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Studies on the Syntheses of Heterocyclic Compounds. DCLXIII.¹⁾ The Reaction of Pyridone Derivatives with Diazoalkane

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The reaction of 3-carboxy-1,2-dihydro-1-methyl-2-oxopyridine (V) with diazomethane afforded 6,7-dihydro-1,6-dimethyl-7-oxopyrazolo[3,4-*c*]pyridine (VI), 4,5,6,7-tetrahydro-1,6-dimethyl-7-oxopyrazolo[3,4-*c*]pyridine (VII), and 1,2-dihydro-3-methoxycarbonyl-1,4-dimethyl-2-oxopyridine (VIII). 1-Ethyl-6,7-dihydro-3,6-dimethyl-7-oxopyrazolo[3,4-*c*]pyridine (XXI), 8 α -ethoxycarbonyl-1,4,4a,7,8,8a-hexahydro-3,4,7-trimethyl-8-oxopyrido[3,4-*c*]pyridazine (XXII), and 3-ethoxycarbonyl-4-ethyl-1,2-dihydro-1-methyl-2-oxopyridine (XXIII) were obtained from the reaction of compound (V) with diazoethane. The treatment of 4-carboxy-1,2-dihydro-1-methyl-2-oxopyridine (XXVIII) with diazomethane gave 1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine (XXIX), 6-methoxycarbonyl-3-methyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXX), and 1,2-dihydro-4-methoxycarbonyl-1,3-dimethyl-2-oxopyridine (XXXI). The reaction of compound (XXIX) with diazoethane afforded 3-ethyl-1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine (XXXII), 6 α -methoxycarbonyl-3,7 β -dimethyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXXIII), and 1-ethyl-6-methoxycarbonyl-3,7-dimethyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXXIV). In case of the treatment of 5-carboxy-1,2-dihydro-1-methyl-2-oxopyridine (XXXV) and 1,5-dihydro-1,5-dioxo-3H-oxazolo[3,4-*a*]pyridine (XXXVIII) with diazomethane, 1,2-dihydro-5-methoxycarbonyl-1-methyl-2-oxopyridine (XXXVI) and 1,2-dihydro-6-methoxycarbonyl-1-methyl-2-oxopyridine (XXXIX) were obtained, respectively.

The reaction of diazoalkanes with a variety of amides has been well investigated from the mechanistic and synthetic points of view.³⁾ Although the reaction of diazoalkane with heterocyclic compounds has been also well documented and the C-alkylated compounds have been obtained by the reaction of diazoalkane with certain heterocyclic compounds,⁴⁾ the reactions of diazoalkane with pyridone⁵⁾ and quinolone derivatives⁶⁾ have been limited. This fact has stimulated us to examine the reaction of diazoalkane with pyridone derivatives and we could obtain the compounds (II) and (III) by the reaction of the pyridone derivatives (I) with diazomethane.⁷⁾ Here we wish to report the above results.

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- 6) a) E.J. Alford and K. Schofield, *J. Chem. Soc.*, **1953**, 1881; b) F. Arndt, L. Ergener, and O. Kutlu, *Chem. Ber.*, **86**, 951 (1953); c) H. Junek and W. Wilfinger, *Monatsh.*, **101**, 1123 (1970).
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At first, the 3-carboxypyridone derivative (V),⁸⁾ which was obtained by a hydrolysis of the 3-cyanopyridone derivative (IV), was treated with diazomethane to give the compounds (VI), (VII), and (VIII) in 53.9, 12.3, and 26.6% yield, respectively.

In the infrared (IR) spectrum (CHCl_3) of the first product (VI), an absorption due to pyridone carbonyl group was observed at 1650 cm^{-1} , and the nuclear magnetic resonance (NMR) spectrum (δ in CCl_4) exhibited two N-methyl groups due to pyrazole and pyridone ring at 4.33 and 3.51 as two singlets, respectively, aromatic proton of pyrazole ring at 7.51 as singlet, and aromatic protons of pyridone ring at 6.34 and 6.76 as doublets with $J=7.0\text{ Hz}$. Thus, the first product (VI) was shown to be 6,7-dihydro-1,6-dimethyl-7-oxopyrazolo[3,4-*c*]pyridine.

The IR spectrum (CHCl_3) of the second compound (VII) exhibited the carbonyl absorption at 1640 cm^{-1} , and the NMR spectrum (δ in CCl_4) revealed the presence of two N-methyl groups at 4.12 and 3.00 as each singlet, the presence of aromatic proton at 7.10 due to pyrazole ring and two methylenes due to dihydropyridone at 2.79 and 3.54 as triplets with $J=7.0\text{ Hz}$. The mass spectrum showed the molecular ion peak at m/e 165. From the results described above, the second product (VII) was shown to be the dihydro derivative of the first product (VI).

The structure of the third compound (VIII) was confirmed by the following data. In the IR spectrum (CHCl_3) of this product (VIII), the absorptions due to pyridone and ester groups were observed at 1645 and 1715 cm^{-1} .

The NMR spectrum (δ in CCl_4) showed N-methyl group at 3.41 as singlet, methoxycarbonyl group at 3.80 as singlet, methyl group on pyridone ring at 2.13 as singlet, and two aromatic protons at 5.87 and 7.21 as doublets with $J=7.0\text{ Hz}$.

The third product (VIII) was synthesized alternatively in order to confirm the position of methyl group on pyridone ring as shown in Chart 2.

