[Chem. Pharm. Bull. 24(4)591—595 (1976)]

UDC 547.594.3.04 : 547.288.1.04

Polycyclic N-Hetero Compounds. X.[1] Reactions of 1,3-Cyclohexanedione and Its Dimer with Formamide or Trisformylaminomethane

Takaji Koyama, Sumio Fukuoka, Takashi Hirota, Jun Maeyama, Shinji Ohmori, and Masatoshi Yamato

Faculty of Pharmaceutical Sciences, Medical School, Okayama University[2]

(Received June 4, 1975)

Condensation of 1,3-cyclohexanedione (I) with formamide gave 9,10-dihydro-1,3,5,7-tetraazaphenanthrene (II), 1,2,3,4,5,6,7,8,9,10-decahydro-11,13-diazabenzo[*g*]chrysene-1,-5-dione (III), 1,2,5,6-tetrahydro-3,7,9,11,13-pentaazadibenzophenanthrene (IV), and 7,8,13,14-tetrahydro-2,4,6,10,12-pentaazabenzo[*c*]chrysene (V). Dehydrogenation of II with sulfur gave 1,3,5,7-tetraazaphenanthrene (VI). To make sure the formation mechanism of IV and V, dimer of I (enol form of VII′) was heated with formamide or trisformylaminomethane and the formation of IV and V were confirmed.

In the previous paper,[1] the direct one-step synthesis of 5,6-dihydrobenzo[*h*]quinazoline or 5,6-dihydrobenzo[*f*]quinazoline from 1-tetralone or 2-tetralone with formamide (FA) or trisformylaminomethane (TFM) was reported. To obtain some fused pyrimidines, we used 1,3-cyclohexanedione (I) and its dimer (VII′ enol form) as carbonyl compounds. The present paper describes the results of I and its dimer with FA or TFM. As the first method, the FA solution of I was gradually heated to 160° under dry ammonia stream and then the reaction mixture was fractionated with alumina column chromatography. As shown in Chart 1, 9,10-dihydro-1,3,5,7-tetraazaphenanthrene (II) and 1,2,3,4,5,6,7,8,9,10-decahydro-11,13-diazabenzo[*g*]chrysene-1,5-dione (III) were obtained. Nuclear magnetic resonance (NMR) spectrum of II exhibited two-methylene groups at δ 3.14, C_8-proton at δ 8.65, C_2 and C_6-protons at δ 9.16, 9.19, and C_4-proton at δ 9.54. Perkampus and Bluhm[3] described that C_5-proton of 2,4-diazaphenanthrene was shifted to lower field *ca.* 0.5 ppm relative to C_5-proton of 1,3-diazaphenanthrene by the paramagnetic effect of nitrogen atom of 4-position. Our observation of C_5-proton chemical shift of II was similar to that of Perkampus and Bluhm.[3]

The infrared (IR) spectrum of III had C=O band at 1676 cm^{-1} and its NMR spectrum exhibited sixteen protons (eight methylene protons) at δ 2.10—3.32 as multiplet and two protons at δ 8.16 and 9.25 (each one-proton singlet) attributable to pyrimidine ring protons. The mass spectrum of III showed the parent peak at *m/e* 318 which agreed with the molecular weight of III. The formation process of III was shown in route A of Chart 2. Another route B was considered but in this case 1,2,3,4,5,6,7,8,9,10-decahydro-12,14-diazabenzo[*g*]chrysene-4,8-dione (X) should be formed. Taking note of pyrimidine ring protons of III and X in NMR spectra in deuterochloroform, III is similar to 9,10-dihydro-1,3-diazaphenanthrene (III′) and X is similar to 9,10-dihydro-2,4-diazaphenanthrene (X′). The chemical shift of pyrimidine ring protons of III′ appeared at δ 8.98, 9.00 (unassigned) and those of X′ at δ 8.50 (C_1–H), 9.10 (C_3–H) (both in deuterochloroform).[1] The pyrimidine ring protons of the obtained compound appeared at δ 8.16, 9.25. The signal of δ 9.25 was assigned to a proton between two nitrogen atoms, with a little lower field shift due to the effect of two carbonyl groups (–R effect) and polycyclic system. However, the higher field signal (δ 8.16) was further shifted to upper field relative to the usual pyrimidine ring proton adjacent to one nitrogen atom (4 or 6-position

