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Unsubstituted **5**, and 2-aryl- **6a-c**, or 2-(2-benzothiazolyl)-substituted 1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-ones **7a-f** were prepared by the reactions of 3-ethoxyoxalyl- **2**, or 3-ethoxycarbonylisochroman-4-one **3** with hydrazine derivatives. The reactions with amidines gave 2-substituted 4-hydroxyisochromano[4,3-*d*]-pyrimidines **8a-c**.

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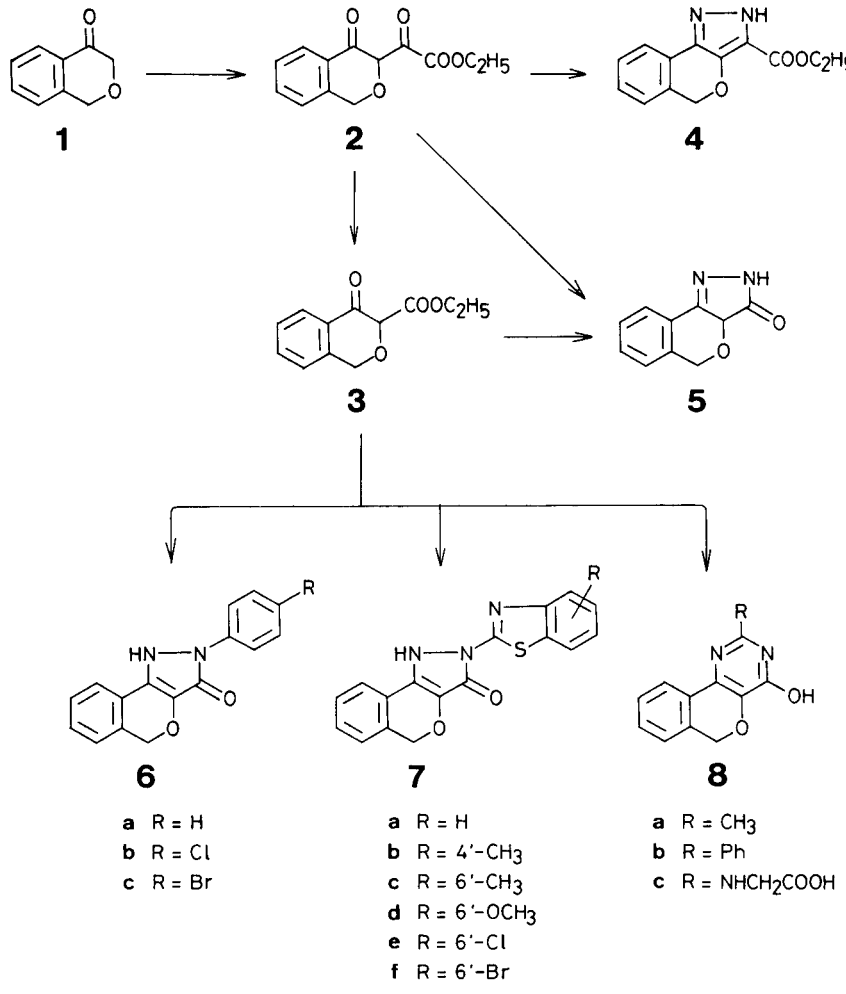
It is well known that six-membered oxygen heterocycles constitute a group of compounds which occur widely throughout the plant kingdom. However, the isochromanone nucleus has not been found in natural products. In synthetic organic chemistry, twenty years ago, isochroman-4-one was prepared by two groups of Colonge [1] and Normant-Chefnay [2]. It has been reported that isochroman-4-one (**1**) and 3-ethoxycarbonylisochroman-4-one (**3**) were converted to isochroman-fused carbocycles [3,4] and heterocycles [5-7] by using various reations. Recently, we reviewed these results [8]. We also found that isochroman-4-one and its derivatives have biological activities [6,7]. In

Scheme I



this paper, we carried out the synthesis of isochroman-fused pyrazolone and pyrimidine derivatives on purpose to obtain more biologically active heterocyclic compounds.

Results and Discussion.

Preparation of Isochroman-4-one Derivatives.