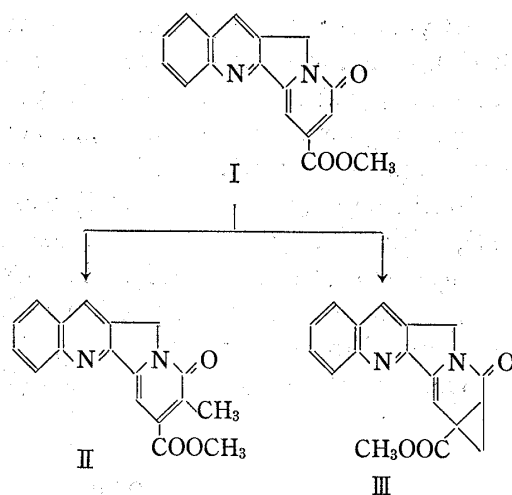


Chart 1

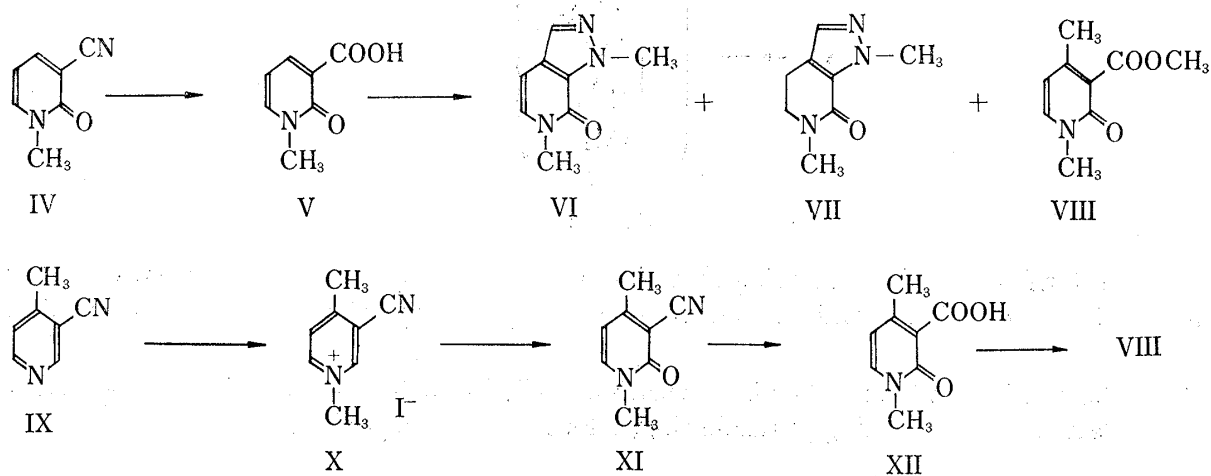


Chart 2

8) E. Späth and G. Koller, *Chem. Ber.*, **56**, 880 (1923).

3-Cyano-4-methylpyridine⁹⁾ was treated with methyl iodide to give the quaternary salt (X), which was oxidized with potassium ferricyanide in the presence of sodium hydroxide to give the pyridone (XI), whose IR spectrum (CHCl_3) showed the absorptions due to pyridone and cyano groups at 1660 and 2226 cm^{-1} . The NMR spectrum (δ in CDCl_3) showed the aromatic protons at 6.12 and 7.40 as doublets with $J=7.2$ Hz.

Next the cyanopyridone (XI) was hydrolyzed to give the pyridone-3-carboxylic acid (XII), which was treated with diazomethane to give 1,2-dihydro-3-methoxycarbonyl-1,4-dimethyl-2-oxopyridine (VIII). The IR and NMR spectra and thin-layer chromatographic (TLC) behavior of this compound was identical with those of the third product (VIII), which was obtained from the reaction of the 3-carboxypyridone (V) with diazomethane.

The formation of the compounds (VI and VII) could be rationalized as shown in Chart 3.

