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246. Tetsuji Kametani,*1 Hiroshi Sugahara,*2 and Kazuko Kanno*2 : Studies on the Syntheses of Heterocyclic Compounds. CCIV.*3 Ring Contraction in the Catalytic Hydrogenation of 3-Oximino-4-oxoisocarbostyril.

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One of two compounds, which were obtained by catalytic hydrogenation of VII in dry methanol using one molar equivalent of dry hydrochloride gas in the presence of platinum oxide, was separated after recrystallization from water. The structure of the above compound was characterized to be XV by acetylation and hydrolysis. In the latter case, the carboxylic acid (X) was obtained and found to be identical with an authentic sample, which was obtained by ring contraction of IX.

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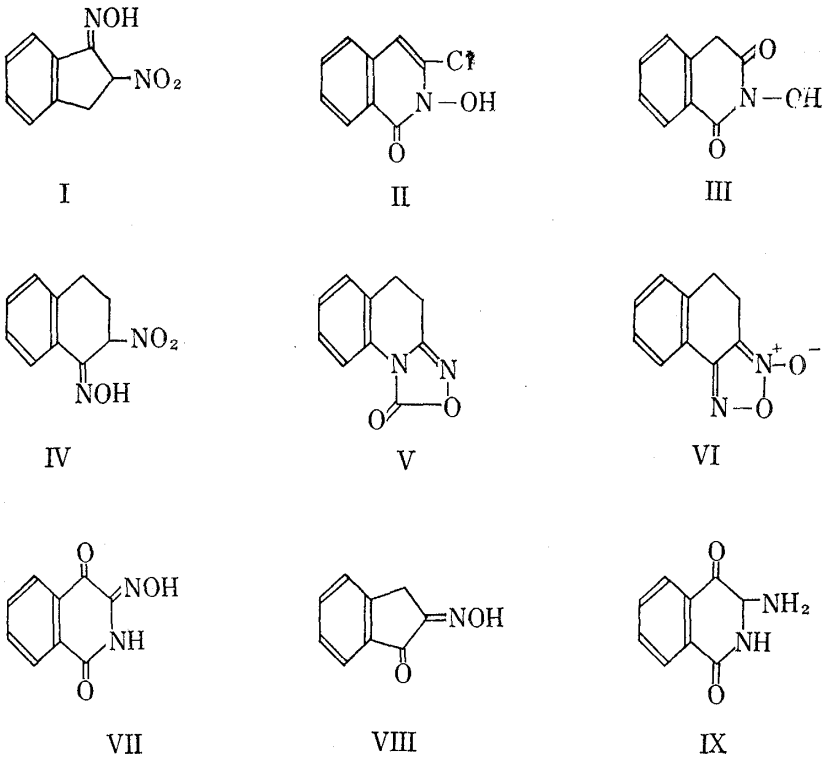
The nitrosation[1] of indene with nitrous acid was shown to give indenepseudonitrosite,[2] which was converted into 2-nitro-1-indanone oxime (I) when refluxed in an excess of ethanol for a long time. On being treated with hydrochloric acid in ethanol, 2-nitro-1-indanone oxime (I) undergoes a novel isomerization to be converted into the ring-expanded isocarbostyril derivatives, 3-chloro-2-hydroxyisocarbostyril (II) and N-hydroxyhomophthalimide (III) unexpectedly.[3] Furthermore, on being treated with polyphosphoric



I II III

IV V VI

VII VIII IX

Chart 1.

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*3 Part CCIII. This Bulletin, **15**, 1910 (1967).

