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Studies on the Syntheses of Heterocyclic Compounds. CDXVII.[1] Syntheses of 1,2-Benzoxazepine, Oxindole and Furanoquinolone Derivatives by Cyclization of Hydroxamic Acid with Polyphosphoric Acid

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Cyclization of 3-(2,3,4-trimethoxyphenyl)propionohydroxamic acid (II), 2-(3,4-dimethoxyphenyl)acetohydroxamic acid (VI) and 3-(α-diethoxybenzyl)-2,3,4,5-tetrahydro-1-hydroxy-2-ketopyrrole (X) with polyphosphoric acid gave 4,5-dihydro-3-oxo-[2H]-1,2-benzoxazepine (IV), 5,6-dimethoxyoxindole (VII) and 2,3,4,9-tetrahydro-4-oxo-furo [2,3-*b*]quinoline (XI), respectively.

Recently, Wassmundt and his co-worker[3] have reported that the reaction of aromatic compounds with hydroxamic acid in hot polyphosphoric acid gave directly acylamide-derivatives of the aromatic compounds. For example, when hydrocinnamohydroxamic acid was heated in polyphosphoric acid, 3,4-dihydrocarbostyril was produced. *p*-Acetaniside was obtained by the reaction of acetohydroxamic acid with anisole in polyphosphoric acid. We now describe the novel reaction of several hydroxamic acid derivatives with polyphosphoric acid.

Cyclization of 3-(2,3,4-trimethoxyphenyl)propionohydroxamic acid (II), obtained from ethyl β-(2,3,4-trimethoxyphenyl)propionate (I), with polyphosphoric acid gave no expected 3,4-dihydro-5,6,7-trimethoxycarbostyril (III) but 4,5-dihydro-3-oxo-[2H]-1,2-benzoxazepine (IV), mp 171°, which was characterized as follows. The microanalysis of IV protons as

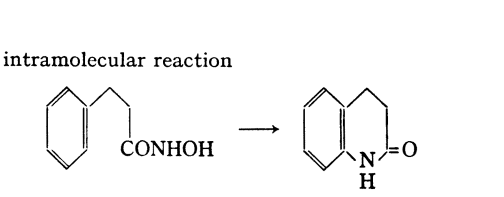


Chart 1

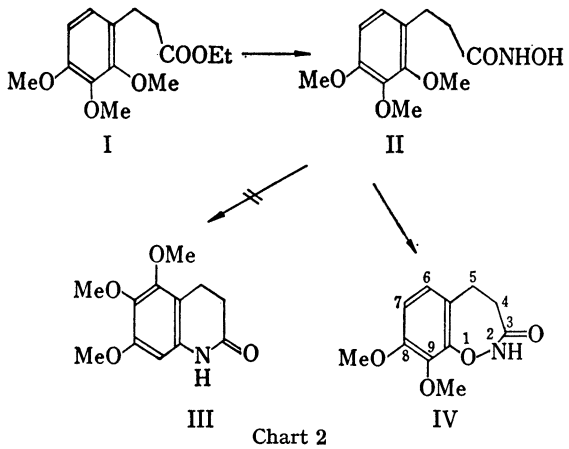


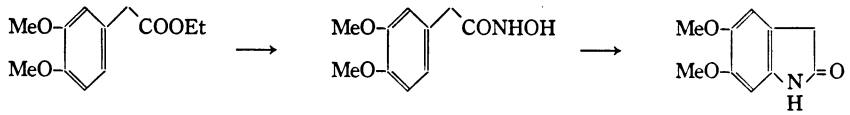
Chart 2

was in agreement with the composition $C_{11}H_{13}O_4N$, and its mass spectrum showed molecular ion peak at *m/e* 223. The infrared (IR) spectrum ($CHCl_3$) of IV showed an NH band at 3400 cm^{-1} and C=O band at 1705 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of IV showed signals due to the methylene protons (4H) as multiplet at 2.0—2.8, methoxy

1) Part CDXVI: The preceding paper.
2) Location: *Aobayama, Sendai.*
3) F.W. Wassmundt and S.J. Radegimas, *J. Am. Chem. Soc.*, **89**, 7131 (1967).

singlet at 3.74 (3H) and 4.10 (3H), aromatic protons as a pair of doublets (J=9.1cps) at 6.10 (1H) and 6.50 (1H) and NH proton as a broad singlet at 6.70 ppm (1H). These facts confirmed the structure of IV.

