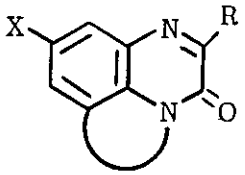
A FACILE SYNTHESIS OF NOVEL TRICYCLIC COMPOUNDS, 2,3-DIHYDRO-1H-PYRIDO[3,2,1-i,j]QUINOXALIN-5-ONES

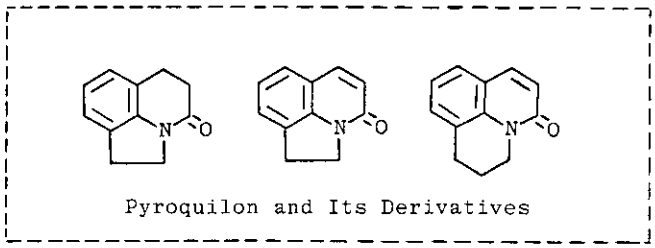
Kenzi MAKINO,* Gozyo SAKATA, and Katsushi MORIMOTO
Central Research Institute, Nissan Chemical Ind., LTD.,
Tsuboi-cho, Funabashi, Chiba 274, Japan
Yoshinori OCHIAI
Biological and Chemical Research Laboratory, Nissan Chemical Ind., LTD., Shiraoka, Saitama 349-02, Japan

Abstract - Novel 2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one-7-oxide (1) was synthesized from 8-nitro-1,2,3,4-tetrahydroquinoline in one pot reaction. 1 could be converted into 2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one (3), 6-methyl-2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one (4), and 6-chloro-2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one (5).

Quinoxaline derivatives are widely used as biologically active compounds. For instance, caroverine, quinacilline, and carbadox are known in the field of pharmaceutical chemicals and particularly in the field of agricultural chemicals, quinomethionate, quinalphos, and NCI-96683 (quizalofop-ethyl)[1] are attracted special interest as a fungicide, an insecticide, and a selective herbicide, respectively. Quinoxaline moieties of these compounds are used as a mother skeleton or building block for the appearance of biological activities. Their structures are shown in Figure 1.

On the other hand, it has been reported that 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]-quinolin-4-one (pyroquilon) and its derivatives have been excellent fungicides against *Pyricularia oryzae* and inhibited the pathway of melanine biosynthesis.[2] In connection with our synthetic and biological studies, we now elaborated facile method for the synthesis of novel tricyclic compounds, which could be regarded as analogues of pyroquilon.

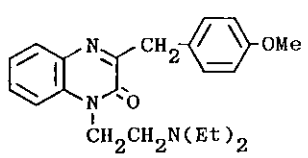




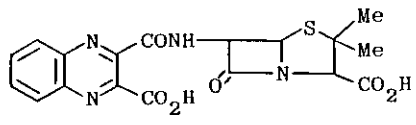
Pyroquilon and Its Derivatives

When a solution of 8-nitro-1,2,3,4-tetrahydroquinoline in toluene was treated with diketene in the presence of a catalytic amount of pyridine, next with aqueous sodium hydroxide, 2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one-7-oxide (1), mp 210-211 °C, was obtained in 70% yield. The same reaction was carried out using 7-nitroindoline and 1,2-dihydropyrrolo[3,2,1-i,j]quinoxalin-4-one-6-oxide (2), mp 208-210 °C, was afforded in 62% yield. In this reaction, compound 1 and 2 could be synthesized from 8-nitro-1,2,3,4-tetrahydroquinoline and 7-nitroindoline in one pot reaction, respectively. When 1 was allowed to react with sodium hydrogensulfite, ethyl acetoacetate, and phosphoryl chloride, 2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one (3), mp 152.5-154 °C, 6-methyl-2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one (4), mp 116-117 °C, and 6-chloro-2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one (5), mp 169.5-171 °C, were obtained in 75, 63, and 67% yield, respectively. These reactions were shown in Scheme 1.