1) M. Denstedt, C. Ahrens : Ber., **28**, 1331 (1895).
2) T. Kametani, H. Sugahara : Yakugaku Zasshi, **84**, 399 (1964); K. Kigasawa, M. Hiiragi, T. Hayasaka, H. Sugahara, T. Kametani : *Ibid.*, **84**, 402 (1964).
3) T. Kametani, H. Sugahara : J. Chem. Soc., **1964**, 3856.

acid, 2-nitro-1-tetralone oxime (Ⅳ) undergoes a novel isomerisation and dehydration in which it is converted into a mixture of 4,5-dihydro-1-oxo-1*H*-[1,2,4]oxadiazolo[4,3-*a*]-quinoline (Ⅴ) and 4,5-dihydronaphtho[1,2-*c*]furazan 3-oxide (Ⅵ).[4] Ring expansion of 2-nitro-1-indanone oxime (Ⅰ) with polyphosphoric acid was also examined to give a mixture of 3-oximino-4-oxoisocarbostyril (Ⅶ) and 1-oxo-2-indanone oxime (Ⅷ).[5] An attempt to reduce the oxime (Ⅶ) by catalytic hydrogenation in the presence of hydrochloric acid was examined, but unexpected compounds were obtained.

In the previous paper,[5] catalytic hydrogenation of Ⅶ in dry methanol using one molar equivalent of dry hydrochloride gas in the presence of platinum oxide afforded a mixture of two compounds, one of which was separated as a basic substance by recrystallization from water and presumed to be 3-amino-3,4-dihydro-4-oxoisocarbostyril (Ⅸ) by infrared (IR) and nuclear magnetic resonance (NMR) spectra, but the structure of the other compound has not yet been determined.

The reaction products in the catalytic hydrogenation of Ⅶ in the presence of dry hydrochloride gas were purified by recrystallization from water to give the compound (Ⅸ). Removal of the solvent from the filtrate on a water-bath *in vacuo* afforded a mixture of the above compound (Ⅸ) and carboxylic acid (Ⅹ), and the latter was dissolved in aqueous sodium bicarbonate solution. In this case evaporation of the above filtrate at atmospheric pressure gave only the compound (Ⅹ). Elementary analysis of the latter compound showed the composition of $C_9H_7O_3N$, and the infrared (IR) spectrum of Ⅹ showed maxima of the OH and C=O of carboxyl group at 3280 and 1700 cm^{-1}, and the NH and C=O of lactam group at 3200 and 1630 cm^{-1}, respectively. Beilstein halogen test was also negative.

Recyclization of phthalonic acid (Ⅺ),[6] which was obtained by oxidation of naphthalene, with hydrazine hydrate gave phthalazinone-4-carboxylic acid (Ⅻ).[7] Reduction of Ⅻ with zinc and hydrochloric acid afforded our expected phthalimidine-3-carboxylic acid

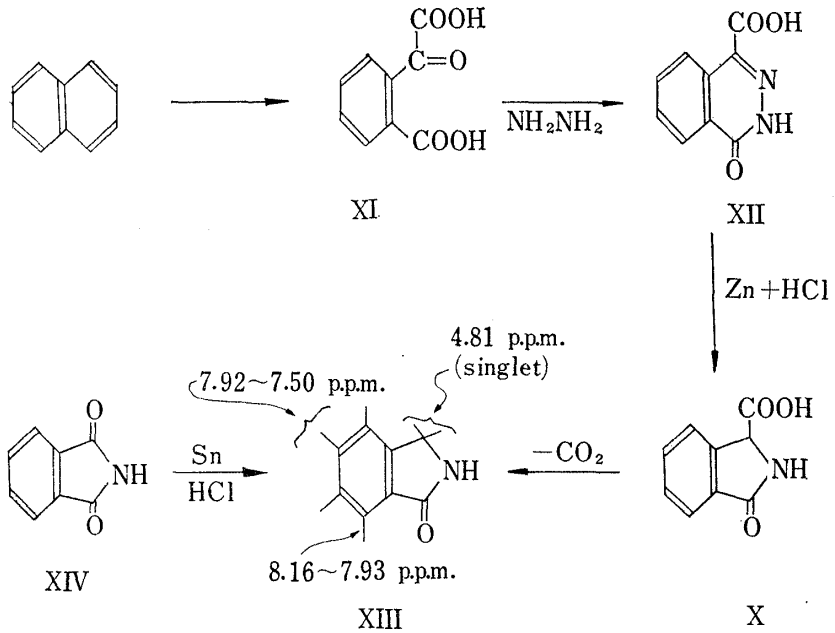


Chart 2.

