Ring Transformation of 1,5-Benzoxazepines into Spirobenzoxazoles. Synthesis of Pyrazolo[1′,5′:3,4][1,2,4]triazino-[5,6-*b*][1,5]benzoxazepines and Spiro[benzoxazole-2′(3′*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazines] [1]

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The reactions of the 3-substituted 4-amino-8-ethoxycarbonyl[5,1-*c*][1,2,4]triazines **1** and **2** with *o*-aminophenol hydrochloride gave the pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **5** and **8**. The alkylation of **5** with methyl iodide and isopropyl iodide afforded the 6-alkoxylpyrazolo[1′,5′:3,4][1,2,4]triazino-[5,6-*b*][1,5]benzoxazepines **6a** and **6b**, respectively. Refluxing of **5**, **6a**, **6b** and **8** in hydrochloric acid/acetic acid resulted in ring transformation to produce the spiro[benzoxazole-2′(3′*H*),4(1*H*)pyrazolo[5,1-*c*][1,2,4]-triazines] **7a**, **7b** and **9**. The screening data of the above compounds was described.

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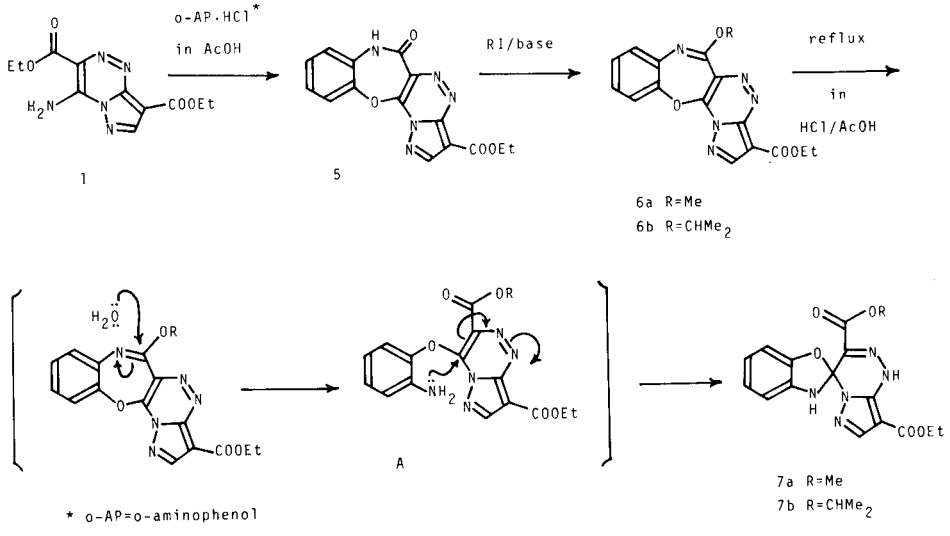
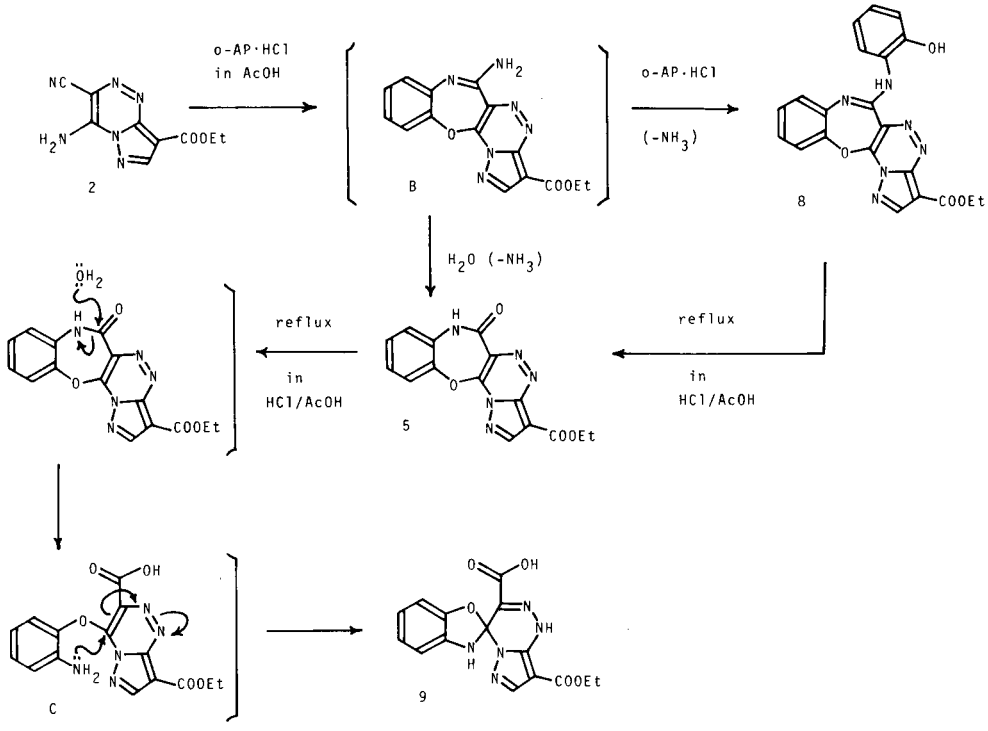
In a previous paper [2], we reported that the reactions of 3-substituted 4-amino-8-ethoxycarbonylpyrazolo[5,1-*c*]-[1,2,4]triazines **1** and **2** with *o*-phenylenediamine dihydrochloride gave the pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*]-[1,5]benzodiazepine **3** and spiro[benzimidazole-2′(3′*H*),-6(5*H*)-pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepine] **4**, respectively (Chart 1). In the present investigation, we found that the reactions of **1** and **2** with *o*-aminophenol hydrochloride conveniently afforded the pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **5** and **8**, respectively. Moreover, the pyrazolo[1′,5′:3,4]-[1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **5**, **6a**, **6b** and **8** were found to be converted into the spiro[benzoxazole-2′(3′*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazines] **7a**, **7b** and **9** under reflux in hydrochloric acid/acetic acid. There have been a few examples concerning the ring transformation of 1,5-benzoxazepine into benzoxazole [2], but its ring transformation into spirobenzoxazole has seldom been reported so far. This paper describes the synthesis of the pyrazolo[1′,5′:3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **5**, **6a**, **6b** and **8** and their ring transformation into the spiro[benzoxazole-2′(3′*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazines] **7a**, **7b** and **9**, together with the screening data of the above compounds.