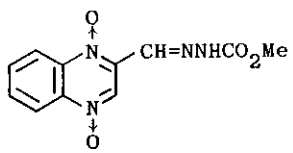
In the synthesis of 1 and 2, the carbanion of acetoacetyl group attacked the



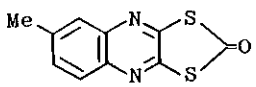
Caroverine



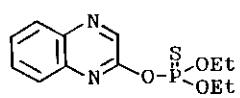
Quinacilline



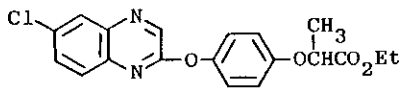
Carbadox



Quinomethionate



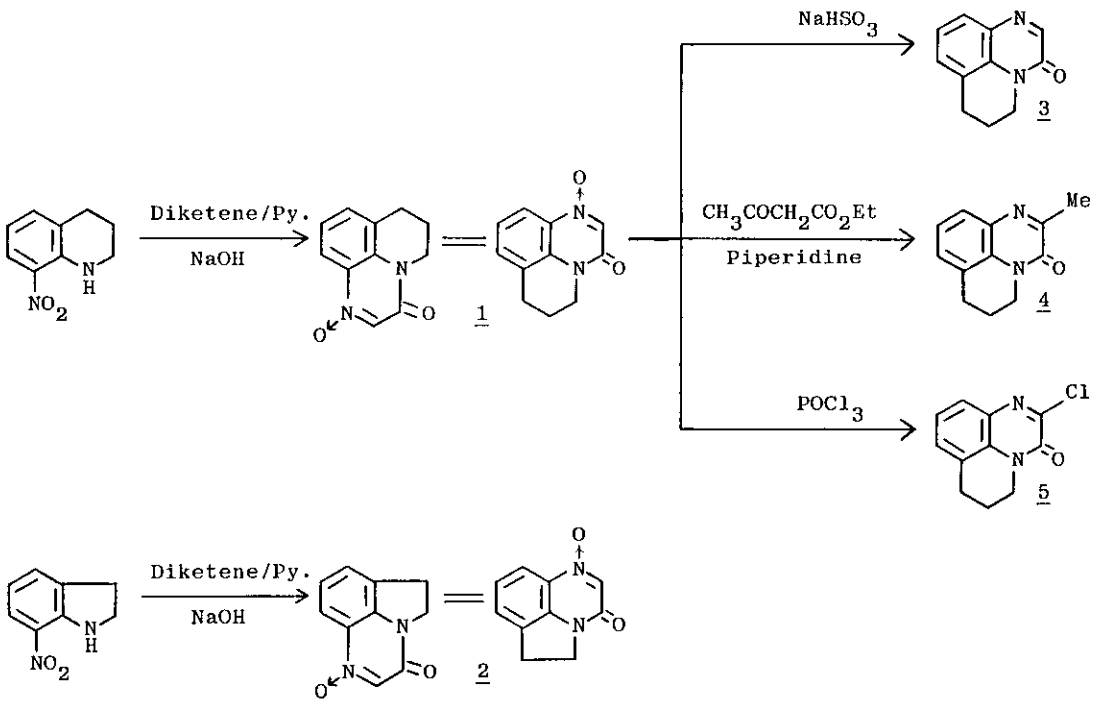
Quinalphos



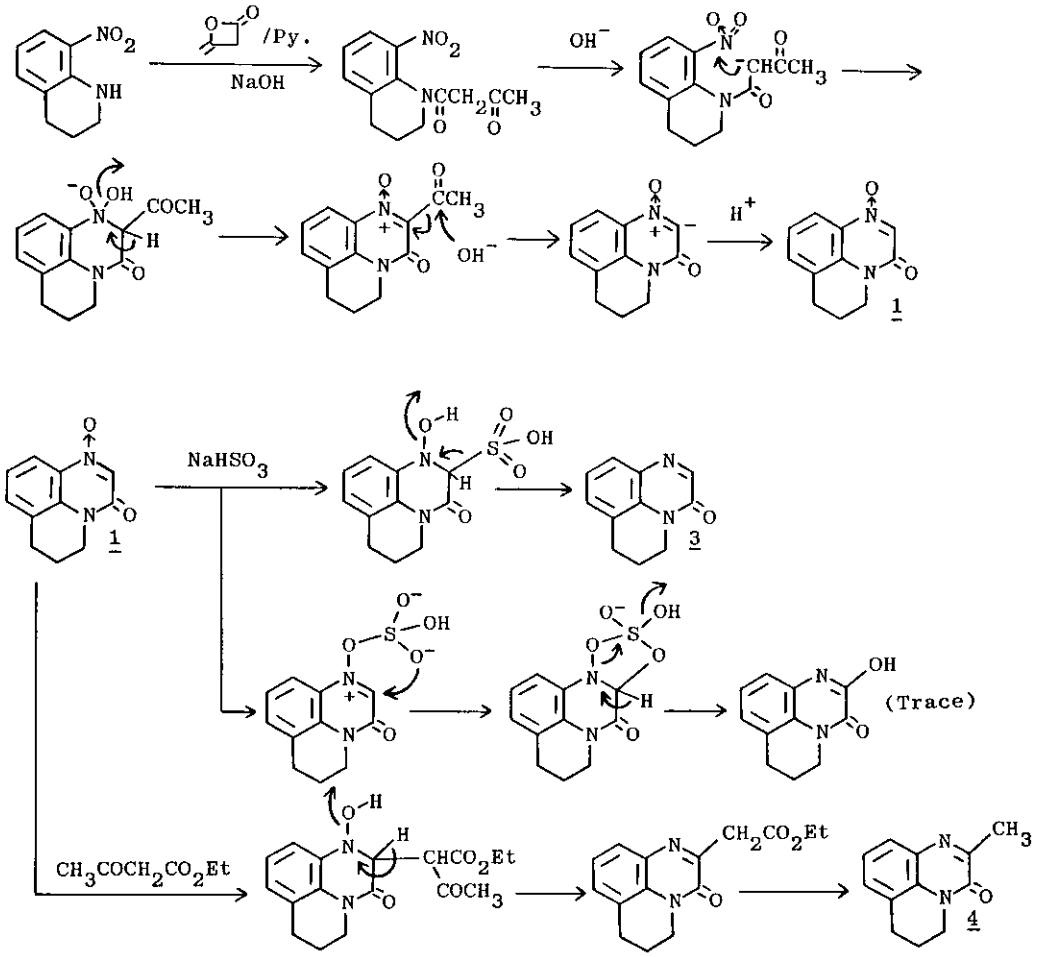
NCI-96683

Figure 1.

neighboring nitro group and next dehydration, furthermore deacetylation occurred. When sodium hydrogensulfite was applied to the reduction of 1, 3 was obtained as well as a small amount of 6-hydroxy-2,3-dihydro-1H-pyrido[3,2,1-i,j]quinoxalin-5-one. It was assumed that the adduct of sodium hydrogensulfite to 1 was formed on the carbon or oxygen atom of nitrone structure and gave different products. But in this case, the adduct on the carbon atom was preferentially formed. In the synthesis of 4, ethyl acetoacetate was reacted at 6-position of 1 and next dehydration, deacetylation, and furthermore decarboxylation occurred. These reaction mechanisms are illustrated in Scheme 2.[3,4]



Scheme 1.*



Scheme 2.

EXPERIMENTAL SECTION