4) T. Kametani, H. Sugahara, H. Yagi : J. Chem. Soc., **1966**, 717.
5) T. Kametani, H. Sugahara, K. Kanno : Yakugaku Zasshi, **87**, 309 (1967).
6) K. Fränkel : Ber., **33**, 2808 (1900).
7) K. Adachi : Yakugaku Zasshi, **75**, 1423 (1955).

(X),[8] which was found to be identical with the above sample by mixed melting point test and IR spectrum.

Furthermore, decarboxylation of X by heating over its melting point was occurred to give a clear solution, which was solidified after cooling. Recrystallization from water gave the substance (XIII), whose IR spectrum showed the lactam band at 1673 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum (in CF_3COOH) of XIII showed the protons (2H) of one methylene group as singlet at 4.81 p.p.m., aromatic protons (3H) at 7.50~7.92 p.p.m., and one aromatic proton adjacent to an amide carbonyl group at 7.93~8.16 p.p.m. The latter signal is presumably due to the anisotropic effect of C=O group. These facts also support the structure of XIII, which is identical with an authentic sample by mixed melting point test and IR spectrum. With regards to the synthesis of phthalamidine (XIII), reduction of phthalimide[9] (XIV) or 2-cyanobenzoic acid[10] has been reported, but reduction of XIV with tin and hydrochloric acid was carried out in this case according to Grabe's method,[9] the compound (XIII) being obtained.

On the other hand, catalytic hydrogenation of VII in ethanol in the presence of concentrated hydrochloric acid solution afforded a mixture of ammonium chloride and neutral substance, the latter of which showed the composition of $C_{11}H_{11}O_3N$ from its elementary analysis. Furthermore, the IR spectrum of this compound showed maxima at 1740 (C=O) and 1690 (C=O) cm^{-1}. The relatively low-frequency at 1690 cm^{-1}

