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SYNTHETIC STUDIES ON INDOLES AND RELATED COMPOUNDS 50.[1] IMPROVED SYNTHESIS OF 7, 9-DIDECARBOXYMETHOXATHINE

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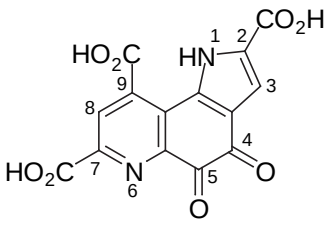
Abstract- An improved synthesis of 7, 9-didecarboxymethoxathine (**2**, R=H) is described.

Methoxathine (Pyrroloquinolinequinone: PQQ, **1**) is a cofactor that was first isolated from the methanol dehydrogenase of methylotropic bacteria.[2] Methoxathine itself was already synthesized[3] and 7-mono-, 9-mono-, and 7, 9-didecarboxy analogues were also synthesized for comparison of biological activity with methoxathine. To synthesize 7, 9-didecarboxymethoxathine (**2**, R=H), two methods have been reported. One method[4] has an excessive number of steps, involving decarboxylation of tricarboxyl compound leading to methoxathine (**1**), and other[5] provides a low yield from starting material (**3**).



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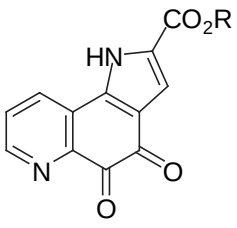

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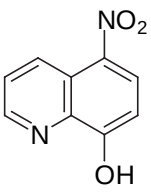

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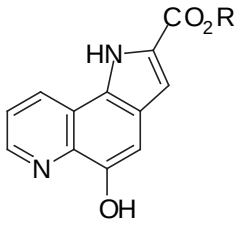

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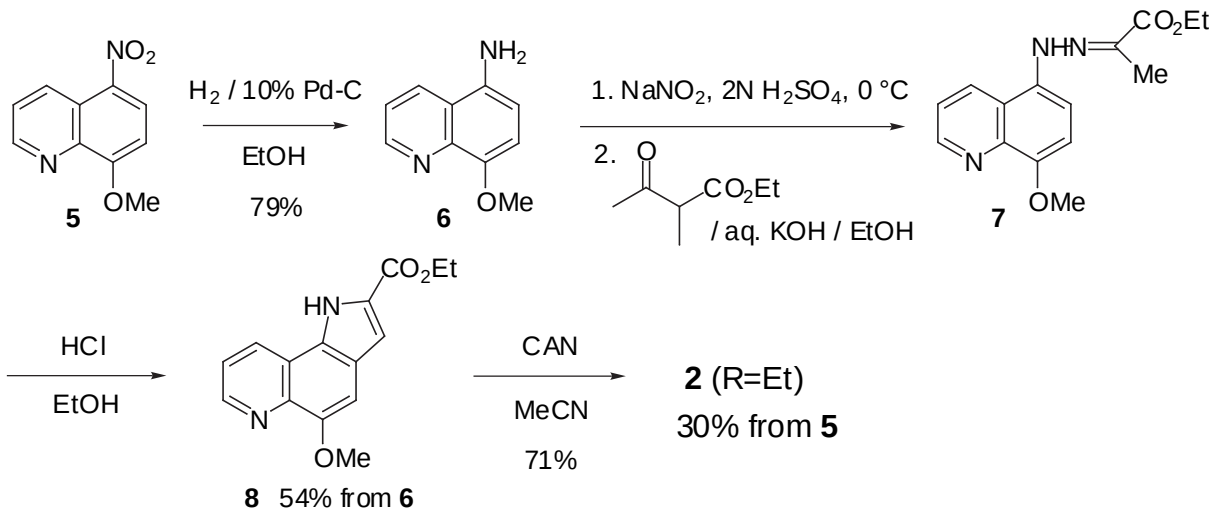
We presumed that the low yield in the later method[5] was derived from Japp-Klingemann reaction followed by Fischer indolization to compound (**4**) using unprotected phenolic intermediates. We report an improved synthesis of **2** (R=H).

To improve the total yield, we chose 8-methoxy-5-nitroquinoline (**5**)[6] as a starting material instead of **3**.

This paper is dedicated to Professor James P. Kutney in celebration of his 70th birthday.

The Japp-Klingemann reaction of the corresponding amine (**6**) gave a mixture of E- and Z- isomers of hydrazone (**7**) in 57% yield, and the subsequent Fischer indolization of the hydrazone (**7**) gave an indole (**8**) in 54% yield from **6**. CAN oxidation[3] of 5-methoxypyrroloquinoline (**8**) gave the *o*-quinone (**2**, R=Et) in 71% yield [total yield is 30% from compound (**5**)]. The ester (**2**, R=Et) has already been converted to carboxylic acid (**2**, R=H) in 75% yield by Bruice *et al.*[5] Thus, the formal total synthesis of 7, 9-didecarboxymethoxathine (**2**, R=H) was achieved in a better yield than the previous one[5] [compound (**2**, R=Et) was synthesized in 20% yield from **3**].

