Compounds Related to Acridine. X.[1] The Reaction of 9-Ethynylacridine with Active Methylene Compounds

Otohiko Tsuge[2] and Akiyoshi Torii*

Research Institute of Industrial Science, Kyushu University, Hakozaki, Higashi-ku, Fukuoka, 812
**Department of Industrial Chemistry, Kurume Technical College, Komorino, Kurume, 830*

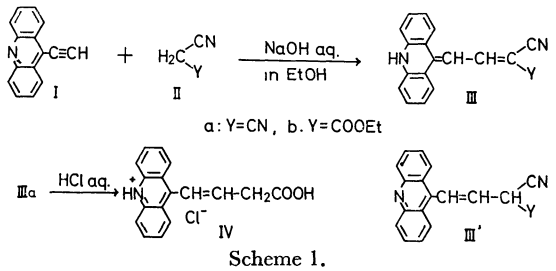
(Received June 28, 1972)

In the presence of aqueous sodium hydroxide, 9-ethynylacridine (I) reacts with malononitrile and with ethyl cyanoacetate to yield the corresponding 1,1-disubstituted 3-(9-acridanylidene)propenes III. A similar reaction of I with diethyl malonate affords a 2: 1 adduct VI and a 1: 2 adduct VII. On the other hand, I reacts with acetylacetone to give 3-acetyl-5-(9-acridanylidene)-1-(9-acridinyl)pent-1,3-diene (IX). In this context, the reaction of 9-chloroacridine (XI) with active methylene compounds has been reinvestigated; XI reacts with malononitrile and with ethyl cyanoacetate to afford products XII with an acridane structure, while with diethyl malonate XI gives 9-di(ethoxycarbonyl)methylacridine (XIII), as has been reported previously.

Little is known about the reaction of heteroaromatics having an ethynyl group. Recently, we have reported[3] a convenient method of the preparation of 9-ethynylacridine (I) and some of its reactions.[3,4] Our previous studies[3,4] suggested that the acetylene I would react easily with active methylene compounds to form 2-substituted 1-(9-acridinyl)ethylenes. We will now report on the novel reaction of the acetylene I with active methylene compounds. In this connection, the present paper will also deal with the reaction of 9-chloroacridine with active methylene compounds.

Results and Discussion

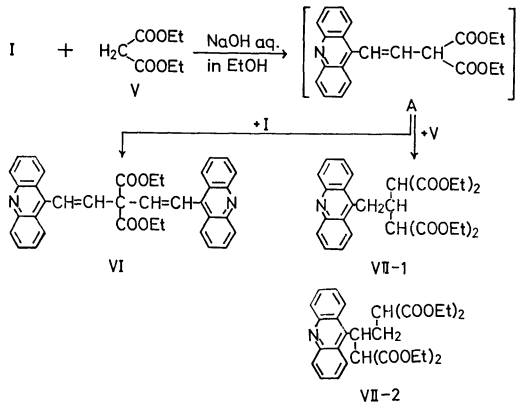
The reaction of the acetylene I with malononitrile (IIa) in the presence of aqueous sodium hydroxide in ethanol at room temperature afforded a 1: 1 adduct IIIa as violet prisms in an excellent yield. The spectral data of IIIa indicated that IIIa was not the expected 1-(9-acridinyl)-3,3-dicyanopropene (III'), but rather 3-(9-acridanylidene)-1,1-dicyanopropene (Scheme 1).



Scheme 1.

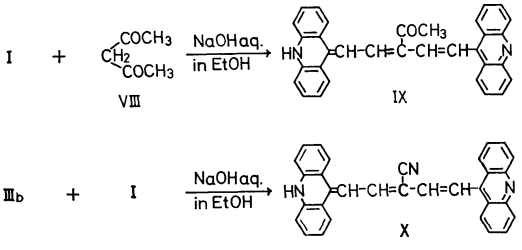
Similarly, the acetylene I reacted with ethyl cyanoacetate (IIb) to give the corresponding acridanylidene derivative IIIb. The hydrolysis of IIIa with hydrochloric acid afforded hydrochloride of 4-(9-acridinyl)-but-2-enoic acid (IV), whose structure was confirmed by the spectral data as well as by the results of microanalysis.

On the other hand, the reaction of acetylene I with diethyl malonate (V) under similar conditions afforded a 2: 1 adduct VI and a 1: 2 adduct VII of I and V, respectively, both as pale yellow prisms, in 36 and 4% yields respectively. On the basis of their spectral data, VI and VII were deduced to be 1,5-di(9-acridinyl)-3,3-di(ethoxycarbonyl)pent-1,4-diene, and either 1,1,3,3-tetra(ethoxycarbonyl)-2-(9-acridinylmethyl)propane (VII-1) or 1,1,4,4-tetra(ethoxycarbonyl)-2-(9-acridinyl)-butane (VII-2), respectively. The structures of VI and VII correspond to those of 1: 1 Michael-type adducts of A to the acetylene I and to V respectively (Scheme 2).