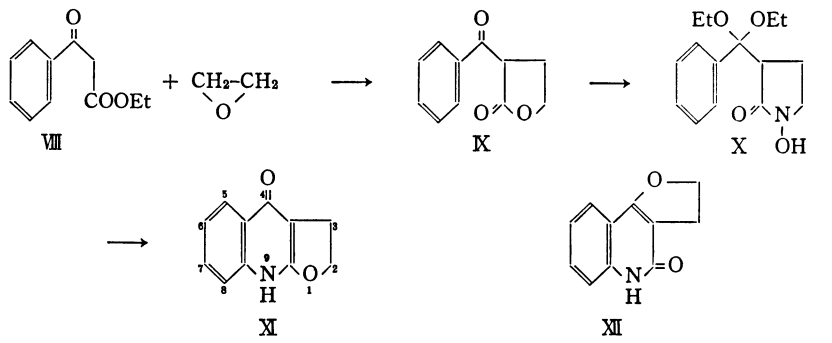
Reaction of 2-(3,4-dimethoxyphenyl)acetohydroxamic acid (VI), which was obtained from V, with polyphosphoric acid afforded 5,6-dimethoxyoxindole (VII), mp 210°, which showed an NH band at 3200 cm^{-1} and C=O band at 1710 cm^{-1} in the IR spectrum (KBr). The NMR spectrum [$(CD_3)_2SO$] of VII showed the signals due to methylene protons as singlet at 3.33 (2H), methoxy protons as singlet at 3.68 (3H) and 3.72 (3H), aromatic protons as singlets at 6.48 (1H) and 6.88 (1H) and NH proton as a broad singlet at 10.10 ppm (1H). Microanalysis of VII was also in agreement with the composition $C_{10}H_{11}O_3N$ and no depression was observed on its mixed melting point test with an authentic sample.[4]



V VI VII

Chart 3

Secondly, we attempted to apply the above reaction of hydroxamic acid with polyphosphoric acid to the synthesis of furanoquinolone derivative. Ethyl benzoylacetate (VIII) were reacted with ethylene oxide in a solution of sodium ethoxide in ethanol to afford α-benzoyl-γ-butyrolactone (IX), which showed a lactone band at 1770 cm^{-1} and a ketone band at 1685 cm^{-1} in the IR spectrum, and showed the signals due to methylene protons as multiplet at 2.2—3.2 (2H), methylene and methine protons as multiplet at 4.2—4.8 (3H), and aromatic protons as multiplet at 7.3—8.2 ppm (5H) in the NMR spectrum ($CDCl_3$). The microanalysis of IX was in agreement with the composition $C_{11}H_{11}O_3$. Treatment of α-benzoyl-γ-butyrolactone (IX) with an excess of hydroxylamine hydrochloride in a solution of sodium ethoxide in ethanol afforded compound (X), which showed C=O band at 1715 and a hydroxyl band at 3300 cm^{-1} in the IR spectrum. Furthermore the signals due to methyl protons as triplet (J=7.0 cps) at 1.15 (6H), three methylene protons as quartet (J=7.0 cps) at 3.6 (4H) and as multiplet at 1.72 (2H), methine proton as multiplet at 2.3—2.7 (1H), hydroxyl proton as a broad singlet at 5.95 (1H) and aromatic protons as a multiplet at 7.30—7.70 ppm (5H) were shown in the NMR spectrum ($CDCl_3$). Treatment of cyclic hydroxamic acid (X) with polyphosphoric acid afforded our expected furanoquinolone (XI). This showed an NH band at 3380 cm^{-1} and C=O at 1658 cm^{-1} in the IR spectrum (KBr) and revealed the signals due to methylene protons as multiplet at 2.8—3.3 (2H), methylene protons as multiplet at 4.5—



VIII IX X XI XII

Chart 4

4) G.N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).