Pmr spectra were obtained on a JEOL FX-90 Spectrometer locked on the tetramethylsilane as an internal reference. Ir spectra were measured on a JASCO A-3 Infrared Spectrophotometer. Mass spectra were measured on a JEOL D-300, JMA 3500 and DX-300, JMA 3100. Elemental analyses were measured on an Elemental Analyzer model 1106 (Carlo Erba Strumentazione). Chemical purities were determined on a Shimazu Liquid Chromatograph LC-3A. All melting points are uncorrected.

Preparation of 1 and 2. Diketene (5.46 g, 65.0 mmol) was added dropwise to a solution of 8-nitro-1,2,3,4-tetrahydroquinoline (11.6 g, 65.2 mmol) and pyridine (0.5 g) in toluene (200 ml) at room temperature. The reaction temperature was elevated and stirring was continued for 6.0 h at 60 °C. Next the reaction mixture was cooled to room temperature and 5% sodium hydroxide (100 ml) was added. After

stirring for 0.5 h at room temperature, 12% hydrochloric acid was added dropwise to acidify the aqueous layer with continuous stirring. The toluene layer was separated and washed with water, next dried over anhydrous sodium sulfate. Removal of the solvent gave a solid, which was purified with column chromatography (silica gel, CH_3CO_2Et) to afford 9.21 g (70%) of 1. ir(KBr): 3450, 1640, 1583, 1532, 1390, and 1238 cm^{-1}. pmr(DMSO-d_6) δ 1.75-2.30(2H, m), 2.94(2H, t, J= 6.0 Hz), 3.97(2H, t, J= 5.7 Hz), 7.90(1H, s), and 7.05-8.20(3H, m). ms m/z 202(M^+, base peak), 187, 171, 157, and 130.