Scheme 2.

The reaction of the acetylene I with acetylacetone (VIII) yielded a product IX, whose molecular formula corresponded to that of the compound derived from a 2: 1 adduct of I and VIII under the elimination of an acetyl group. From the inspection of its spectral data, IX was identified as 3-acetyl-5-(9-acridanylidene)-1-(9-acridinyl)pent-1,3-diene.



Scheme 3.

The two products VI and IX correspond to the compounds obtainable from two moles of the acetylene I and one mole of an active methylene compound.

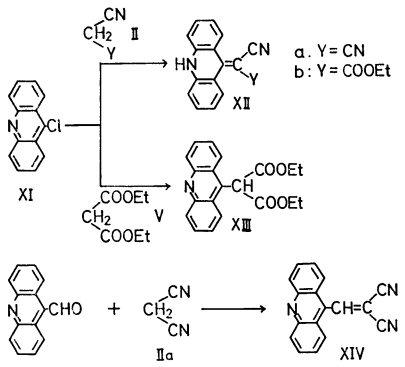
1) Part IX of this series: O. Tsuge and A. Torii, *Org. Prep. Proced. Int.*, in press (1972).
2) To whom inquiries should be directed.
3) O. Tsuge and A. Torii, This Bulletin, **43**, 2920 (1970).
4) O. Tsuge and A. Torii, *Org. Prep. Proced. Int.*, in press (1972).

Therefore, the 1: 1 adduct would be expected to react with the acetylene I to give compounds of the VI or IX type.

Although IIIa did not react with the acetylene I, the reaction of IIIb with I afforded 5-(9-acridanylidene)-1-(9-acridinyl)-3-cyanopent-1,3-diene (X), whose structure corresponds to that of the compound derived from a 1: 1 adduct by decarbethoxylation. The structure of X was confirmed by the spectral data as well as by the results of microanalysis. The pathway for the formation of IX and X is not yet clear, however.

In view of the formation of the acridane-like compound III, it is conceivable that the products from the reaction of 9-chloroacridine (XI) with active methylene compounds have acridane-like structures. Investigations on the reaction of XI with active methylene compounds have been reported by several workers. Most of them[5-7] have reported the products to be derivatives of 9-methylacridine. Only Kröhnke and Honig[8] discussed the possibility of an equilibrium between acridine and acridane structures.

We investigated the reaction of XI with active methylene compounds in order to determine whether or not the products had the acridane structure. The reaction of XI with malononitrile (IIa) and with ethyl cyanoacetate (IIb) afforded products of the acridane type, XIIa and XIIb, while XI reacted with diethyl malonate (V) to give 9-di(ethoxycarbonyl)methylacridine (XIII), as has been reported in the literature.[5]



Scheme 4.

The UV spectra of the acridanylidene compounds, III, X, and XII, exhibited absorption bands in a longer-wavelength region. The UV spectrum of XIIa showed a strong band at 480 nm, while an absorption band appeared at 366 nm in the spectrum of 1-(9-acridinyl)-2,2-dicyanoethylene (XIV). This can be explained by the longer conjugation of the acridanylidene structures.

Experimental

All the melting points are uncorrected. The IR spectra were measured as KBr pellets, and the UV spectra were determined in ethanol solutions. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet and an ionization energy of 70 eV, while the NMR spectra were determined at 60 MHz with a Hitach-R-20 NMR spectrometer, with TMS as the internal reference. The microanalyses were performed by Miss M. Akita of our laboratory.

Reaction of the Acetylene I with Malononitrile (IIa). A solution of 0.3 g of I, 0.1 g of IIa, and one drop of an aqueous saturated sodium hydroxide solution in 5 ml of ethanol was stirred at room temperature for 1 hr; during this time crystals were deposited. Filtration gave 0.36 g (91%) of violet crystals which, on recrystallization from ethanol, afforded 3-(9-acridanylidene)-1,1-dicyanopropene (IIIa), mp 280—281 °C, as violet prisms.

Found: C, 80.49; H, 3.95; N, 15.36%. Calcd for $C_{18}H_{11}N_3$: C, 80.28; H, 4.12; N, 15.61%.

IR cm^{-1}: ν_{NH} 3300, $\nu_{C\equiv N}$ 2240. NMR (DMSO-d_6) δ ppm: 6.85 (1H, doublet, =C**H**, 12 Hz), 7.15—8.1 (9H, complicated signal, =C**H** and aromatic protons (8H)), 12.1 (1H, singlet, N**H**, exchanged with D_2O). UV λ_{max} nm (log ε): 253 (4.65), 318 (4.0), 570 (4.5). Mass spectrum *m/e*: 269 (M^+).