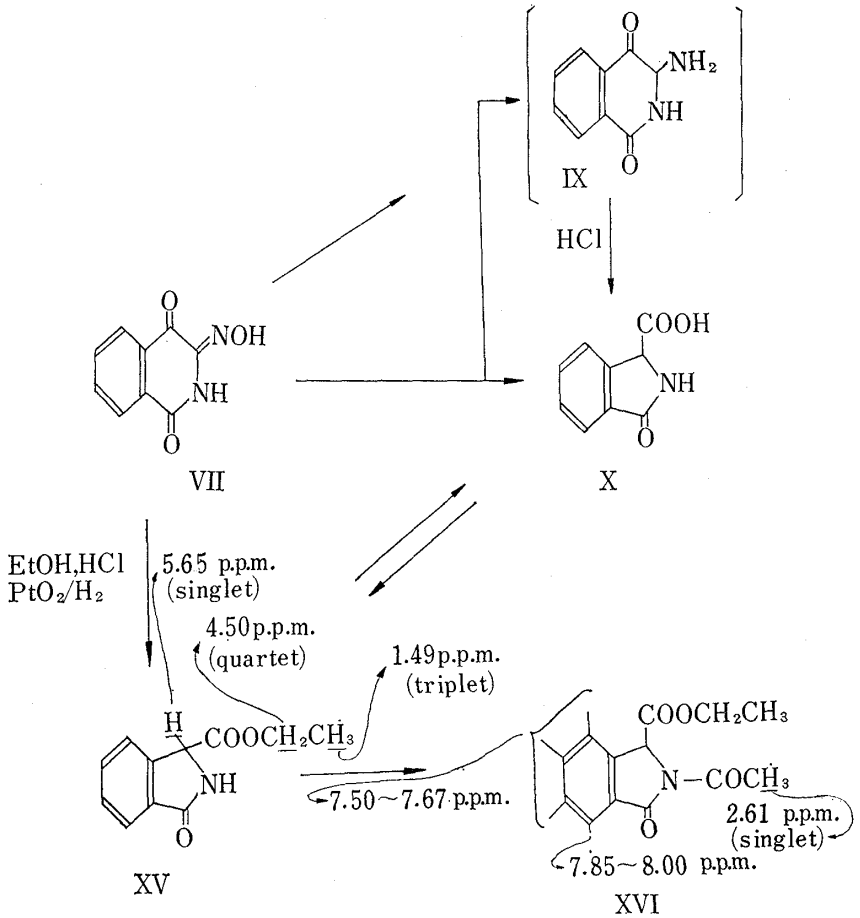
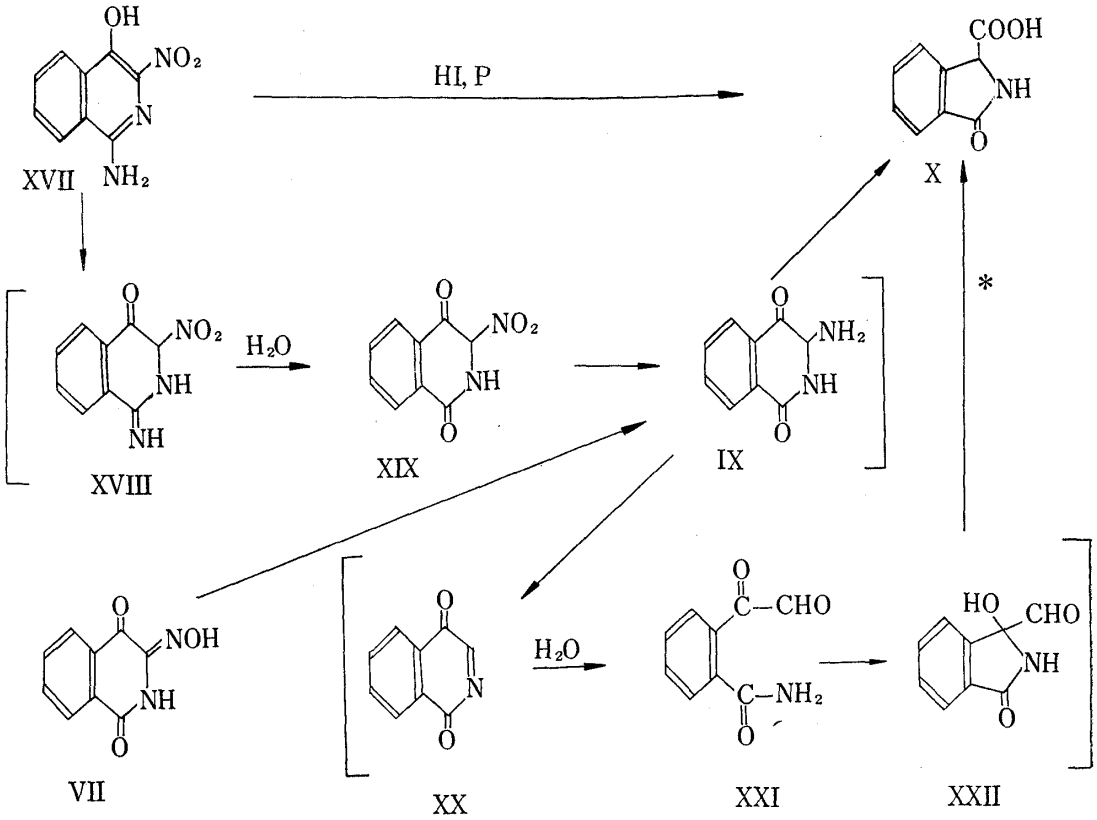


Chart 3.

8) A. Darapsky, P. Heinrichs: J. prakt. Chem., **146**, 307 (1936).
9) C. Grabe: Ber., **17**, 2598 (1884).
10) S. Gabriel, W. Landsberger: *Ibid.*, **31**, 2739 (1898).

is attributed to the amide carbonyl group. The NMR spectrum (in CF_3COOH) showed the proton (1H) of methine group at 5.65 p.p.m., and the protons (5H) of ethyl group at 1.49 p.p.m. as triplet and 4.50 p.p.m. as quartet, respectively. Furthermore, acetylation of this compound gave acetyl derivative, which also showed the signals due to the ethyl group in its NMR spectrum and lacked the NH band in its IR spectrum. Accordingly, the acetyl derivative was characterized as the compound (XVI) from the IR and NMR spectral determination and analytical data. These facts prove that the reduction product in case of catalytic hydrogenation in the presence of hydrochloric acid solution has the structure of XV.