1) Part IX: T. Koyama, T. Hirota, F. Yagi, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **23**, 3151 (1975).
2) Location: *1-1, Tsushima-naka 1-chome, Okayama, 700, Japan.*
3) H.H. Perkampus and T. Bluhm, *Tetrahedron*, **28**, 2099 (1972).

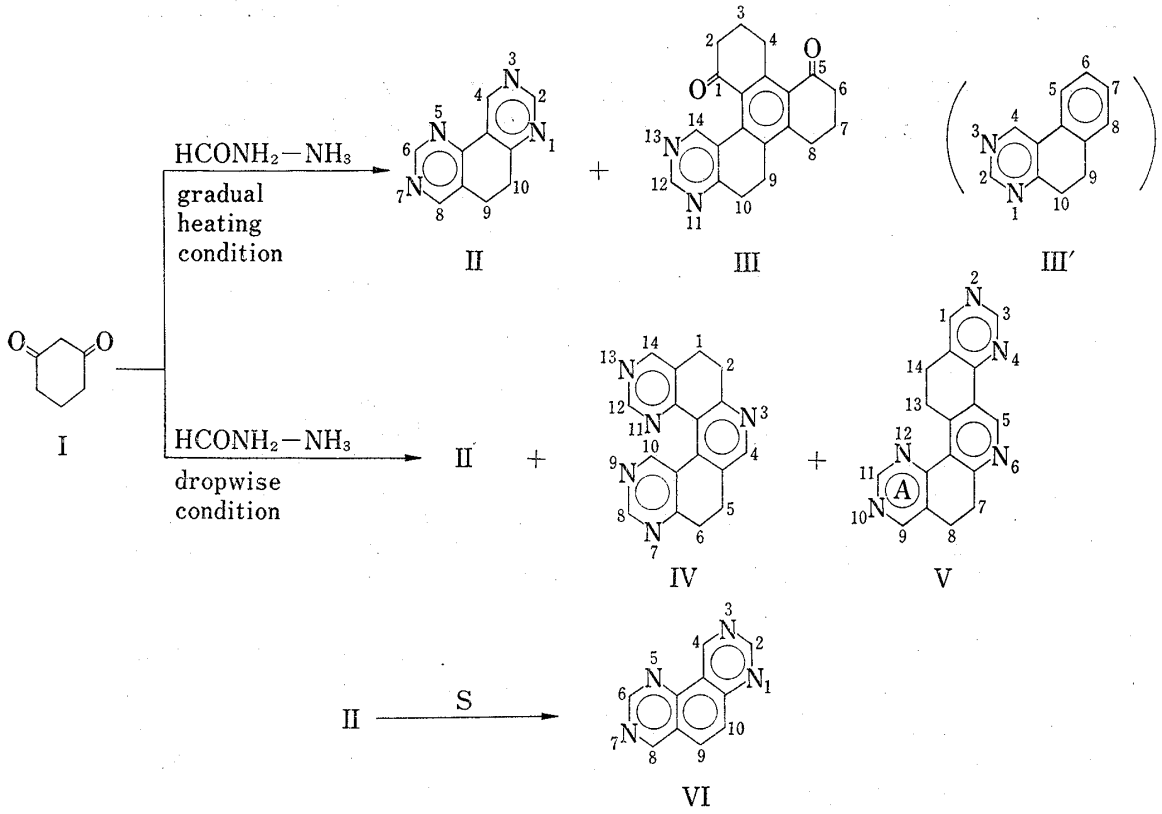

Chart 1

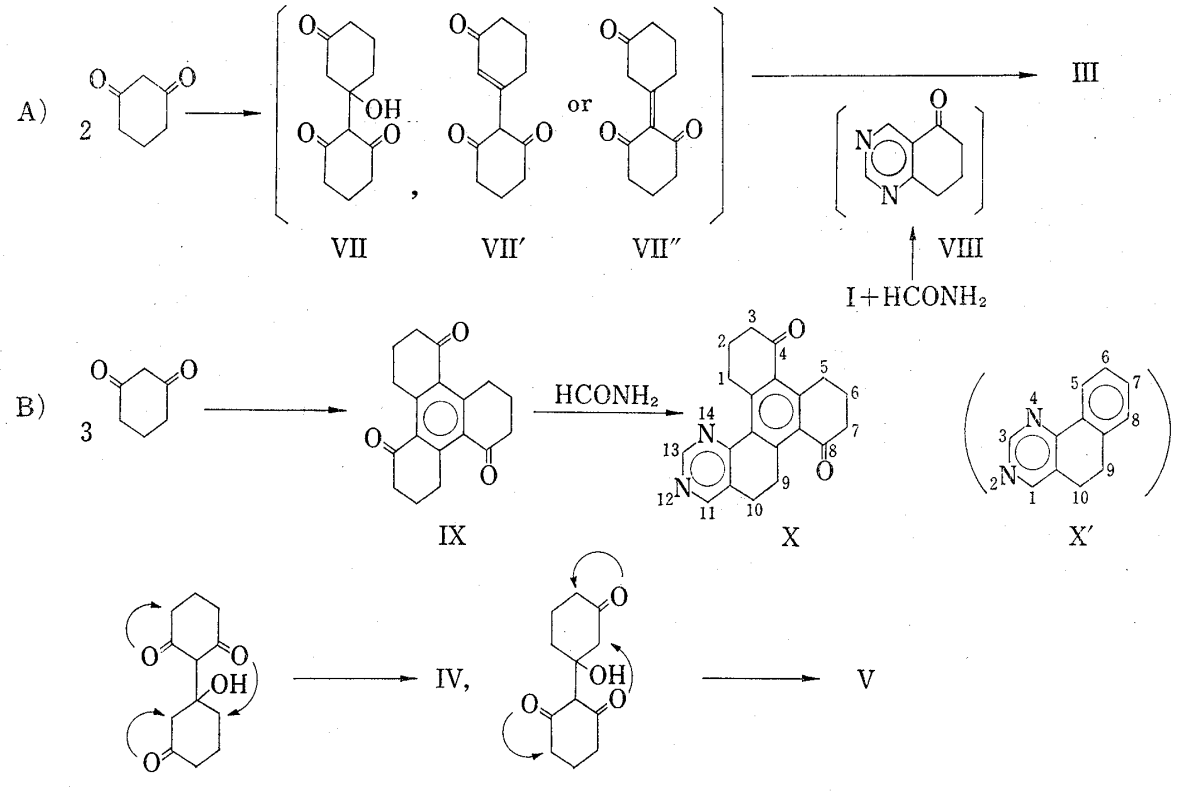

Chart 2

of pyrimidine ring). The C_{11}-proton of X has no factor to shift upper field than δ 8.50 (C_1-proton of X′), but considering from the Dreiding model, C_{14}-proton of III should be much

subjected to the anisotropic effect of upper field shift by C_1-carbonyl group. The structure of III was determined by the above reasons.

In order to cyclize the two residual carbonyl groups of III to fused pyrimidine rings, similar reaction was carried out until disappearance of the spot of III on thin-layer chromatography (TLC). But only II was isolated, identical with the specimen with above method. Dehydrogenation of II with sulfur gave 1,3,5,7-tetraazaphenanthrene (VI) easily.