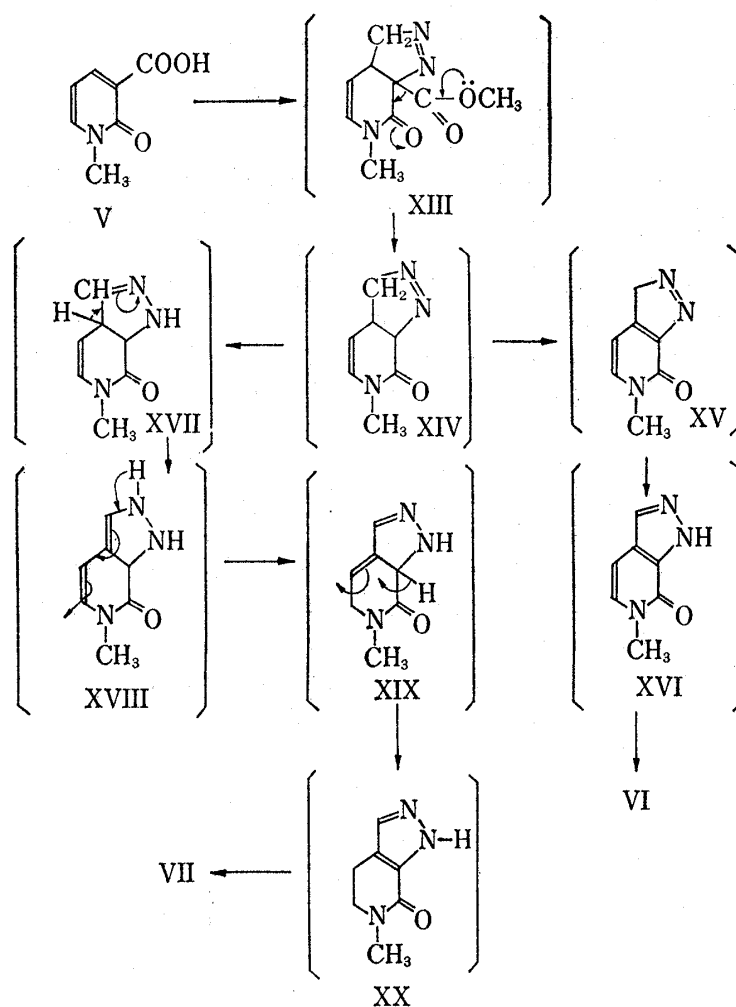


Chart 3

The esterification of the starting material (V), followed by the adduct formation of this ester with diazomethane and successive demethoxycarbonylation, gave an intermediate (XIV), whose oxidation¹⁰⁾ and then isomerization of $-\text{CH}_2-\text{N}=\text{N}-$ to $-\text{CH}=\text{N}-\overset{\text{H}}{\underset{|}{\text{N}}}-$,¹¹⁾ followed by N-methylation of the resulting pyrazole ring, afforded the first product (VI).

9) J.M. Bobbitt and D.A. Scola, *J. Org. Chem.*, **25**, 560 (1960).

10) M. Frankneumann and D. Martina, *Tetrahedron Letters*, **1975**, 1755.

11) a) R. Huttel, *Chem. Ber.*, **74**, 1680 (1941); b) L.I. Smith and W.B. Pings, *J. Org. Chem.*, **2**, 23 (1937);

c) K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim, and J. Schnieder, *Annalen*, **589**, 122 (1954).

The formation of the second product (VII) could also be rationalized by the isomerization through the intermediates XVII, XVIII, XIX and XX from XVI.

In case of the third product (VIII), a direct methylation could be formulated.¹²⁾ It seemed to be true that the first product (VI) was not formed through the second product (VII) because the second compound (VII) was not transformed to the first compound (VI) under a variety of oxidative conditions. For example, palladium in xylene and 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) in benzene were used.

The 3-carboxypyridone (V) was also treated with diazoethane to give the three compounds (XXI, XXII, and XXIII) in 26.7, 7.9, and 27.4% yield, respectively. In the IR spectrum (CHCl_3) of the first compound (XXI), mp 114.5–115°, the absorption due to pyridone carbonyl group was observed at 1655 cm^{-1} , and the NMR spectrum (δ in CCl_4) exhibited N-methyl group at 3.50 as singlet, methyl and methylene protons due to N-ethyl group at 1.45 as triplet with $J=7.0$ Hz and 4.46 as quartet with $J=7.0$ Hz, respectively, C-methyl group on the pyrazole ring at 2.34 as singlet, and aromatic protons on the pyridone ring at 6.15 and 6.67 as doublets with $J=7.0$ Hz. Thus, the first compound (XXI) was found to be 1-ethyl-6,7-dihydro-3,6-dimethyl-7-oxopyrazolo[3,4-*c*]pyridine.

The IR spectrum (CHCl_3) of the third compound (XXIII) showed the absorptions due to pyridone and ester groups at 1650 and 1720 cm^{-1} , respectively, and the NMR (δ in CCl_4) spectrum exhibited N-methyl group at 3.40 as singlet, methyl and methylene protons due to ethoxycarbonyl at 1.35 as triplet with $J=7.2$ Hz and 4.26 as quartet with $J=7.2$ Hz, methyl and methylene protons due to ethyl group on the pyridone ring at 1.16 as triplet with $J=7.4$ Hz and 2.40 as quartet with $J=7.4$ Hz and aromatic protons on pyridone ring at 5.85 and 7.15 as doublets with $J=7.2$ Hz. Thus the structure of the third compound (XXIII) was assigned to be 3-ethoxycarbonyl-4-ethyl-1,2-dihydro-1-methyl-2-oxopyridine.

Secondly, the structure of the second compound (XXII) was assigned to be 8a-ethoxycarbonyl-1,4,4a,7,8,8a-hexahydro-3,4,7-trimethyl-8-oxopyrido[3,4-*c*]pyridazine as follows. This compound (XXII), mp 95.5–96.5°, showed the molecular formula, $\text{C}_{13}\text{H}_{19}\text{O}_3\text{N}_3$, by microanalysis and mass spectrum (m/e 265, M^+). The IR spectrum (CHCl_3) showed the absorptions due to ester and amide carbonyl groups at 1742 and 1665 cm^{-1} , respectively, and the NMR spectrum (δ in CDCl_3) exhibited N-methyl group at 3.00 as singlet, methyl and methylene protons due to ethoxycarbonyl at 1.22 as triplet with $J=7.2$ Hz and 3.9–4.3 as quartet with $J=7.2$ Hz, C_3 -methyl group at 1.95 as singlet, C_4 -methyl group at 1.30 as doublet with $J=7.2$ Hz, C_{4a} -methine proton at 2.5–2.9 as multiplet, C_5 -methine proton at 5.32 as triple doublets with $J=8.0$, 6.0, and 2.0 Hz, C_6 -methine proton at 5.64 as double doublets with $J=8.0$ and 2.0, and NH proton at 6.51 as broad singlet, which was disappeared with D_2O -exchange. The presence of the couplings between C_4 -methyl proton and C_4 -methine proton and between C_4 -methine proton and C_{4a} -methine proton was confirmed by double irradiation study. The formation of the compounds (XXI and XXIII) could be rationalized in the same manner as the compounds (VI and VIII) as shown in Chart 2 and 3, and the reaction pathway for the second compound (XXII) could be formulated as shown in Chart 4. The addition of diazomethane to the ester derivative of the starting compound (V), followed by isomerization of the resulting intermediate (XXIV) could give the other intermediate (XXV), and then the ring expansion of the resulting intermediate (XXVI), followed by the isomerization of XXVII, could afford the second compound (XXII).