Similarly, the acetylene I reacted with ethyl cyanoacetate (IIb) to give a 98% yield of the corresponding acridanylidene derivative IIIb, mp 246°C, as violet prisms (from ethanol).

Found: C, 76.20; H, 5.08; N, 8.67%. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86%.

IR cm^{-1}: ν_{NH} 3290, $\nu_{C\equiv N}$ 2245, $\nu_{C=O}$ 1675. NMR (DMSO-d_6) δ ppm: 1.28 (3H, triplet, C**H**$_3$), 4.19 (2H, quartet, C**H**$_2$), 6.8—8.5 (10H, complicated, olefinic (2H) and aromatic protons (8H)), 11.7 (1H, singlet, N**H**, exchanged with D_2O). UV λ_{max} nm (log ε): 252 (4.65), 316 (3.95), 550 (4.4). Mass spectrum *m/e*: 316 (M^+).

Hydrochloride of 4-(9-Acridinyl)but-2-enoic acid (IV). A suspension of 0.5 g of IIIa in 5 ml of concentrated hydrochloric acid was stirred at 95°C for 2 hr. Filtration gave 0.35 g (56%) of IV, mp 200—201°C, as yellow prisms.

Found: C, 68.14; H, 4.62; N, 4.85%. Calcd for $C_{17}H_{13}NO_2 \cdot HCl$: C, 68.11; H, 4.67; N, 4.67%.

IR cm^{-1}: ν_{NH} and ν_{OH} 3000—2300, $\nu_{C=O}$ 1730, Mass spectrum *m/e*: 263 ($C_{17}H_{13}NO_2^+$), 218 (263$^+$—COOH, base peak), 204 (218$^+$—CH_2), 178 (204$^+$—C_2H_2).

Reaction of the Acetylene I with Diethyl Malonate (V). A solution of 0.3 g of I and 0.2 g of V in 5 ml of ethanol containing one drop of an aqueous saturated sodium hydroxide solution was stirred at room temperature for 1 hr. The reaction mixture was then concentrated *in vacuo* to leave a residue which, on recrystallization from petroleum ether (bp 40—65°C), gave 1,5-(9-acridinyl)-3,3-di(ethoxycarbonyl)-pent-1,4-diene (VI), mp 197—198°C, as pale yellow prisms. Yield, 0.15 g (36%).

Found: C, 76.28; H, 5.39; N, 4.84%. Calcd for $C_{37}H_{30}N_2O_4 \cdot H_2O$: C, 76.01; H, 5.52; N, 4.79%.

IR cm^{-1}: $\nu_{C=O}$ 1735. NMR ($CDCl_3$) δ ppm: 1.0 (6H, triplet, C**H**$_3$), 3.5 (4H, quartet, C**H**$_2$), 6.7—8.6 (20H, complicated, olefinic (4H) and aromatic protons (16H)). Mass spectrum *m/e*: 566 (M^+), 493 (M^+—COOEt), 420 (493$^+$—COOEt).

The mother liquor was evaporated *in vacuo* to leave a residue, which was then chromatographed on alumina, using benzene as the eluent, to give 30 mg (4%) of a 1: 2 adduct VII. Recrystallization from petroleum ether (bp 40—60°C) afforded pure VII, mp 102—103°C, as pale yellow prisms.

Found: C, 66.71; H, 6.33; N, 3.03%. Calcd for $C_{29}H_{33}NO_8$: C, 66.52; H, 6.35; N, 2.68%.

IR cm^{-1}: $\nu_{C=O}$ 1755, 1735. NMR ($CDCl_3$) δ ppm: 1.0

5) Y. Mizuno, K. Adachi, and K. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **2**, 225 (1954).
6) A. A. Goldberg and Wm. Kelly, Brit. 600354 (1948).
7) E. N. Morgan and D. J. Tivey, Brit. 789696 (1958).
8) F. Kröhnke and H. L. Honig, *Ann. Chem.*, **624**, **97** (1959).

(12H, sextet, CH_3), 4.0 (13H, multiplet, CH_2 (10H) and CH (3H)), 8.0 (8H, multiplet, aromatic protons). Mass spectrum *m/e*: 523 (M^+), 450 ($M^+-COOEt$), 363 ($M^+-CH_2(COOEt)_2$), 204 ($363^+-CH(COOEt)_2$).

Reaction of the Acetylene I with Acetylacetone (VIII). To a solution of 0.5 g of I and 0.2 g of VIII in 10 ml of ethanol was added two drops of an aqueous sodium hydroxide solution; the reaction mixture was then stirred at room temperature for 15 hr. After it had been allowed to stand overnight, filtration gave 0.16 g (22%) of crystals. Recrystallization from dioxane afforded 3-acetyl-5-(9-acridanylidene)-1-(9-acridinyl)pent-1,3-diene (IX), mp 223—224°C, as violet prisms.