The reaction of **1** with *o*-aminophenol hydrochloride gave 9-ethoxycarbonyl-6-oxo-5,6-dihydropyrazolo[1′,5′:-



Scheme 1



Scheme 2

3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepine **5** (66%). The reactions of **5** with methyl iodide and isopropyl iodide provided 9-ethoxycarbonyl-6-methoxylpyrazolo[1′,5′:3,4]-[1,2,4]triazino[5,6-*b*][1,5]benzoxazepine **6a** (80%) and 9-ethoxycarbonyl-6-isopropoxylpyrazolo[1′,5′:3,4][1,2,4]-triazino[5,6-*b*][1,5]benzoxazepine **6b** (51%), respectively. Refluxing of **6a** and **6b** in hydrochloric acid/acetic acid resulted in ring transformation to afford 8-ethoxycarbonyl-3-methoxycarbonylspiro[benzoxazole-2′(3′*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazine] **7a** (93%) and 8-ethoxycarbonyl-3-isopropoxycarbonylspiro[benzoxazole-2′(3′*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazine] **7b** (59%), respectively, presumably *via* an intermediate **A** (Scheme 1).

The reaction of **2** with a 3-fold molar amount of *o*-aminophenol hydrochloride produced 9-ethoxycarbonyl-6-(*o*-hydroxyphenyl)aminopyrazolo[1′,5′:3,4][1,2,4]triazino-[5,6-*b*][1,5]benzoxazepine **8** (68%) and **5** (22%), presumably *via* an intermediate **B** [2] (Scheme 2). Refluxing of **5** and **8** in hydrochloric acid/acetic acid also effected ring transformation to afford 8-ethoxycarbonylspiro[benzoxazole-2′(3′*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]-triazine]-3-carboxylic acid **9** in 86% and 83% yields, respectively, presumably *via* an intermediate **C**.