Thirdly, the reaction of the 4-carboxypyridone derivative with diazoalkanes was studied. 4-Carboxy-1,2-dihydro-1-methyl-2-oxopyridine (XXVIII)¹³⁾ was treated with diazomethane to give the compounds (XXIX, XXX, and XXXI) in 30.1, 26.2, and 33% yield, respectively.

12) a) M. Alguero, J. Bosch, J. Castaner, J. Castella, J. Castells, R. Mestres, J. Pascual, and F. Serratosa, *Tetrahedron*, **18**, 1381 (1962); b) F.D. Popp and A. Catala, *J. Org. Chem.*, **26**, 2738 (1961); c) J. Fried and R.C. Elderfield, *J. Org. Chem.*, **6**, 577 (1941).

13) M.H. Fronk and H.S. Mosher, *J. Org. Chem.*, **24**, 196 (1959).

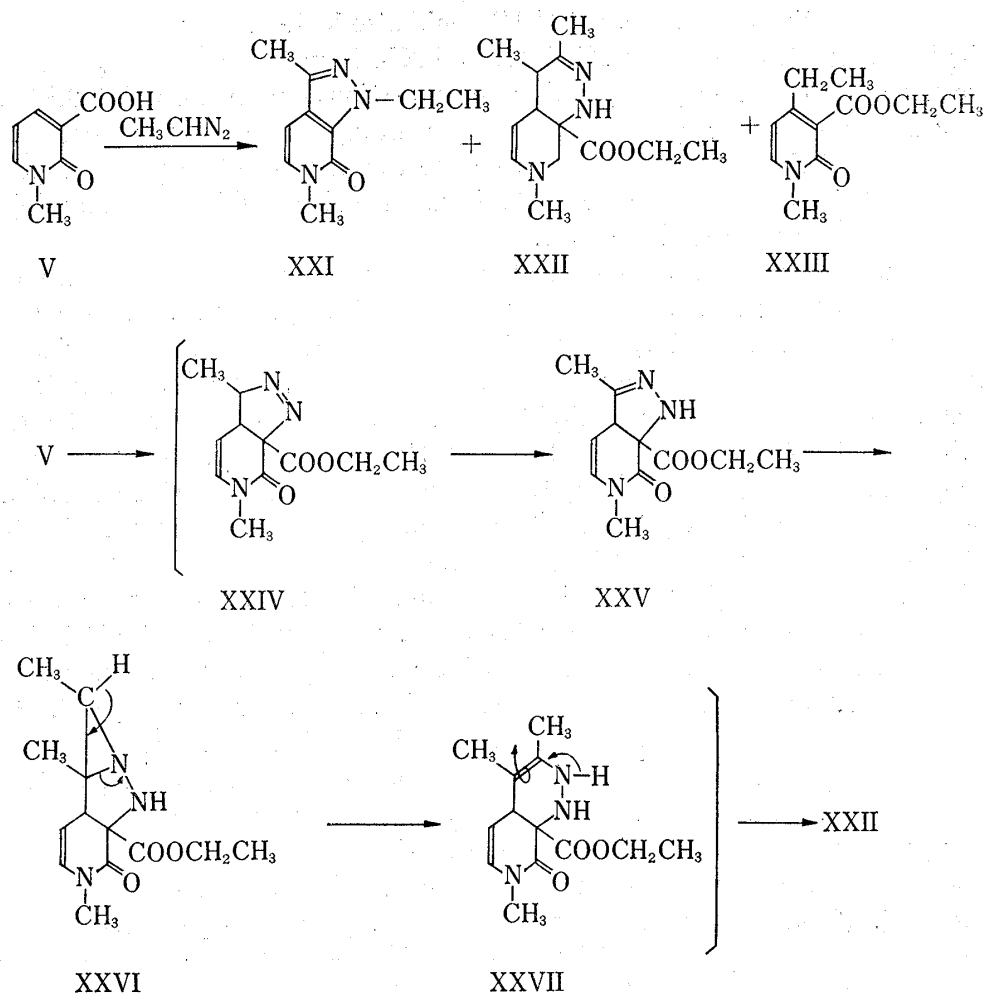


Chart 4

The first product (XXIX) was confirmed to be 1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine by direct comparison with the authentic specimen prepared by the esterification of the starting material (XXVIII) with sulfuric acid in methanol. In the IR spectrum (CHCl_3) of the second product (XXX), mp $158\text{--}159^\circ$, the absorption due to ester and amide carbonyl groups appeared at 1720 and 1650 cm^{-1} , and the NMR spectrum (δ in CCl_4) exhibited N-methyl group at 3.03 as singlet, methyl protons due to methoxycarbonyl group at 3.67 as singlet, olefinic protons at 5.53 and 5.87 as doublets with $J=8.0\text{ Hz}$, and the characteristic signals due to cyclopropane ring appeared at 0.80 as double doublets with $J=6.0$ and 4.0 Hz , and 2.55 as triple doublets with $J=10.0$, 6.0 , and 1.2 Hz . Thus the second compound (XXX) was shown to be 6-methoxycarbonyl-3-methyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene. The IR spectrum (CHCl_3) of the third compound (XXXI) showed the absorptions due to ester and amide carbonyls at 1720 and 1645 cm^{-1} , and the NMR spectrum (δ in CCl_4) exhibited N-methyl group at 3.48 as singlet, methyl protons due to methoxycarbonyl group at 3.85 as singlet, C_3 -methyl group at 2.28 as singlet, and aromatic protons at 6.26 and 7.09 as doublets with $J=7.2\text{ Hz}$.