According to the above results, the compound (IX) in case of catalytic hydrogenation in an anhydrous state would be first formed and then hydrolyzed with hydrochloric acid. In fact, hydrolysis of IX with 5% aqueous hydrochloric acid solution gave the compound (X). In these cases, the formation of both compound, (IX) and (X), seems to depend upon the time and temperature of the reaction and the amount of the water which existed during reaction. On the other hand, when the compound (VII) was hydrogenated in the presence of an excess of concentrated hydrochloric acid solution, only the compound (X) would be formed by hydrolysis as an intermediate, which seems to be immediately converted into the ester (XV) by esterification. The formation of XV was



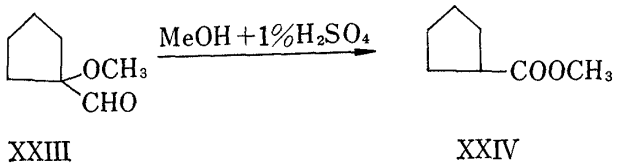


Chart 4.

also proved by conversion into the acid (X) by hydrolysis. The esterification of X also gave the ester (XV).

The ring contraction of IX in case of catalytic hydrogenation of VII in the presence of hydrochloric acid seems to be similar to the formation of X by reduction of 1-amino-4-hydroxy-3-nitroisocarbostyril (XVII) with hydroiodic acid and red phosphorus by Zelmenis and Vanags,[11] but they have not touched upon the reaction mechanism. Perhaps the simplest mechanism to explain the formation of X would initially involve the formation of ketoform (XVIII) of isoquinoline and its hydrolyzed product (XIX) in acid media to afford IX as an intermediate by reduction and then to give the compound (X) *via* XX, XXI, and XXII. The reaction mechanism in the final stage from XXII to X seems to be explained by the conversion of 1-formyl-1-methoxycyclopentane (XXIII) into 1-methoxycarbonylcyclopentane (XXIV) by treatment with methanol and 1% sulfuric acid solution.[12]

Experimental*4

3-Amino-3,4-dihydro-4-oxoisocarbostyril (IX) and Phthalimidine-3-carboxylic Acid (X)——A solution of 2 g. of 3-oximino-4-oxoisocarbostyril (VII) in 300 ml. of dry MeOH containing 0.384 g. of HCl gas was hydrogenated with H_2 in the presence of 0.3 g. of PtO_2, two molar equivalents of H_2 being absorbed for 1.5 hr. After the catalyst had been removed by filtration, evaporation of the filtrate gave the residue, to which MeOH was added and filtered in order to remove the starting material (VII). To the above filtrate was added ether, and 1.8 g. of crude crystals precipitated were collected by filtration. The Beilstein halogen test was positive. Recrystallization from water gave 160 mg. of IX as colorless needles, m.p. 268°(decomp.), whose Beilstein test was negative. This was identical with an authentic sample.[5]

Secondly, the above aqueous filtrate in case of recrystallization was evaporated to dryness in a shale on a water-bath to give 1.1 g. of crude crystals, whose recrystallization from MeOH-H_2O gave X as colorless prisms, m.p. 152°(decomp.). *Anal.* Calcd. for $C_9H_7O_3N$: C, 61.01; H, 3.98; N, 7.91. Found: C, 61.22; H, 4.40; N, 8.04. IR cm^{-1}(KBr): ν_{OH} 3280, $\nu_{C=O}$ 1700, ν_{NH} 3200, $\nu_{C=O}$ 1630. This substance (X) was identical with an authentic sample, which was obtained from phthalonic acid (XI) *via* XII,[6~8] by mixed melting point test and IR spectrum.