Scheme



EXPERIMENTAL

All melting points were determined on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a Shimadzu IR-400 spectrophotometer in Nujol mull. ^{1}H-NMR spectra were recorded on a Hitachi R-24B (60 MHz) and JEOL AL-400 (400 MHz) spectrometers with tetramethylsilane as an internal reference. ^{13}C-NMR spectra were recorded on a JEOL AL-400 (100 MHz) spectrometer. MS spectra were measured on JEOL JMS D-300 spectrometer with a direct inlet system. For column chromatography, silica gel 60 (70 - 230 mesh ASTM, Merck) was used. For TLC, silica gel 60F_{254} (Merck) was used.

5-Amino-8-methoxyquinoline (6)

A solution of 8-methoxy-5-nitroquinoline (**5**)[6] (3.595 g, 17.6 mmol) and 10% Pd-C (400 mg) in EtOH (250 mL) was stirred under hydrogen at rt for 8.5 h. The catalyst was removed by filtration and the solvent was evaporated to dryness *in vacuo*. The residual solid was recrystallized from AcOEt-hexane to give pale yellow prisms (**6**) (2.529 g, 83%) (mp 150-156°C, lit.,[6] 157.5-159.5°C). IR υ_{max}cm^{-1}: 3400-3100

(NH). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ : 3.50 (2H, br s, NH), 3.99 (3H, s, OCH_3), 6.68 (1H, d, *J*=8.0 Hz, C^6 or C^7-H), 6.87 (1H, d, *J*=8.0 Hz, C^6 or C^7-H) 7.32 (1H, dd, *J*=8.5 and 4.0 Hz, C^3-H), 8.12 (1H, dd, *J*=8.5 and 1.5 Hz, C^4-H), 8.86 (1H, dd, *J*=4.0 and 1.5 Hz, C^2-H).

Ethyl pyruvate(8-methoxyquinolin-5-yl)hydrazone (Z-**7 and** E-**7)**

Sodium nitrite (213 mg, 3.1 mmol) was added to a stirred solution of 5-amino-8-methoxyquinoline (**6**) (522 mg, 3.0 mmol) in 2N H_2SO_4 (6 mL) at 0-5 °C. The resulting diazonium salt solution was added to a mixture of ethyl α-methylacetoacetate and 10 N KOH (1.4 mL) in EtOH (3 mL) at 0 °C. After 30 min, the reaction mixture was poured into ice water, extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, and then evaporated to dryness *in vacuo*. The residual solid (293 mg) was separated into Fr-A and Fr-B by column chromatography (AcOEt:hexane;5:1).

Z-form (Z-**7)**

The Fr-A gave Z-form of the hydrazone (Z-**7**) as crystals (27 mg, 8%). Recrystallization from AcOEt-hexane gave brown needles (mp 137.5-139.5°C). *Anal*. Calcd for $C_{15}H_{17}N_3O_3$; C:62.71, H:5.96, N:14.62, Found; C: 62.45; H, 5.93; N, 14.57. IR υ_{max}cm^{-1}: 3260 (NH), 1678 (C=O). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ : 1.37 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.19 (3H, s, N=C-CH_3), 4.02 (3H, s, OCH_3), 4.29 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.98 (1H, d, *J*=8.5 Hz, C_7-H), 7.38 (1H, dd, *J*=8.5 and 4.0 Hz, C_3-H), 7.50 (1H, d, *J*=8.5 Hz, C^6-H), 8.21 (1H, dd, *J*=8.5 and 1.5 Hz, C^4-H), 8.88 (1H, dd, *J*=4.0 and 1.5 Hz, C^2-H), 12.63 (1H, br s, N-H). MS *m/z*; 287 (M^+, BP).

E-form (E-**7)**

The Fr-B gave E-form of the hydrazone (E-**7**) as crystals (145 mg, 45%). Recrystallization from AcOEt-hexane gave yellow prisms (mp 186.5-196°C). *Anal*. Calcd for $C_{15}H_{17}N_3O_3$; C:62.71, H:5.96, N:14.62, Found; C: 62.44; H, 5.95; N, 14.62. IR υ_{max}cm^{-1}: 3265 (NH), 1687 (C=O). ^{1}H-NMR ($CDCl_3$, 60 MHz) δ : 1.36 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 2.17 (3H, s, N=C-CH_3), 3.99 (3H, s, OCH_3), 4.31 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 6.93 (1H, d, *J*=8.5 Hz, C_7-H), 7.32 (1H, dd, *J*=8.5 and 4.0 Hz, C_3-H), 7.42 (1H, d, *J*=8.5 Hz, C^6-H), 8.01 (1H, br s, N-H), 8.28 (1H, dd, *J*=8.5 and 1.5 Hz, C^4-H), 8.83 (1H, dd, *J*=4.0 and 1.5 Hz, C^2-H). MS *m/z*; 287 (M^+, BP).

