Using a similar procedure described above for IX, compound X was obtained from V (204 mg.) and dimethyl acetylenedicarboxylate (142 mg.), m.p. 133-134° (from methanol), yield, 73 mg. (32%); ir (chloroform): cm^{-1} 1735 and 1705; nmr (deuterochloroform): δ 1.29 (s, 3H, CH_3), 3.89 (s, 2 x 3H, 2 x CO_2CH_3), 4.82 (s, 1H, H-3), and 7.0-8.0 (m, 8H).

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.61; H, 5.16; N, 8.03.

Ethyl Pyrazolo[1,5-*f*]phenanthridine-3-carboxylate (XII).

(A) From IV.

Potassium carbonate (213 mg.) was added to a stirred solution of IV (394 mg.) and ethyl propiolate (147 mg.) in dimethylformamide (5 ml.) at 80° and the mixture was stirred at 80° for 4 hours. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water and concentrated. The residue was purified by preparative tlc on alumina with benzene-*n*-hexane (1:1) to give white crystals of XII, m.p. 132-133° (from methanol), yield, 61 mg. (21%); ir (chloroform): cm^{-1} 1700; nmr (deuterochloroform): δ 1.47 (t, 3H, J = 7 Hz, $CO_2CH_2CH_3$), 4.47 (q, 2H, J = 7 Hz, $CO_2CH_2CH_3$), 8.43 (s, 1H, H-2), 7.4-7.8 (m, 4H), 8.25-8.75 (m, 3H), and 9.3-9.9 (m, 1H).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.40; H, 4.89; N, 9.61.

(B) From VI.

A solution of VI (100 mg.) and ethyl propiolate (50 mg.) in benzene (5 ml.) was stirred for 24 hours at room temperature. The reaction mixture was evaporated off *in vacuo* and the resiude was recrystallized from methanol to give XII, m.p. 132-133°, yield, 60 mg. (61%).

3-Benzoylpyrazolo[1,5-*f*]phenanthridine (XIII).

(A) From IV.

By using a procedure (A) described for XII, IV (394 mg.) and benzoylacetylene (185 mg.) gave white crystals of XIII, m.p. 151-152° (from methanol), yield, 76 mg. (24%); ir (chloroform): cm^{-1} 1640; nmr (deuterochloroform): δ 8.14 (s, 1H, H-2) and 7.35-9.45 (m, 13H).

Anal. Calcd. for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.80; H, 4.43; N, 8.77.

(B) From VI.

By using a procedure (B) described for XII, V (100 mg.) and benzoylacetylene (65 mg.) gave XIII, m.p. 151-152°, yield, 72 mg. (65%).

Dimethyl Pyrazolo[1,5-*f*]phenanthridine-2,3-dicarboxylate (XIV).

(A) From IX.

A solution of IX (72 mg.) and DDQ (49 mg.) in toluene (5 ml.) was heated under reflux for 1 hour. The mixture was evaporated off *in vacuo* and the residue was purified by chromatography on alumina using ethyl acetate as solvent to give white needles of XIV, m.p. 157-158° (from methanol), [lit. (8) m.p. 136°], yield, 46 mg. (64%); ir (chloroform): cm^{-1} 1720; nmr (deuterochloroform): δ 4.05 (s, 6H, 2 x CO_2CH_3) and 7.40-8.75 (m, 8H).

Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.25; H, 4.22; N, 8.38. Found: C, 68.47; H, 4.23; N, 8.35.

(B) By Treatment of XV with Sodium Methoxide.

A solution of XV (66 mg.) and sodium methoxide (70 mg.) in absolute methanol (5 ml.) was stirred at room temperature for 1 hour. The precipitated crystals were collected and recrystallized from methanol to give XIV, m.p. 157-158°, yield, 12 mg. (24%).

(C) By Treatment of XV with Ethyl Propiolate.

A solution of XV (50 mg.) and ethyl propiolate (11 mg.) in benzene (4 ml.) was stirred at room temperature for 5 hours. The mixture was evaporated off *in vacuo* and the residue was recrystallized from methanol to give XIV, m.p. 157-158°, yield, 26 mg. (69%).

Dimethyl 1-Benzoyl-1,3a-dihydro pyrazolo[1,5-*f*]phenanthridine-2,3-dicarboxylate (XV).

A solution of VI (100 mg.) and dimethyl acetylenedicarboxylate (71 mg.) in benzene (5 ml.) was stirred for 10 hours at room temperature. The reaction mixture was evaporated off *in vacuo* and the residue was recrystallized from methanol to give white crystals of XV, m.p. 188-189°; ir (chloroform): cm^{-1} 1740, 1715, 1650; nmr (deuterochloroform): δ 3.60 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 5.87 (s, 1H, H-3a), 7.2-8.2 (m, 13H).

Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.71; H, 4.56; N, 6.29.

Methyl 1-Benzoyl-1,3a-dihydro-2-phenylpyrazolo[1,5-*f*]phenanthridine-3-carboxylate (XVI).

A solution of VI (100 mg.) and methyl phenylpropiolate (80 mg.) in benzene (5 ml.) was heated under reflux for 12 hours. The reaction mixture was evaporated off *in vauco*, and the residue was recrystallized from acetone to give white crystals of XVI, m.p. 209-211°, yield, 84 mg. (55%); ir (chloroform): cm^{-1} 1705, 1660; nmr (deuterochloroform): δ 3.44 (s, 3H, CO_2CH_3), 5.82 (s, 1H, H-3a), and 7.25-8.2 (m, 18H).

Anal. Calcd. for $C_{30}H_{22}N_2O_3$: C, 78.58; H, 4.84; N, 6.11. Found: C, 78.35; H, 4.86; N, 6.15.

REFERENCES AND NOTES

(1a) R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Letters*, 387 (1962); (b) V. Boekelheide and N. A. Fedruk, *J. Org. Chem.*, **33**, 2062 (1968); (c) Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocyclic Chem.*, **10**, 447 (1973); (d) K. Kasuga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.*, **22**, 1814 (1974); (e) Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocyclic Chem.*, **12**, 119 (1975).

(2a) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36**, 2978 (1971); (b) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Bull. Chem. Soc. Japan*, **45**, 2050 (1972); (c) Y. Tamura, Y. Miki, K. Nakamura, and M. Ikeda, *J. Heterocyclic Chem.*, in press.

(3) Exceptions to this are *N*-acylimino-2-methylpyridinium betaines (2a, b) and 1-benzoyliminoquinazolinium and 2-benzoyliminophthalazinium betaines (2c).

(4) Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 4133 (1972).

(5) T. Kutsuma, Y. Sekine, K. Fujiyama, and Y. Kobayashi, *Chem. Pharm. Bull.*, **20**, 2701 (1972).

(6) N. S. Basketter and A. O. Plunkett, *J. Chem. Soc., Chem. Commun.*, 594 (1974).

(7) Similar treatment of XV with dimethyl acetylenedicarboxylate resulted in the recovery of the starting material.

(8) J. van Alphen, *Rec. Trav. Chim.*, **62**, 334 (1943).