In the above method, many spots were observed on TLC, consequently fractionation and purification of the reaction mixture were difficult. As the second method, to a one-hr heated FA at 140° under dry ammonia stream, the cold FA solution of I was added dropwise during *ca.* 0.5 hr. Considerable reduction of spots on TLC was observed. Fractionation of the reaction mixture with alumina column chromatography and preparative silica gel TLC gave three compounds containing fused pyrimidine ring, that is, II, 1,2,5,6-tetrahydro-3,7,9,11,13-pentaazadibenzophenanthrene (IV), and 7,8,13,14-tetrahydro-2,4,6,10,12-pentaazabenzo[*c*]chrysene (V). II was identical with the specimen prepared from the above method (mixed mp, IR, NMR, and TLC). Both molecular formula of IV and V agreed with $C_{17}H_{13}N_5$ which were determined with elemental analyses and molecular weight determination by mass spectroscopy. The NMR spectra of IV and V were shown in Fig. 1 and Fig. 2. Whereas the chemical shift

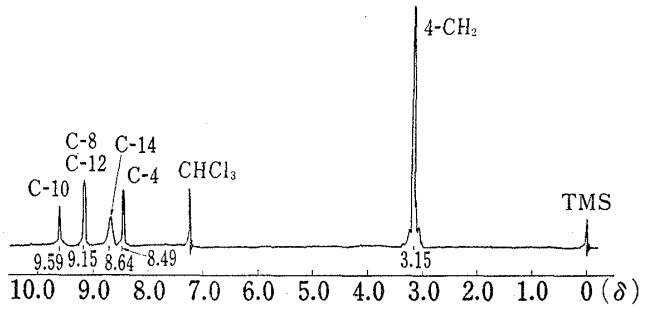

Fig. 1. NMR Spectrum of IV in $CDCl_3$ (90 MHz)

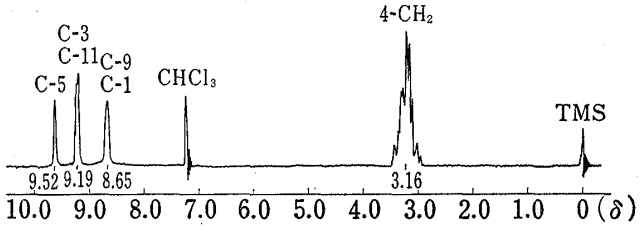

Fig. 2. NMR Spectrum of V in $CDCl_3$ (90 MHz)

of four-methylene protons of IV seems to be similar in NMR, methylene protons of V should be considered splitting to multiplet by the anisotropic effect of pyrimidine ring (A ring in Chart 1) and the paramagnetic effect of nitrogen atom of 12-position. Moreover, whereas C_1,C_9-protons of V may be resonanced at almost same field, C_4,C_{14}-protons of IV seems to be appeared at different fields. The structures of IV and V were distinguished by the above reasons.

The presumed cyclization mechanisms of IV and V are shown in Chart 2, that is, at first 2-(1-hydroxy-3-oxocyclohexyl)-1,3-cyclohexanedione (VII) or dehydrated VII′, VII″ was formed[4] by aldol condensation of I and then cyclization occurred toward arrow marks. To make sure this assumption, reactions of dehydrated compound of VII with FA or TFM were carried out. Dehydration of VII with conc. sulfuric acid gave two spots on TLC (perhaps VII′ and VII″) but recrystallization of the mixture from ethyl acetate gave pure compound (mp 155—156°) which had C=O bands at 1660 and 1630 cm^{-1} and O–H band at 2600 cm^{-1} as broad absorption in IR spectrum and its NMR spectrum exhibited six-methylene protons at higher field and vinyl proton at δ 5.96. These data suggested the enol form of VII′, 2-(3-oxo-1-cyclohexenyl)-3-hydroxy-2-cyclohexen-1-one. As shown in Chart 3, reaction of VII′ (enol form) with FA in dry ammonia stream under dropwise condition gave II and III in mixture and 2-(3-oxo-1-cyclohexenyl)-1,3-phenylenediamine (XI). The IR spectrum of XI had C=O band at 1655 cm^{-1} and its NMR spectrum exhibited two-proton multiplet at δ 1.88 attributable to $C_{5'}$-methylene, eight-proton multiplet at δ 2.54 for two NH_2 groups and $C_{4'}$,$C_{6'}$-