The structural assignments for the above compounds **5-9** were based on their analytical and spectral data. Especially, the ^{13}C-nmr spectra of the spiro compounds **7a, 7b, 9** and **4** [2] showed the spiro carbon signals at δ

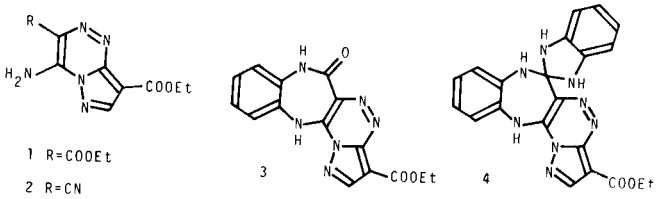
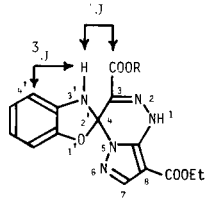


Chart 1

98.82, 98.08, 97.45 and 96 ppm, respectively. Moreover, the spiro ring structure was supported by the long range ^{13}C-^{1}H COSY spectra of **7a, 7b** and **9**, which clarified the long range C-H coupling between $C_{4'}$ ($\delta \cong 120$ ppm) and N_3-H ($^3J \cong 5$ Hz) and between C_3-carbonyl C ($\delta \cong 15$ ppm) and N_3-H ($^4J \cong 2$ Hz) (Chart 2). The detailed long range C-H coupling data will be described elsewhere. On the other hand, Takagi *et al.* reported some examples of the heterocyclic spiro ring opening in an acidic medium



7a, 7b, 9

Chart 2

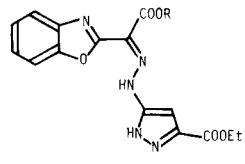


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Chart 3

[4], and the spiro ring opening of **7a**, **7b** and **9** would provide the compounds such as **10** shown in Chart 3. However, the above ^{13}C-nmr spectral data excluded the spiro ring opened structure for **7a**, **7b** and **9**. The ^{13}C-nmr spectrum of **8** exhibited no signal due to the spiro carbon between δ 110 and 60 ppm, denying the spiro ring structure for **8**.

Compound **5** showed a weak antibacterial activity against *Xanthomonas oryzae* (100% growth inhibition at concentration of 100 ppm), and **6a**, **6b** and **8** exhibited a very weak antifungal activity against *Rhizoctonia solani* and *Pythium debaryanum* (26-57% growth inhibition at 100 ppm) (Table). The spiro compounds **7a**, **7b** and **9** showed no antibacterial and antifungal activities against the above microorganisms.

Table

Antimicrobial Activity of Compounds **5**, **6a**, **6b** and **8** at a Concentration of 100 ppm

Compound	Activity [a] X.o.	R.s.	P.d. [b]
5	100	-	-
6a	-	26	-
6b	-	-	57
8	-	26	-

[a] Growth inhibition (%). [b] X.o.: *Xanthomonas oryzae* (bacteria); R.s.: *Rhizoctonia solani* (fungi); P.d.: *Pythium debaryanum* (fungi).

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The pmr and ^{13}C-nmr spectra were measured in deuteriodimethylsulfoxide with an EM 390 and an XL-400 spectrometers at 90 and 400 MHz, respectively, using tetramethylsilane as an internal reference. Chemical shifts are given in the δ scale, relative to the internal reference. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

9-Ethoxycarbonyl-6-oxo-5,6-dihydropyrazolo[1',5':3,4][1,2,4]triazino-[5,6-*b*][1,5]benzoxazepine **5**.

A solution of **1** (5 g, 17.90 mmoles) and *o*-aminophenol hydrochloride (7.82 g, 53.80 mmoles) in acetic acid (300 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave yellow crystals **5**, which were triturated with hot ethanol/water and then collected by suction filtration (3.82 g, 66%). Recrystallization from *N,N*-dimethylformamide/ethanol afforded yellow needles, mp 306-307°; ir: ν cm^{-1} 3160, 1720, 1660, 1600; ms: m/z 325 (M$^+$); pmr: 8.42 (s, 1H, C_{10}-H), 8.00-7.67 (m, 2H, aromatic), 7.63-7.33 (m, 2H, aromatic), 4.35 (q, J = 7 Hz, 2H, CH_2), 3.90-2.60 (br, NH and H_2O), 1.33 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{11}N_5O_4$: C, 55.38; H, 3.51; N, 21.53. Found: C, 55.39; H, 3.26; N, 21.59.