Found: C, 85.13; H, 5.38; N, 5.82%. Calcd for $C_{33}H_{24}N_2O$: C, 85.32; H, 5.21; N, 6.03%.

IR cm^{-1}: ν_{NH} 3280, $\nu_{C=O}$ 1620. UV λ_{max} nm (log ε): 249 (5.1), 346 (4.1), 525 (4.3). Mass spectrum *m/e*: 464 (M^+), 421 (M^+-COCH_3), 286 (M^+—acridinyl), 260 (M^+—9-ethynylacridine), 217 (260^+-COCH_3), 204 (9-ethynylacridine$^+$), 193 (base peak), 179 (acridine$^+$).

Reaction of the Acetylene I with the Acridanylidene Derivative IIIb. A solution of 0.15 g of I and 0.2 g of IIIb in 5 ml of ethanol was stirred at room temperature for 4.5 hr; during this time crystals were deposited. Filtration and recrystallization from dioxane gave 0.2 g (71%) of 5-(9-acridanylidene)-1-(9-acridinyl)-3-cyanopent-1,3-diene (X), mp 264—265°C, as violet prisms.

Found: C, 85.92; H, 4.56; N, 9.06%. Calcd for $C_{32}H_{21}N_3$: C, 85.88; H, 4.73; N, 9.39%.

IR cm^{-1}: ν_{NH} 3300, $\nu_{C\equiv N}$ 2220. UV λ_{max} nm (log ε): 250 (4.9), 318 (4.0), 570 (4.5). Mass spectrum *m/e*: 447 (M^+), 268 (M^+—acridine), 243 (M^+—9-ethynylacridine), 217 (243^+-CN), 204 (9-ethynylacridine$^+$), 193 (base peak), 179 (acridine$^+$).

Reaction of 9-Chloroacridine (XI) with Malononitrile (IIa). To a solution of 0.5 g of XI[9] and 0.5 g of IIa in 5 ml of ethanol was added four drops of an aqueous sodium hydroxide solution; the reaction mixture was then stirred at room temperature for 1.5 hr; during which time crystals were precipitated. Filtration gave 0.34 g (60%) of reddish orange crystals. Recrystallization from nitrobenzene afforded the 9-acridanylidene derivative XIIa, mp 339°C (lit,[7] mp 342°C), as reddish orange prisms.

IR cm^{-1}: ν_{NH} 3280, $\nu_{C\equiv N}$ 2215. UV λ_{max} nm (log ε): 240 (4.3), 294 (4.0), 480 (4.1). NMR (DMSO-d_6) δ ppm: 7.2—8.8 (8H, complicated, aromatic protons), 12.5 (1H, broad, NH, exchanged with D_2O).

Similarly, XI reacted with ethyl cyanoacetate (IIb) to give a 60% yield of the 9-acridanylidene derivative XIIb, mp 218°C (lit,[6] mp 222—224°C), as violet prisms.

IR cm^{-1}: ν_{NH} 3280, $\nu_{C\equiv N}$ 2210, $\nu_{C=O}$ 1660. UV λ_{max} nm (log ε): 247 (4.7), 293 (4.1), 480 (3.9). NMR (DMSO-d_6) δ ppm: 1.19 (3H, triplet, CH_3), 4.20 (2H, quartet, CH_2), 7.2—8.4 (8H, multiplet, aromatic protons), 12.40 (1H, broad, NH, exchanged with D_2O).

On the other hand, the reaction of XI with diethyl malonate (V) according to the reported method[5] gave the 9-methylacridine derivative XIII, mp 102—103°C (lit,[5] mp 100—102°C), as pale yellow prisms, as has been reported previously.

1-(9-Acridinyl)-2,2-dicyanoethylene (XIV). A solution of 1.0 g of acridine-9-carboxaldehyde[10] and 0.32 g of IIa in 10 ml of ethanol containing one drop of an aqueous sodium hydroxide solution was stirred at 60°C for 5 min. After the reaction mixture had been cooled, filtration gave 1.2 g (97%) of yellow crystals. Recrystallization from benzene afforded XIV, mp 181—182°C (decomp.), as yellow plates.

Found: C, 80.11; H, 3.65; N, 16.53%. Calcd for $C_{17}H_9N_3$: C, 79.98; H, 3.55; N, 16.46%. UV λ_{max} nm (log ε): 248 (4.9), 366 (3.8).

9) A. Albert and B. Ritchie, "Organic Syntheses," Coll. Vol. III, p. 53 (1955).

10) O. Tsuge, M. Nishinohara, and M. Tashiro, This Bulletin, **36**, 1477 (1963).