4) H. Stetter and E. Siehnhold, *Chem. Ber.*, **86**, 1308 (1953).

methylene groups, one-proton singlet at δ 5.27 for vinyl proton, each one-proton broad doublet (J=8 Hz) at δ 6.85, 6.78 for C_4,C_6-protons, and one-proton broad triplet (J=8 Hz) at δ 7.45 for C_5-proton, but the mechanism of aromatic ring formation was unconfirmed. The mixture of II and VI was identified with authentic samples by NMR measurement and TLC. The formation of II and VI suggested that at first the retroaldol condensation of VII′ occurred during the reaction and then formed I was condensed with FA to II or VI.

Condensation of VII′ (enol form) with TFM expectedly observed IV and V on TLC but the isolation of IV was onlv successful.

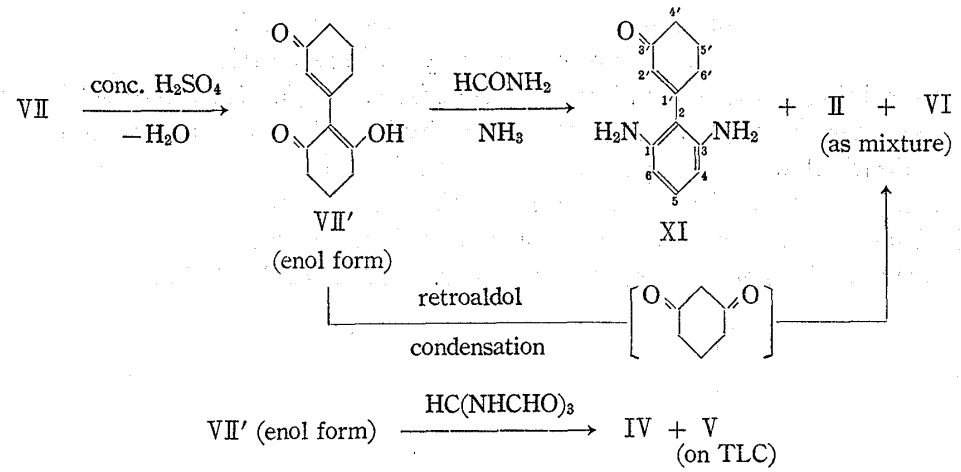

Chart 3

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi R-22 spectrometer (90 MHz) in $CDCl_3$ (TMS, δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Mass spectra were taken on a Shimadzu-LKB 9000 spectrometer. IR spectra were taken on a Japan Spectroscopic Company DS-301 spectrometer. Ultraviolet (UV) spectrum was taken on a Hitachi EPS-2 spectrophotometer in 99% EtOH.

Reaction of 1,3-Cyclohexanedione (I) with Formamide (FA)——a) Five grams of I in 40 ml of FA was gradually heated to 160° during *ca.* 1.5 hr under NH_3 stream and heating was continued at that temperature for 5 hr. After the reaction, excess FA was distilled off *in vacuo*. The residue was suspended with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The residue was chromatographed over alumina with benzene. The benzene eluate was recrystallized from benzene–cyclohexane to 16 mg (0.2%) of 9,10-dihydro-1,3,5,7-tetraazaphenanthrene (II) as pale yellow needles, mp 150—151°. *Anal.* Calcd. for $C_{10}H_8N_4$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.54; H, 4.31; N, 30.53. Mass Spectrum *m/e*: 184 (M^+). NMR: 3.14 (4H, bs, C_9, C_{10}-H), 8.65 (1H, s, C_8-H), 9.16, 9.19 (each 1H, s, C_2, C_6-H), 9.54 (1H, s, C_4-H).