The reaction of the first product (XXIX) with diazoethane was also carried out to afford 3-ethyl-1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine (XXXII), mp $114\text{--}115^\circ$, 6 α -methoxycarbonyl-3,7 β -dimethyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXXIII), and 1-ethyl-6-methoxycarbonyl-3,7-dimethyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXXIV), mp $73\text{--}74^\circ$, in 9.8, 12.4, and 43% yield, respectively. In the IR spectrum (CHCl_3) of the com-

pound (XXXII), the absorptions due to ester and amide carbonyl groups appeared at 1722 and 1642 cm^{-1} , and the NMR spectrum (δ in CCl_4) exhibited methyl and methylene protons due to C_3 -ethyl group at 1.10 as triplet and 2.76 as quartet with $J=7.2$ Hz. The IR spectrum of the compound (XXXIII) showed the absorptions due to ester and amide carbonyl groups at 1725 and 1650 cm^{-1} , and the NMR spectrum (δ in CCl_4) revealed the presence of methine protons on the cyclopropane ring which were appeared at 1.5—2.4 as multiplet and 2.55 as double doublets with $J=10.5$ and 1.2 Hz, and methyl group on the cyclopropane ring appeared at 0.87 as doublet with $J=6.0$ Hz. The coupling constant¹⁴⁾ with 10.5 Hz between C_1 -proton and C_7 -proton suggested that these two protons were located *cis* each other. The compound (XXXIV) showed the molecular formula, $\text{C}_{12}\text{H}_{17}\text{O}_3\text{N}$, by microanalysis and mass spectrum (m/e 223, M^+). The IR spectrum (CHCl_3) showed the absorptions due to ester and amide carbonyl groups at 1710 and 1652 cm^{-1} , and the NMR spectrum (δ in CCl_4) exhibited N-methyl and methoxycarbonyl groups at 2.88 and 3.68 as singlets, methyl and methylene protons due to ethyl group at 1.25 as triplet and 1.71 as quartet with $J=5.2$ Hz, C_7 -methyl group as doublet with $J=7.0$ Hz, olefinic protons at 5.56 and 5.89 as doublets with $J=9.8$ Hz. Thus, the structure of the compound (XXXIV) was confirmed.

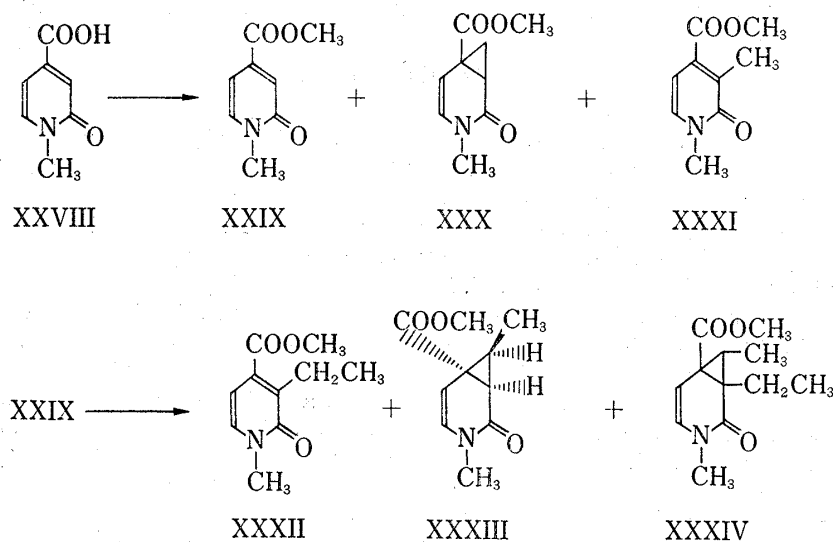


Chart 5

Finally, the reaction of the 2-pyridone-5-carboxylic acid (XXXV)¹⁵⁾ and 6-carboxylate (XXXVIII) with diazomethane was studied. In case of the former acid (XXXV), the single product, which was isolated in 67.2% yield, was found to be 1,2-dihydro-5-methoxycarbonyl-1-methyl-2-oxopyridine (XXXVI), mp 138—139° (lit.¹⁶⁾ 138.3—139.2°).

The second starting compound (XXXVIII) was obtained from methyl 2-pyridone-6-carboxylate (XXXVII)¹⁷⁾ and formaldehyde and the IR spectrum (KBr) showed the absorptions at 1785 and 1665 cm^{-1} . The NMR spectrum (δ in DMSO) exhibited methylene group at 5.15 as singlet and aromatic protons at 6.76 as double doublets with $J=10.0$ and 1.0 Hz, 7.07 as double doublets with $J=7.0$ and 1.0 Hz, and 7.78 as double doublets with $J=10.0$ and 7.0 Hz.

14) a) H.M. Hutton and T. Schaefer, *Can. J. Chem.*, **40**, 875 (1962); b) J.D. Graham and M.T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962); c) T. Shono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Letters*, 1964, 791.

15) H.L. Bradlow and C.A. Vanderwerf, *J. Org. Chem.*, **16**, 79 (1951).

16) M.L. Peterson, *J. Org. Chem.*, **25**, 567 (1960).

17) T. Kametani, H. Nemoto, H. Takeda, and S. Takano, *Tetrahedron*, **26**, 5753 (1970).

Na_2SO_4 and evaporated to give a brownish oil, which was triturated with EtOAc to afford 3-cyano-1,2-dihydro-1,4-dimethyl-2-oxopyridine (XI) as pale brownish needles (277 mg), mp 165.5–167° (from EtOAc). IR (CHCl_3) cm^{-1} : 2226 (CN), 1660 (C=O). NMR (CDCl_3) δ : 2.44 (3H, s, $\text{C}_4\text{-CH}_3$), 3.57 (3H, s, N- CH_3), 6.12 (1H, d, $J=7.2$ Hz, $\text{C}_5\text{-H}$), 7.40 (1H, d, $J=7.2$ Hz, $\text{C}_6\text{-H}$). Mass Spectrum m/e : 148 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_8\text{ON}_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.62; H, 5.44; N, 18.88.