5.0 ppm (2H), three aromatic protons as multiplet at 7.1—7.7 and one aromatic proton as multiplet at 8.0—8.3 ppm in the NMR spectrum [$(CD_3)_2SO$]. The mass spectrum of XI showed the molecular ion peak at *m/e* 187. Its microanalysis was in agreement with the composition $C_{11}H_9O_2N$. Although two possible structures XI, XII could be assigned to this compound, the structure (XII) was ruled out by comparison of its melting point.[5] The NMR spectrum of XI showed the signal of C_5 aromatic proton at 8.00—8.30ppm. This chemical shift was characteristic in 4-quinolone series as XI. On the other hand, the signal of C_5 aromatic proton in 2-quinolone series as XII was observed at 7.52 ppm.[6] Therefore, this compound could be assigned to XI.

Experimental[7]

3-(2,3,4-Trimethoxyphenyl)propionohydroxamic Acid (II)——A solution of 4.6 g of hydroxylamine hydrochloride in EtOH was added to an ethanolic solution of NaOEt [prepared with 1.6 g of Na and 50 ml of EtOH]. After the precipitate had been filtered off, 4.42 g of ethyl 3-(2,3,4-trimethoxyphenyl)propionate was added to the filtrate. The stirring was continued for 30 min at room temperature and the reaction mixture was refluxed for 30 min. After evaporation of EtOH *in vacuo*, water was added. The aqueous solution was acidified with AcOH to give a colorless powder, which was recrystallized from $CHCl_3$ to give 2.0 g (47.6%) of II as colorless plates, mp 130°. *Anal.* Calcd. for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.67; H, 6.80; N, 5.31.

2-(3,4-Dimethoxyphenyl)acetohydroxamic Acid (VI)——A solution of 4.6 g of hydroxylamine hydrochloride in EtOH was added to an ethanolic solution of NaOEt [prepared with 1.6 g of Na and 50 ml of EtOH]. After the precipitate had been filtered off, 3.3 g of ethyl 2-(3,4-dimethoxyphenyl)acetate was added to the filtrate. The stirring was continued for 30 min at room temperature and the reaction mixture was refluxed for 30 min. After evaporation of EtOH *in vacuo*, water was added. The aqueous solution was acidified with AcOH to give a colorless powder, which was recrystallized from $CHCl_3$ to give 1.8 g (58%) of VI as fine colorless needles, mp 145°. *Anal.* Calcd. for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.73; H, 6.34; N, 6.63.

The Reaction of 3-(2,3,4-Trimethoxyphenyl)propionohydroxamic Acid with Polyphosphoric Acid——A mixture of 1 g of 3-(2,3,4-trimethoxyphenyl)propionohydroxamic acid and 32 g of polyphosphoric acid was heated at 100° for 5 hr. After cooling, the reaction mixture was poured into 200 ml of ice-water. The aqueous layer was extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to give a colorless powder, which was recrystallized from $CHCl_3$–hexane to give 340 mg (39%) of 2,3,4,5-tetrahydro-8,9-dimethoxy-3-oxo-1,2-benzoxazepine (IV) as colorless needles, mp 171°. *Anal.* Calcd. for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.28. Found: C, 58.89; H, 5.85; N, 6.41. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (C=O), 3400 (NH). NMR (δ) (in $CDCl_3$): 2.0—2.8 (4H, multiplet, $-CH_2-CH_2-$), 3.74 (3H, singlet, OCH_3), 4.10 (3H, singlet, OCH_3), 6.10 (1H, doublet, J=9.1 cps, aromatic H), 6.50 (1H, doublet, J=9.1 cps, aromatic H), 6.70 (1H, broad singlet, NH). Mass Spectrum *m/e*: 223 (M^+).

The Reaction of 2-(3,4-Dimethoxyphenyl)acetohydroxamic Acid with Polyphosphoric Acid——A mixture of 1 g of 2-(3,4-dimethoxyphenyl)acetohydroxamic acid and 32 g of polyphosphoric acid was heated at 100° for 5 hr. After cooling, the reaction mixture was poured into 300 ml of ice-water. The aqueous solution was extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to give a colorless powder, which was recrystallized from $CHCl_3$ to give 450 mg (49%) of VII as colorless needles, mp 210°. *Anal.* Calcd. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.93; H, 5.81; N, 7.12. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O), 3200 (NH). NMR (δ) (in $(CD_3)_2SO$): 3.33 (2H, singlet, $-CH_2-$), 3.68 (3H, singlet, OCH_3), 3.72 (3H, singlet, OCH_3), 6.48 (1H, singlet, aromatic H), 6.88 (1H, singlet, aromatic H), 10.10 (1H, broad singlet, NH).