Ethyl 5-methoxy-1*H*-pyrrolo[2,3-*f*]quinoline-2-carboxylate (8)

A mixture of Z- and E-form of the hydrazones (**7**) prepared from amine (**6**, 2.090 g, 12 mmol) as descrived above was stirred in EtOH (40 mL) saturated with HCl at rt for 24 h. The reaction mixture was evaporated to remove HCl gas and EtOH *in vacuo*. The residual solid was poured into ice-water, then basified with sat. aqueous $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$, evaporated to dryness *in vacuo*. The residual solid (3.19 g) was purified by column chromatography (AcOEt:hexane;1:1) to give colorless crystals. Recrystallization from $CHCl_3$-

hexane gave colorless prisms (**8**) (1.701 g, 54% from **6**, mp 246.5-248°C). *Anal*. Calcd for $C_{15}H_{14}N_2O_3$; C:66.66, H:5.22, N:10.36, Found; C: 66.45; H, 5.48; N, 10.09. IR υ_{max} cm^{-1}: 3310 (NH), 1675 (C=O). ^{1}H-NMR (DMSO-d_6, 60 MHz) δ : 1.36 (3H, t, *J*=7 Hz, OCH_2CH_3), 3.93 (3H, s, OCH_3), 4.36 (2H, q, *J*=7 Hz, OCH_2CH_3), 7.18 (1H, d, *J*=1.5 Hz, C^3-H), 7.28 (1H, s, C^4-H), 7.56 (1H, dd, *J*=8.0 and 4.5 Hz, C^8-H), 8.77 (1H, dd, *J*=4,5 and 1.5 Hz, C^7-H), 9.05 (1H, dd, *J*=8.0 and 1.5 Hz, C^9-H), 12.61 (1H, br s, N-H). MS *m/z*; 270 (M^+, BP).

Ethyl 4,5-dihydro-4,5-dioxo-1*H*-pyrrolo[2,3-*f*]quinoline-2-carboxylate (2, R=Et)

To a solution of ethyl 5-methoxy-1*H*-pyrrolo[2,3-*f*]quinoline-2-carboxylate (**8**) (500 mg, 1.85 mmol) in acetonitrile (100 mL) was added ceric ammonium nitrate [(CAN), 5.578 g, 10.17 mmol], and the mixture was stirred at 0 °C for 0.5 h. The reaction mixture was poured into ice-water (200 mL), the precipitates were extracted with large excess of AcOEt:CH_2Cl_2 (4:1, 1000 mL) and the resultant emulsion was filtered off using a celite pad. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness in *vacuo*. Residual solid was suspended in AcOEt (10 mL), and then collected by filtration to give orange crystals **2** (R=Et) (355 mg, 71%). Recrystallization from DMSO-H_2O gave orange needles (mp > 300 °C). *Anal.* Calcd for $C_{14}H_{10}N_2O_4 \cdot 1/2\,H_2O$; C:60.22, H:3.97, N:10.03, Found; C: 59.96; H, 3.71; N, 9.84. IR υ_{max} cm^{-1}: 3280-3025 (NH), 1712 and 1660 (C=O). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ : 1.32 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.32 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 7.13 (1H, d, *J*=2.0 Hz, C^3-H), 7.65 (1H, dd, *J*=8.1 and 4.6 Hz, C^8-H), 8.63 (1H, dd, *J*=4.6 and 1.5 Hz, C^7-H), 8.65 (1H, dd, *J*=8.1 and 1.5 Hz, C^9-H), 13.24 (1H, br s, N-H). ^{13}C-NMR (DMSO-d_6) δ: 14.3, 60.7, 114.2, 121.7, 126.4, 126.7, 127.6, 130.8, 137.9, 145.9, 149.2, 159.5, 173.0, 179.0. MS *m/z*; 270 (M^+, 30%), 196 (BP).

REFERENCES

1. Part 49: "Unexpected Formation of Quinolone Derivatives in Reissert Indole Synthesis", H. Suzuki, H. Gyoutoku, H. Yokoo, M. Shinba, Y. Sato, H. Yamada, and Y. Murakami, *Synlett*, 2000, 1196.
2. S. A. Salisbury, H. S. Forrest, W. B. T. Cruse, and O. Kennard, *Nature* (London), 1979, **280**, 843.
3. E. J. Corey and A. Tramontano, *J. Am. Chem. Soc*., 1981, **103**, 5599.
4. S. Itoh, J. Kato, T. Inoue, Y. Kitamura, M. Komatsu, and Y. Ohshiro, *Synthesis*, 1987, 1067.
5. P. R. Sleath, J. B. Noar, G. A. Eberlein, and T. C. Bruice, *J. Am. Chem. Soc*., 1985, **107**, 3328.
6. I. E. Balaban, *J. Chem. Soc*., 1932, 2624.