1,2-Dihydro-3-methoxycarbonyl-1,4-dimethyl-2-oxopyridine (VIII)—To a solution of NaOMe in MeOH (28 ml), prepared from Na (1.4 g) and MeOH (28 ml), the compound (XI) (277 mg) was added. After the mixture had been refluxed for 8.5 days, the solvent was distilled off and the residue was acidified with 10% HCl solution, which was evaporated to leave a solid. The resulting residue was extracted with EtOH and the extract was evaporated to give a brownish oil, which was used for the next reaction without purification. To a solution of 3-carboxy-1,2-dihydro-1,4-dimethyl-2-oxopyridine (XII) (441 mg) obtained as above was added a solution of diazomethane¹⁹ in ether (10 ml), which was prepared from *p*-tolylsulfonylethylmethyl nitrosamide (7.1 g) at 0°. After being allowed to stand for 3 hr at 0°, the solvent was distilled off and the residue was chromatographed on silica gel (3.5 g). Elution with benzene–EtOAc (25:4) afforded 1,2-dihydro-3-methoxycarbonyl-1,4-dimethyl-2-oxopyridine (VIII) as a pale brownish oil (25 mg). This was identical with the compound, which was obtained by the reaction of compound (V) with diazomethane, by comparison of those spectroscopic data.

The Reaction of Compound (V) with Diazoethane—To a mixture of compound (V) (1 g), CHCl_3 (40 ml), and EtOH (100 ml) was added a solution of diazoethane²⁰ in ether (400 ml), which was prepared from N-ethyl-N-nitrosourea (40 g). After the mixture had been allowed to stand for 7 days at room temperature, the solvent was distilled off to leave a pale brownish oil, which was chromatographed on silica gel (55 g). Elution with benzene–EtOAc (40:1) afforded 1-ethyl-6,7-dihydro-3,6-dimethyl-7-oxopyrazolo[3,4-*c*]pyridine (XXI) (333 mg) as colorless needles, mp 114.5–115° (from hexane). IR (CHCl_3) cm^{-1} : 1655 (C=O). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm: 305, 266, 258. NMR (CCl_4) δ : 1.45 (3H, t, $J=7.0$ Hz, $-\text{CH}_2\text{-CH}_3$), 2.34 (3H, s, $\text{C}_3\text{-CH}_3$), 3.50 (3H, s, N- CH_3), 4.64 (2H, q, $J=7.0$ Hz, $-\text{CH}_2\text{-CH}_3$), 6.15 (1H, d, $J=7.0$ Hz, $\text{C}_4\text{-H}$), 6.67 (1H, d, $J=7.0$ Hz, $\text{C}_5\text{-H}$). Mass Spectrum m/e : 191 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{ON}_3$: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.97; H, 6.94; N, 22.04. Elution with benzene–EtOAc (20:1) gave 8a-ethoxycarbonyl-1,4,4a,7,8,8a-hexahydro-3,4,7-trimethyl-8-oxopyrido[3,4-*c*]pyridazine (XXII) (137 mg) as colorless prisms, mp 95.5–96.5° (from ether). IR (CHCl_3) cm^{-1} : 1742, 1665 (C=O). NMR (CDCl_3) δ : 1.22 (3H, t, $J=7.2$ Hz, $-\text{COOCH}_2\text{CH}_3$), 1.30 (3H, d, $J=7.0$ Hz, $\text{C}_4\text{-CH}_3$), 1.95 (3H, s, $\text{C}_3\text{-CH}_3$), 2.5–2.9 (1H, m, $\text{C}_{4a}\text{-H}$), 3.00 (3H, s, N- CH_3), 3.9–4.3 (2H, q, $J=7.2$ Hz, $-\text{COOCH}_2\text{CH}_3$ and 1H, m, $\text{C}_4\text{-H}$), 5.32 (1H, d, d, $J=8.0, 6.0, 2.0$ Hz, $\text{C}_5\text{-H}$), 5.64 (1H, d, d, $J=8.0, 2.0$ Hz, $\text{C}_6\text{-H}$), 6.51 (1H, broad s, N- H , exchangeable with D_2O). Mass Spectrum m/e : 265 (M^+). Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_3\text{N}_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.87; H, 7.16; N, 15.83. Successive elution with benzene–EtOAc (5:1) afforded 3-ethoxycarbonyl-4-ethyl-1,2-dihydro-1-methyl-2-oxopyridine (XXIII) (374 mg) as a colorless oil, bp 97–98° (0.03 mmHg). IR (CHCl_3) cm^{-1} : 1720, 1650 (C=O). NMR (CCl_4) δ : 1.16 (3H, t, $J=7.4$ Hz, $\text{C}_4\text{-CH}_2\text{-CH}_3$), 1.35 (3H, t, $J=7.2$ Hz, $-\text{COOCH}_2\text{CH}_3$), 2.40 (2H, q, $J=7.4$ Hz, $\text{C}_4\text{-CH}_2\text{-CH}_3$), 3.40 (3H, s, N- CH_3), 4.26 (2H, q, $J=7.2$ Hz, $-\text{COOCH}_2\text{CH}_3$), 5.85 (1H, d, $J=7.2$ Hz, $\text{C}_5\text{-H}$), 7.15 (1H, d, $J=7.2$ Hz, $\text{C}_6\text{-H}$). Mass Spectrum m/e : 209 (M^+). Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_3\text{N}$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.69; H, 7.29; N, 6.91.