Ethyl Phthalimidine-3-carboxylate (XV)——The preceding compound (VII) (1 g.) in 300 ml. of EtOH was hydrogenated in the presence of 0.2 g. of PtO_2 and 5 ml. of conc. HCl, 2 moles of H_2 being absorbed within 3 hr. After removal of the catalyst, the filtrate was evaporated to dryness to give the residue, to which was added EtOH. Removal of the solvent from the above mixture gave the crude crystals which were again dissolved in warm EtOH in order to remove NH_4Cl. Filtration and distillation gave the solid, whose recrystallization from EtOH-H_2O afforded 0.2 g. of XV as colorless needles, m.p. 180~181°. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.80. Found: C, 64.18; H, 5.25; N, 6.76. IR cm^{-1}(KBr): ν_{NH} 3200, $\nu_{C=O}$ 1740 (ester), $\nu_{C=O}$ 1690 (lactam). NMR (p.p.m.) (CF_3CO_2H): 1.49 (3H, $-CO_2CH_2C\underline{H}_3$, triplet, J=8 c.p.s.), 4.50 (2H, $-CO_2C\underline{H}_2CH_3$, quartet J=8 c.p.s.), 5.65 (1H, >CH–, singlet,). UV λ_{max}^{EtOH} mμ (log ε): 264.6 (2.93), 271.3 (3.01), 278.3 (2.97).

Ethyl 2-Acetylphthalimidine-3-carboxylate (XVI)——A mixture of 0.5 g. of XV and 15 ml. of Ac_2O was heated under reflux in an oil-bath for 3 hr. After the reaction, removal of the excess of reagent *in vacuo* gave the residue, to which ice-water was added and stirred for some time to separate 0.4 g. of the crude crystals. Recrystallization from isoPrOH gave the compound (XVI) as colorless needles, m.p. 80°. *Anal.* Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.07; H, 5.65; N, 5.56. IR cm^{-1}(KBr): $\nu_{-CO-N-CO-}$ 1745, 1690, $\nu_{C=O}$ 1740 (ester). NMR (p.p.m.) (CCl_4): 7.50~7.67 (3H, aromatic protons, multiplet), 5.50 (1H, >CH–, singlet), 4.00~8.00 (1H, C_7–H, multiplet), 4.21 (2H, $-CO_2C\underline{H}_2CH_3$, quartet, J=8 c.p.s.), 1.28 (3H, $-CO_2CH_2C\underline{H}_3$, triplet, J=8 c.p.s.).

Hydrolysis of IX——A mixture of 200 mg. of IX and 10 ml. of 5% HCl aq. solution was heated on a water-bath for 1 hr. and then evaporated to dryness in a shale. Recrystallization of the resultant crystals from MeOH-H_2O gave 150 mg. of X as colorless needles, m.p. 152°(decomp.), identical with an authentic sample as above.

Esterification of X——After dry HCl gas had been introduced with stirring into a heated suspension of 0.5 g. of X in dry EtOH for 2 hr., removal of the solvent gave the residue, which was dissolved in $CHCl_3$. The solvent was washed with 10% Na_2CO_3 aq. solution, dried on Na_2SO_4, and distilled to give the crude

*4 Melting point was not corrected.

11) V. Zelmenis, G. Vanags: Zhur. Obshchei. Khim., **27**, 1353 (1957).

12) M. Mousseron, R. Tacquier, A. Fontaine: Bull. soc. chim. France, (5) **19**, 767 (1952).

crystals. Recrystallization from EtOH afforded 0.4 g. of XV as colorless needles, m.p. 180~181°, identical with the authentic sample as above.

Hydrolysis of XV——A mixture of 0.5 g. of XV and 20 ml. of 10% HCl aq. solution was heated on a water-bath for 2 hr., and evaporation of the resultant reaction mixture in a shale to dryness gave 0.35 g. of the solid. Recrystallization from MeOH-H_2O gave the compound (X) as colorless prisms, m.p. 152° (decomp.), whose IR spectrum was identical with that of an authentic sample.

Decarboxylation of X——When 0.5 g. of X in a test tube was carefully immersed in an oil-bath at 200°, a severe evolution of CO_2 was observed, after which a clear oil formed and solidified after cooling. Recrystallization from water gave 0.32 g. of XIII as colorless needles, m.p. 150~151°, identical with an authentic sample. *Anal.* Calcd. for C_8H_7ON: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.08; H, 5.43; N, 10.52.

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