The benzene–CH_2Cl_2 (9: 1) eluate was recrystallized from EtOH to 70 mg (1.5%) of 1,2,3,4,5,6,7,8,9,10-decahydrobenzo[*g*]chrysene-1,5-dione (III) as pale yellow needles, mp 280—282°. *Anal.* Calcd. for $C_{20}H_{18}O_2N_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 74.98; H, 5.73; N, 8.72. IR ν_{max}^{KBr} cm^{-1}: 1676 (C=O). Mass Spectrum *m/e*: 318 (M^+). NMR: 2.23 (4H, m, C_3, C_7-H), 2.71 (4H, m, C_2, C_6-H), 3.15 (8H, m, C_4, C_8, C_9, C_{10}-H), 8.16 (1H, s, C_{14}-H), 9.25 (1H, s, C_{12}-H).

b) Five grams of I in 40 ml of FA was gradually heated to 160° during *ca.* 1.5 hr under dry NH_3 stream and heating was continued at that temperature for 4.5 hr. Then additional 40 ml of FA was poured into the reaction mixture and heating was continued at 160° for another 5.5 hr. Excess FA was distilled off *in vacuo*, the residue was suspended with H_2O, and the suspension was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The benzene-soluble fraction of the residue was chromatographed over alumina with benzene. The benzene eluate was recrystallized from benzene–cyclohexane to 33 mg (0.4%) of II as pale yellow needles, mp 150—151°, identical with the specimen prepared from the method (a) (mixed mp, IR, NMR, and TLC).

c) To 88 ml of FA heated to 140° for 1 hr under dry NH_3 stream, 5 g of I in 72 ml of FA was added dropwise during *ca.* 0.5 hr. After addition was completed, the solution was heated at 160—180° for 10 hr. Excess FA was distilled off *in vacuo*, the residue was suspended with H_2O, and the suspension was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The CH_2Cl_2–soluble fraction of the

residue was chromatographed over alumina with CH_2Cl_2. The CH_2Cl_2 eluate was recrystallized from EtOH to 790 mg (9.6%) of II as pale yellow needles, mp 151—152°, identical with the product of the above method (mixed mp, IR, NMR, and TLC). The CH_2Cl_2–$CHCl_3$ (1: 1) eluate was fractionated with preparative TLC (Merck Kieselguhr, Me_2CO: $CHCl_3$=1: 1). The fraction of *Rf* value *ca.* 0.6 was collected and recrystallized from EtOH to 25 mg (0.4%) of 1,2,5,6-tetrahydro-3,7,9,11,13-pentaazadibenzophenanthrene (IV) as white plates, mp>300°. *Anal.* Calcd. for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.38. Found: C, 71.27; H, 4.57; N, 23.93. Mass Spectrum *m/e*: 287 (M^+). NMR spectrum is shown in Fig. 1. The fraction of *Rf* value *ca.* 0.5 was collected and recrystallized from EtOH to 9 mg (0.14%) of 7,8,13,14-tetrahydro-2,4,6,10,12-pentaazabenzo[*c*]chrysene (V) as colorless needles, mp 296—297°. *Anal.* Calcd. for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.38. Found: C, 71.40; H, 4.41; N, 24.18. Mass Spectrum *m/e*: 287.1269 (calcd. for $C_{17}H_{13}N_5$: 287.1171). NMR spectrum of V is shown in Fig. 2.