α-Benzoyl-γ-butyrolactone (IX)——To a solution of 3.62 g of ethyl benzoylacetate in an ethanolic solution of NaOEt [prepared with 0.5 g of Na and 20 ml of EtOH], 3 g of ethylene oxide was added under ice-cooling and the stirring was continued for 15 hr at room temperature. After evaporation of EtOH *in vacuo*, water was added. The aqueous solution was acidified with conc. HCl and then extracted with $CHCl_3$. The

5) M.F. Grundon, N.J. McCorkindale, and M.N. Rodger, *J. Chem. Soc.*, **1955**, 4284.
6) NMR spectra Catalog compiled by N.S. Bhacca, L.F. Johonson, J.N. Shoolery of the Instrument Division of Varian Associates, Vol. I, 311, 312, 313, 325 (1962).
7) Melting points were uncorrected. IR spectra were recorded on a type EPI Hitachi recording spectrophotometer in potassium bromide or in chloroform solution. NMR spectra were measured on a Hitachi R-20 spectrometer in deuteriochloroform or deuteriodimethylsulfoxide using tetramethylsilane as an internal reference.

extract was dried over anhyd. Na_2SO_4. Filtration and evaporation gave a yellow oil, which, on distillation under reduced pressure, gave 550 mg (16%) of IX as a colorless oil, bp 169° (3 mmHg). *Anal.* Calcd. for $C_{11}H_{11}O_3$: C, 69.10; H, 5.80. Found: C, 69.73; H, 5.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (C=O), 1685 (C=O). NMR (δ) ($CDCl_3$): 2.2—3.2 (2H, multiplet, $-CH-C\underline{H}_2-CH_2-O$), 4.2—4.8 (3H, multiplet, $-C\underline{H}-CH_2-C\underline{H}_2-O$), 7.3—8.2 (5H, multiplet, aromatic H).

2,3,4,9-Tetrahydro-4-oxo-furo[2,3-*b*]quinoline (XI) through α-Benzoyl-γ-butyrolactone (IX) and 3-(α-Diethoxybenzyl)-2,3,4,5-tetrahydro-1-hydroxy-2-ketopyrrole (X)——A solution of 1.5 g of hydroxylamine hydrochloride in EtOH was added to an ethanolic solution of NaOEt [prepared with 0.7 g of Na and 20 ml of EtOH]. After the precipitate had been filtered off, 0.9 g of α-benzoyl-γ-butyrolactone was added to the filtrate and the resulting mixture was refluxed for 12 hr. After evaporation of EtOH *in vacuo*, water was added. The aqueous layer was extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to give 500 mg (38%) of X as a yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C=O), 3300 (OH). NMR (δ) (in $CDCl_3$): 1.15 (6H, triplet, $J=7.0$ cps, $2\times OCH_2C\underline{H}_3$), 3.6 (4H, quartet, $J=7.0$ cps, $2\times OC\underline{H}_2CH_3$), 1.72 (2H, multiplet, $CH-C\underline{H}_2-CH_2-N$), 2.85 (2H, multiplet, $-CH_2-C\underline{H}_2-N$), 2.3—2.7 (1H, multiplet, $-C\underline{H}-CH_2-$), 5.95 (1H, broad singlet, $N-O\underline{H}$), 7.3—7.7 (5H, multiplet, aromatic H). A mixture of 1.1 g of compound (X) and 32 g of polyphosphoric acid was heated at 160—170° for 2 hr. After cooling, the reaction mixture was poured into 50 ml of ice-water. The aqueous layer was extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to give a colorless powder, which was recrystallized from $CHCl_3$ to give 300 mg (46%) of XI as colorless needles, mp 243°. *Anal.* Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.53; H, 4.99; N, 7.56. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (NH), 1658 (C=O), 1635 (C=C). NMR (δ) ($(CD_3)_2SO$): 2.8—3.3 (2H, multiplet, $-C\underline{H}_2-CH_2-O$), 4.5—5.0 (2H, multiplet, $-CH_2-C\underline{H}_2-O$), 7.1—7.7 (3H, multiplet, aromatic H), 8.00—8.30 (1H, multiplet, aromatic H), 4.0—4.2 (1H, broad singlet, $N\underline{H}$). Mass Spectrum *m/e*: 187 (M^+).

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