9-Ethoxycarbonyl-6-methoxylpyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]-benzoxazepine **6a**.

Methyl iodide (2.62 g, 18.46 mmoles) was added to a suspension of **5** (5 g, 15.38 mmoles) and sodium hydroxide (0.74 g, 18.46 mmoles) in dioxane (200 ml)/water (100 ml), and the suspension was heated on a boiling water bath for 2 hours to give a clear solution. Evaporation of the solvent *in vacuo* afforded yellow crystals **6a**, which were collected by suction filtration (4.15 g, 80%). Recrystallization from *N,N*-dimethylformamide/-methanol furnished yellow needles, mp 259-260°; ir: ν cm^{-1} 1700, 1550, 1500; ms: m/z 339 (M$^+$); pmr: 8.48 (s, 1H, C_{10}-H), 8.00-7.73 (m, 2H, aromatic), 7.66-7.33 (m, 2H, aromatic), 4.40 (s, 3H, OCH_3), 4.32 (q, J = 7 Hz, 2H, CH_2), 1.33 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{13}N_5O_4$: C, 56.63; H, 3.86; N, 20.64. Found: C, 56.54; H, 3.81; N, 20.67.

9-Ethoxycarbonyl-6-isopropoxylpyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*]-[1,5]benzoxazepine **6b**.

A solution of **5** (5 g, 15.4 mmoles), isopropyl iodide (3.92 g, 23.1 mmoles) and 1,8-diazabicyclo[5,4,0]-7-undecene (3.51 g, 23.1 mmoles) in *N,N*-dimethylformamide (150 ml) was refluxed in an oil bath for 1 hour. After acetic acid (10 ml) was added to the reaction mixture with stirring, the solvent was evaporated *in vacuo* to give an oily residue, which was dissolved in ethanol and water with heating and then allowed to stand at room temperature to provide yellow crystals. Recrystallization of these yellow crystals from ethanol and then from ethanol/water afforded yellow needles **6b** (2.89 g, 51%), mp 192-193°; ir: ν cm^{-1} 2980, 1715; ms: m/z 367 (M$^+$); pmr: 8.52 (s, 1H, C_{10}-H), 7.96-7.87 (m, 2H, aromatic), 7.55-7.46 (m, 2H, aromatic), 6.00 (qq, J = 6.5 Hz, 1H, CH), 4.34 (q, J = 7 Hz, 2H, CH_2), 1.53 (d, J = 6.5 Hz, 6H, 2 CH_3), 1.35 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.67; N, 19.06. Found: C, 58.84; H, 4.59; N, 19.09.

8-Ethoxycarbonyl-3-methoxycarbonylspiro[benzoxazole-2'(3'*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazine] **7a**.

A solution of **6a** (5 g) in concentrated hydrochloric acid (10 ml)/acetic acid (190 ml) was refluxed in an oil bath for 4 hours to precipitate yellow needles **7a**, which were collected by suction filtration (4.91 g, 93%). Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles, mp 310-311°; ir: ν cm^{-1} 1690, 1590, 1540, 1500; ms: m/z 357 (M$^+$); pmr: 11.00 (s, 1H, NH), 10.23 (s, 1H, NH), 8.57 (s, 1H, C_7-H), 8.70-8.00 (m, 1H, aromatic), 7.15-6.75 (m, 3H, aromatic), 4.43 (s, 3H, CH_3), 4.37 (q, J = 7 Hz, 2H, CH_2), 1.35 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{15}N_5O_5$: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.53; H, 4.22; N, 19.57.

8-Ethoxycarbonyl-3-isopropoxycarbonylspiro[benzoxazole-2'(3'*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]triazine] **7b**.

A solution of **6b** (2 g) in concentrated hydrochloric acid (4 ml)/acetic acid (80 ml) was refluxed in an oil bath for 4 hours to give a clear solution. Evaporation of the solvent *in vacuo* gave yellow crystals **7b** (1.24 g, 59%). Recrystallization from ethanol afforded yellow needles, mp 273-274°; ir: ν cm^{-1} 3150, 1690, 1650; ms: m/z 385 (M$^+$); pmr: 10.93 (s, 1H, NH), 10.25 (s, 1H, NH), 8.55 (s, 1H, C_7-H), 8.37 (d, J = 8 Hz, 1H, aromatic), 7.00-6.81 (m, 3H, aromatic), 5.97 (qq, J = 6.5 Hz, 1H, CH), 4.33 (q, J = 7 Hz, 2H, CH_2), 1.49 (d, J = 6.5 Hz, 6H, 2 CH_3), 1.37 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{19}N_5O_5$: C, 56.10; H, 4.97; N, 18.17. Found: C, 56.11; H, 5.01; N, 18.26.