Dehydrogenation of II——A mixture of fine powdered 184 mg of II and 64 mg of sulfur was heated at 230° for 45 min in a long test tube (*ca.* 40 cm). The reaction mixture was subjected to high vacuum sublimation and the sublimate was recrystallized from EtOH to 112 mg (61.5%) of 1,3,5,7-tetraazaphenanthrene (VI) as pale yellow needles, mp 194—196°. *Anal.* Calcd. for $C_{10}H_6N_4$: C, 65.92; H, 3.32; N, 30.76. Found: C, 65.70; H, 3.42; N, 30.65. Mass Spectrum *m/e*: 182 (M^+). UV λ_{max}^{EtOH} nm (log ε): 222 (4.46), 253 (4.34), 283 (3.70), 316 (3.93), 328 (3.59). NMR: 8.15 (2H, ABq, C_9, C_{10}-H), 9.48 (1H, s, C_8-H), 9.57, 9.67 (each 1H, s, C_2, C_6-H), 10.95 (1H, s, C_4-H).

Dehydration of VII[4]——Four grams of VII dissolved in 22 ml of conc. H_2SO_4 under stirring and the solution was allowed to stand 3 hr. The reaction mixture was diluted with H_2O and the deposited solid was recrystallized from AcOEt to 2.8 g (76.4%) of 2-(3-oxo-1-cyclohexenyl)-3-hydroxy-2-cyclohexen-1-one (enol form of VII′) as colorless prisms, mp 155—156°. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.02; H, 6.73. IR ν_{max}^{KBr} cm^{-1}: 2600 (O–H), 1660, 1630 (C=O). NMR: 1.78—2.63 (12H, m, 6-CH_2), 5.96 (1H, bs, vinyl-H). 8.7—9.8 (1H, b, OH). Mass Spectrum *m/e*: 206 (M^+). UV λ_{max}^{EtOH} nm (log ε): 236 (4.10), 261 (4.24).

Reaction of VII′ (enol form) with FA——To 50 ml of FA heated to 140° for 1 hr under dry ammonia stream, 2.06 g of VII′ in 40 ml of FA was added dropwise during 0.5 hr and then heating was continued at 160—180° for additional 10 hr. Excess FA was distilled off under reduced pressure, the residue was suspended with H_2O, and the suspension was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The dark brown residue was chromatographed over alumina with CH_2Cl_2. The eighth fraction of 80 ml portion of CH_2Cl_2 eluate was recrystallized from cyclohexane to 20 mg (0.1%) of 2-(3-oxo-1-cyclohexenyl)-1,3-phenylenediamine (XI) as white needles, mp 104—105°. *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.12; H, 7.00; N, 13.86. Mass Spectrum *m/e*: 202 (M^+). NMR: 1.88 (2H, m, $C_{5'}$–H), 2.54 (8H, m, 2–NH_2, $C_{4'}$, $C_{6'}$–H), 5.27 (1H, s, $C_{2'}$–H), 6.78, 6.85 (each 1H, bd, J=8 Hz, C_4, C_6–H), 7.45 (1H, t, J=8 Hz, C_5–H). IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O).

The fifteenth to eighteenth fraction of 80 ml portion of CH_2Cl_2 eluate was recrystallized from EtOH to 80 mg of mixture of II and VI which were identical with the authentic samples (NMR and TLC).

Reaction of VII′ (enol form) with TFM——A mixture of 2.0 g of VII′, 10 g of TFM, 15 ml of FA, and 0.5 g of *p*-toluenesulfonic acid was heated at 160—170° for 8 hr. The reaction mixture was made alkaline with 0.1 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated. The residue was chromatographed over alumina with CH_2Cl_2. The CH_2Cl_2 eluate was fractionated with preparative TLC (Merck, Kieselguhr, benzene–CH_2Cl_2=1: 2). The fraction of *Rf* value *ca.* 0.5 was collected and recrystallized from EtOH to 35 mg (1.2%) of IV as white plates, mp>300°, identical with the specimen prepared from I and FA (mixed mp, IR, NMR, and TLC). V was identified with authentic sample on TLC but its isolation failed.

Acknowledgement The authors are grateful to Mr. A. Iwadoh for microanalyses and measurement of mass spectra.