As the same manner, 2 was synthesized from 7-nitroindoline in 62% yield. ir(KBr): 3425, 1638, 1600, 1524, 1432, 1402, and 1259 cm^{-1}. pmr(DMSO-d_6) δ 3.44(2H, t, J= 8.0 Hz), 4.33(2H, t, J= 8.0 Hz), 7.80(1H, s), and 7.05-8.00(3H, m). ms m/z 188(M^+, base peak), 172, 143, and 116.

Preparation of 3. 1 (1.50 g, 7.43 mmol) was dissolved in a solution of 3% sodium hydroxide (30 ml) and ethyl alcohol (30 ml). Sodium hydrogensulfite (2.32 g, 22.3 mmol) was added portionwise at room temperature and stirring was continued for 1.0 h. After removal of a small amount of insoluble substance with filtration, the filtrate was neutralized with 12% hydrochloric acid. The solution was partly evaporated under reduced pressure and cooled to 0-5 °C. The resulting solid was collected and washed with water. It was dried in vacuo and recrystallized from ethyl alcohol/n-heptane to afford 1.04 g (75%) of 3. ir(KBr): 3440, 1660, 1590, 1478, 1328, and 755 cm^{-1}. pmr(DMSO-d_6) δ 1.65-2.30(2H, m), 2.93(2H, t, J= 6.6 Hz), 3.99(2H, t, J= 6.0 Hz), 7.00-7.75(3H, m), and 8.13(1H, s). ms m/z 186(M^+, base peak), 171, 157, and 130.

Preparation of 4. Ethyl acetoacetate (1.68 g, 12.9 mmol) and piperidine (2.6 ml) were successively added to a solution of 1 (1.75 g, 8.66 mmol) in ethyl alcohol (100 ml). After reflux for 2.0 h, 10% potassium hydroxide (50 ml) was added dropwise at room temperature and stirring was continued for 0.5 h. Ethyl alcohol was removed under reduced pressure and water (50 ml) was added. The aqueous solution was adjusted to pH 3 with 12% hydrochloric acid and the resulting solid was filtered off. Next with 5% potassium hydroxide, the filtrate was adjusted to pH 10-12 and the solvent was partly removed under reduced pressure. The resulting solid was collected and washed with water. It was dried in vacuo and recrystallized from ethyl alcohol/n-heptane to afford 1.10 g (63%) of 4. ir(KBr): 3525, 1642, 1595, 1482, 1375, and 760 cm^{-1}. pmr(DMSO-d_6) δ 1.75-2.25(2H, m), 2.39 (3H, s), 2.87(2H, t, J= 6.0 Hz), 3.95(2H, t, J= 5.7 Hz), and 7.10-7.70(3H, m). ms

m/z 200(M^+, base peak), 185, 172, 171, and 130.

Preparation of 5. 1 (1.00 g, 4.95 mmol) was refluxed with phosphoryl chloride (15 ml) for 2.0 h. After removal of excess phosphoryl chloride under reduced pressure, crude product was slowly added into ice-water. The tarry substance was separated and dissolved in acetone. After the solvent was partly removed under reduced pressure, the resulting solid was collected and then washed with water. It was dried in vacuo and recrystallized from ethyl alcohol/n-heptane to afford 0.73 g (67%) of 5. ir(KBr): 3425, 1644, 1589, 1468, 1140, 1035, and 759 cm^{-1}. pmr(DMSO-d_6) δ 1.80-2.30(2H, m), 2.94(2H, t, J= 6.2 Hz), 4.07(2H, t, J= 5.7 Hz), and 7.05-7.70(3H, m). ms m/z 220(M^+, base peak), 205, 191, 156, and 130.

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* All new compounds gave satisfactory elemental analyses.

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