The Reaction of 4-Carboxy-1,2-dihydro-1-methyl-2-oxopyridine¹³ (XXVIII) with Diazomethane—To a solution of compound (XXVIII) (700 mg) in MeOH (50 ml) was added a solution of diazomethane in ether (400 ml), prepared from N-methyl-N-nitrosourea (43 g). After being allowed to stand for 3 days at room temperature, the solvent was distilled off and the residue was triturated with benzene–hexane to give 1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine (XXIX) (140 mg) as colorless needles, mp 154–155° (from benzene), which was identical with the authentic specimen prepared as described later, by comparison of those spectroscopic data and mixed melting point test. After filtration of the compound (XXIX), the filtrate was chromatographed on silica gel (30 g). Elution with benzene–EtOAc (20:1) afforded 6-methoxycarbonyl-3-methyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXX) (217 mg) as a colorless oil. IR (CHCl_3) cm^{-1} : 1720, 1650 (C=O). NMR (CCl_4) δ : 0.80 (1H, d, d, $J=6.0, 4.0$ Hz, $\text{C}_7\text{-H}\beta$), 1.97 (1H, d, d, $J=10.0, 4.0$ Hz, $\text{C}_7\text{-H}\alpha$), 2.55 (1H, d, d, $J=10.0, 6.0, 1.2$ Hz, $\text{C}_1\text{-H}\alpha$), 3.03 (3H, s, N- CH_3), 3.67 (3H, s, $-\text{COOCH}_3$), 5.53 (1H, d, d, $J=8.0, 1.2$ Hz, $\text{C}_5\text{-H}$), 5.87 (1H, d, $J=8$ Hz, $\text{C}_4\text{-H}$). Mass Spectrum m/e : 181 (M^+). The hydrazide formed colorless prisms, mp 158–159° (from MeOH). Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{O}_2\text{N}_3$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.93; H, 6.25; N, 22.80. Successive elution with benzene–EtOAc (20:1) gave 1,2-dihydro-4-methoxycarbonyl-1,3-dimethyl-2-oxopyridine (XXXI) (276 mg) as a colorless oil. IR (CHCl_3) cm^{-1} : 1720, 1645 (C=O). NMR (CCl_4) δ : 2.28 (3H, s, $\text{C}_3\text{-CH}_3$), 3.48 (3H, s, N- CH_3), 3.85 (3H, s, $-\text{COOCH}_3$), 6.26 (1H, d, $J=7.2$ Hz, $\text{C}_5\text{-H}$), 7.09 (1H, d, $J=7.2$ Hz, $\text{C}_6\text{-H}$). Mass Spectrum m/e : 181 (M^+). The hydrazide formed colorless prisms, mp 168–169° (from MeOH). Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{O}_2\text{N}_3$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.88; H, 6.25; N, 23.22. The compound (XXIX) (90 mg) was obtained from the last fraction.

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1,2-Dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine (XXIX)—A mixture of compound (XXVIII) (9.0 g), MeOH (450 ml) and conc. H_2SO_4 (14 ml) was refluxed for 12 hr. After evaporation of MeOH, the residue was basified with 28% NH_4OH aq. solution and extracted with CHCl_3 . The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give a brownish powder, which was crystallized from benzene to give colorless needles (8.0 g), mp 154–155°. IR (CHCl_3) cm^{-1} : 1725, 1660 ($\text{C}=\text{O}$). NMR (CDCl_3) δ : 3.57 (3H, s, $\text{N}-\text{CH}_3$), 3.91 (3H, s, $-\text{COOCH}_3$), 6.62 (1H, d, d, $J=6.8, 1.6$ Hz, C_5-H), 7.18 (1H, d, $J=1.6$ Hz, C_3-H), 7.35 (1H, d, $J=6.8$ Hz, C_6-H). Mass Spectrum m/e : 167 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_9\text{O}_3\text{N}$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.51; H, 5.47; N, 8.47.

The Treatment of Compound (XXIX) with Diazoethane—To a solution of compound (XXIX) (4 g) in MeOH (200 ml) was added a solution of diazoethane in ether (800 ml), prepared from N-ethyl-N-nitrosourea (74.4 g). After standing for 5 days at room temperature, the solvent was removed by distillation and the residue was chromatographed on silica gel (185 g). Elution with benzene afforded the crude 1-ethyl-6-methoxycarbonyl-3,7-dimethyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXXIV) which was subjected to gas chromatography and shown to have retention time (29.7 min) at column temperature 130°. The amount of pure compound (XXXIV) (2.3 g) was calculated by taking pure sample from gas chromatography as colorless needles, mp 73–74° (from hexane). IR (CHCl_3) cm^{-1} : 1710, 1652 ($\text{C}=\text{O}$). NMR (CCl_4) δ : 1.25 (3H, t, $J=5.2$ Hz, $-\text{CH}_2\text{CH}_3$), 1.27 (3H, d, $J=7.0$ Hz, C_7-CH_3), 1.71 (2H, q, $J=5.2$ Hz, $-\text{CH}_2-\text{CH}_3$), 2.72 (1H, q, $J=7.0$ Hz, C_7-H), 2.88 (3H, s, $\text{N}-\text{CH}_3$), 3.68 (3H, s, COOCH_3), 5.56 (1H, d, $J=9.8$ Hz, C_5-H), 5.89 (1H, d, $J=9.8$ Hz, C_6-H). Mass Spectrum m/e : 223 (M^+). Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_3\text{N}$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.59; H, 7.94; N, 6.27.