9-Ethoxycarbonyl-6-(*o*-hydroxyphenyl)aminopyrazolo[1',5':3,4][1,2,4]-triazino[5,6-*b*][1,5]benzoxazepine **8** and Compound **5**.

A solution of **2** (5 g, 18.0 mmoles) and *o*-aminophenol hydrochloride (9.32 g, 54.0 mmoles) in acetic acid (300 ml) was refluxed in an oil bath for 5 hours. Evaporation of the solvent *in vacuo* gave yellow crystals, which were triturated with water and then collected by suction filtration. Recrystallization of the yellow crystals from ethanol gave yellow needles **8**, which were collected by suction filtration (5.10 g, 68%). Evaporation of the filtrate *in vacuo* afforded yellow crystals **5**, which were collected by suction filtration (1.28 g, 22%).

Compound **8** was recrystallized once more from ethanol to give an analytically pure sample as half hydrate, mp 276-277°; ir: ν cm^{-1} 1700, 1590, 1510; ms: m/z 416 (M$^+$); pmr: 14.08 (s, 1H, OH or NH), 13.38 (brs, 1H, NH or OH), 8.27 (s, 1H, C_{10}-H), 8.10-7.73 (m, 4H, aromatic), 7.73-7.27 (m, 4H, aromatic), 4.44 (q, J = 7 Hz, 2H, CH_2), 1.36 (t, J = 7 Hz, 3H,

CH_3).

Anal. Calcd. for $C_{21}H_{16}N_6O_4 \cdot 1/2\ H_2O$: C, 59.29; H, 4.03; N, 19.76. Found: C, 59.02; H, 4.21; N, 19.64.

8-Ethoxycarbonylspiro[benzoxazole-2'(3'*H*),4(1*H*)-pyrazolo[5,1-*c*][1,2,4]-triazine]-3-carboxylic Acid **9**.

A solution of **5** (2 g) or **8** (2 g) in concentrated hydrochloric acid (5 ml)/acetic acid (80 ml) was refluxed in an oil bath for 3 hours to precipitate yellow crystals **9**, which were collected by suction filtration after cooling to room temperature [1.81 g (86%) from **5**; 1.37 g (83%) from **8**]. Recrystallization from *N,N*-dimethylformamide/ethanol gave yellow needles, mp 326-327°; ir: ν cm^{-1} 1680, 1650, 1585, 1540, 1510; ms: m/z 343 (M^+); pmr: 10.97 (s, 1H, NH), 10.20 (s, 1H, NH), 8.48 (s, 1H, C_7-H), 8.60-8.30 (m, 1H, aromatic), 7.10-6.67 (m, 3H, aromatic), 4.38 (q, J = 7 Hz, 2H, CH_2), 1.34 (t, J = 7 Hz, 3H, CH_3). The C_3-carboxylic proton signal was unobservable presumably due to broadening.

Anal. Calcd. for $C_{15}H_{13}N_5O_5$: C, 52.48; H, 3.82; N, 20.40. Found: C, 52.42; H, 3.94; N, 20.41.

REFERENCES AND NOTES

[1] Preliminary report: Y. Kurasawa, M. Okiyama, Y. Kamigaki, M. Kanoh, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **24**, 1805 (1987).

[2] Y. Kurasawa, Y. Okamoto and A. Takada, *J. Heterocyclic Chem.*, **24**, 1799 (1987).

[3] F. J. McEvoy and G. R. Allen, Jr., *J. Org. Chem.*, **35**, 1183 (1970).

[4] K. Takagi, T. Aotsuka, H. Morita and Y. Okamoto, *J. Heterocyclic Chem.*, **23**, 1443 (1986); T. Aotsuka, H. Morita, K. Takagi and Y. Okamoto, *Synthesis*, 668 (1986).