Elution with benzene-EtOAc (40:1) gave 6 α -methoxycarbonyl-3,7 β -dimethyl-2-oxo-3-azabicyclo[4.1.0]hept-4-ene (XXXIII) (577 mg) as a colorless oil, bp 86° (0.02 mmHg). IR (CHCl_3) cm^{-1} : 1725, 1650 ($\text{C}=\text{O}$). NMR (CCl_4) δ : 0.87 (3H, d, $J=6.0$ Hz, $\text{C}_{7\beta}-\text{CH}_3$), 1.5–2.4 (1H, m, $\text{C}_{7\alpha}-\text{H}$), 2.55 (1H, d, d, $J=10.5, 1.2$ Hz, $\text{C}_{12}-\text{H}$), 3.04 (3H, s, $\text{N}-\text{CH}_3$), 3.66 (3H, s, $-\text{COOCH}_3$), 5.35 (1H, d, d, $J=8.4, 1.2$ Hz, C_5-H), 6.00 (1H, d, $J=8.4$ Hz, C_4-H). Mass Spectrum m/e : 195 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_3\text{N}$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.25; H, 6.88; N, 7.16. The retention time (9 min) on gas chromatography was determined at column temperature 145°. Successive elution with benzene-EtOAc (1:1) afforded 3-ethyl-1,2-dihydro-4-methoxycarbonyl-1-methyl-2-oxopyridine (XXXII) (458 mg) as colorless needles, mp 114–115° (from hexane). IR (CHCl_3) cm^{-1} : 1722, 1642 ($\text{C}=\text{O}$). NMR (CCl_4) δ : 1.10 (3H, t, $J=7.2$ Hz, $-\text{CH}_2-\text{CH}_3$), 2.76 (2H, q, $J=7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 3.47 (3H, s, $\text{N}-\text{CH}_3$), 3.84 (3H, s, $-\text{COOCH}_3$), 6.21 (1H, d, $J=7.2$ Hz, C_5-H), 7.09 (1H, d, $J=7.2$ Hz, C_6-H). Mass Spectrum m/e : 195 (M^+). Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_3\text{N}$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.58; H, 6.87; N, 7.26.

The Reaction of 5-Carboxy-1,2-dihydro-1-methyl-2-oxopyridine (XXXV) with Diazomethane—To a solution of compound (XXXV)¹⁵ (1.5 g) in MeOH (200 ml) was added a solution of diazomethane in ether (400 ml), which was prepared from N-methyl-N-nitrosourea (41.2 g), and the mixture was allowed to stand for 12 days at room temperature. After evaporation of the solvent, the residue was triturated with benzene-hexane to give 1,2-dihydro-5-methoxycarbonyl-1-methyl-2-oxopyridine (XXXVI) (1.1 g) as colorless needles, mp 138–139° (lit.¹⁶ mp 138.3–139.2°). IR (CHCl_3) cm^{-1} : 1715, 1659 ($\text{C}=\text{O}$). NMR (CDCl_3) δ : 3.61 (3H, s, $\text{N}-\text{CH}_3$), 3.86 (3H, s, $-\text{COOCH}_3$), 6.54 (1H, d, $J=9.4$ Hz, C_3-H), 7.84 (1H, d, d, $J=9.4, 2.4$ Hz, C_4-H), 8.17 (1H, d, $J=2.4$ Hz, C_6-H).

1,5-Dihydro-1,5-dioxo-3H-oxazolo[3,4-a]pyridine (XXXVIII)—A mixture of 1,2-dihydro-1H-6-methoxycarbonyl-2-oxopyridine¹⁷ (XXXVII) (500 mg), dioxane (20 ml), paraformaldehyde (1 g), and catalytic amount of conc. H_2SO_4 was heated at 100° for 16 hr in a sealed tube. After evaporation of the solvent, the residue was triturated with MeOH to give the compound (XXXVIII) (200 mg) as colorless prisms, mp 153–154° (from MeOH). IR (KBr) cm^{-1} : 1785, 1665 ($\text{C}=\text{O}$). NMR ($\text{DMSO}-d_6$) δ : 5.15 (2H, s, $\text{N}-\text{CH}_2-\text{O}-$), 6.76 (1H, d, d, $J=10.0, 1.0$ Hz, C_6-H), 7.07 (1H, d, d, $J=7.0, 1.0$ Hz, C_8-H), 7.78 (1H, d, d, $J=10.0, 7.0$ Hz, C_7-H). Mass Spectrum m/e : 151 (M^+). Anal. Calcd. for $\text{C}_7\text{H}_5\text{O}_3\text{N}$: C, 55.64; H, 3.33; N, 9.27. Found: C, 55.67; H, 3.38; N, 9.12.

The Reaction of Compound XXXVIII with Diazomethane—To a solution of compound (XXXVIII) (460 mg) in MeOH (50 ml) was added a solution of diazomethane in ether (200 ml), prepared from *p*-tolylsulfonylethylmethylnitrosamide (21.5 g). After standing for 5 days at room temperature, the solvent was distilled off to leave a pale yellowish powder, which was crystallized from ether to give 1,2-dihydro-6-methoxycarbonyl-1-methyl-2-oxopyridine (XXXIX) (183 mg) as colorless needles, mp 53–54°. IR (CHCl_3) cm^{-1} : 1720, 1650 ($\text{C}=\text{O}$). NMR (CCl_4) δ : 3.57 (3H, s, $\text{N}-\text{CH}_3$), 3.87 (3H, s, $-\text{COOCH}_3$), 6.53 (1H, d, d, $J=12.6, 2.4$ Hz, C_5-H), 6.61 (1H, d, d, $J=10.8, 2.4$ Hz, C_5-H), 7.21 (1H, d, d, $J=12.6, 10.8$ Hz, C_4-H). Mass Spectrum m/e : 167 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_9\text{O}_3\text{N}$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.79; H, 5.63; N, 8.39.

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