As the starting material, 3-ethoxyoxalylisochroman-4-one (**2**) was newly obtained as yellow needles (mp 40-41°) by the reaction of isochroman-4-one (**1**) [1,2] with diethyl oxalate in the presence of sodium hydride under nitrogen atmosphere. In the ^{1}H nmr spectrum, a signal for the H-3 was not observed, since this compound is enolizable. This compound **2** was refluxed for 36 hours in absolute ethanol, followed by heating for 3 hours at reduced pressure in the presence of iron powder, to convert to 3-ethoxycarbonylisochroman-4-one (**3**) [9]. These compounds **2** and **3** have a β-diketone structure and are expected as useful precursors to heterocycle-fused isochroman derivatives.

Reactions of Isochroman-4-ones with Hydrazines and Amidines.

Hydrazines reacted with β-dicarbonyl compounds to give pyrazolone derivatives. A mixture of 3-ethoxyoxalylisochroman-4-one (**2**) and hydrazine hydrate in acetic acid was refluxed for 3 hours to afford 3-ethoxycarbonyl-2*H*-isochromano[4,3-*c*]pyrazole (**4**) in 72% yield. When this reaction was carried out under alkaline conditions, 3,3a-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**5**) [6,7] was obtained in 76% yield. Another 3-ethoxycarbonylisochroman-4-one (**3**) reacted with hydrazine in alkaline condition to give compound **5** in 86% yield. Previously, Ghosh reported that 3-carboxybenzo-4-pyrone reacted with phenylhydrazine to give 2-phenylbenzopyrano[4,3-*c*]pyrazol-3(2*H*)-one [10]. A solution of 3-ethoxycarbonylisochroman-4-one (**3**) and phenylhydrazine in ethanol was refluxed for 10 hours to give 2-phenyl-1,3-dihydroisochromano[4,3-*c*]-pyrazol-3(2*H*)-one (**6a**) as yellow crystals in 65% yield. 4-Chloro- and 4-bromo-substituted phenylhydrazines also reacted with compound **3** to give the corresponding halo-substituted compounds **6b,c** in 80 and 73% yields, respectively. Furthermore, the reactions of six 2-hydrazinobenzothiazoles with **3** were carried out and the benzothiazolyl-substituted compounds **7a-f** were obtained in 52-77% yields. Similarly, compound **2** reacted with 2-hydrazinobenzothiazole to afford **7a** in 86% yield.

On the other hand, it has been reported that 3-formyl-4-benzopyrone reacted with benzamidine to give 4-hydroxy-2-phenylbenzopyrano[4,3-*d*]pyrimidine [11,12]. The reactions with amidines were examined. When a mixture of 3-ethoxycarbonylisochroman-4-one (**3**) and acetamidine was heated at 110° for 4.5 hours in the presence of sodium butoxide, 4-hydroxy-2-methylisochromano[4,3-*d*]pyrimidine (**8a**) was isolated in 80% yield. The reactions with benzamidine and gylcocyamine also gave 2-substituted 4-hydroxyisochromano[4,3-*d*]pyrimidines **8b,c** in 82 and 69% yields, respectively.

In conclusion, it was found that 3-ethoxyoxalyl- **2**, and 3-ethoxycarbonylisochroman-4-one (**3**) are very useful synthons for synthesis of pyrazolone- and pyrimidine-fused isochromans.

EXPERIMENTAL

Measurements.

The ir spectra were taken on a Perkin-Elmer 1700 spectrophotometer. The ^{1}H nmr spectra were measured with a JEOL JNM-PMX60SI spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ values.

3-Ethoxyoxalylisochroman-4-one (2).

To a suspension of 80% sodium hydride (300 mg, 10 mmoles) in dry toluene (7.5 ml) was added a solution of isochroman-4-one (**1**) (500 mg, 3.4 mmoles) and diethyl oxalate (1.5 g) in dry toluene (5 ml) under a nitrogen atmosphere. After addition of absolute ethanol (2 drops), the mixture was stirred for 12 hours at 25° in the same atmosphere. Then, the mixture was triturated with ice (7 g), stirred for 1 hour, and allowed to stand overnight. The aqueous layer was separated, and the organic layer was extracted five times with water (each 2 ml). The combined aqueous layer was acidified with concentrated hydrochloric acid to deposit yellow crystals, which was recrystallized from 90% ethanol to give 3-ethoxyoxalylisochroman-4-one (**2**) as yellow needles, yield, 640 mg (76%), mp 40-41°; ir (potassium bromide): ν max 1720 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.34 (3H, t, J = 7.0 Hz, CH_3), 4.31 (2H, q, J = 7.0 Hz, $COOCH_2$), 5.16 (2H, s, 1-CH_2), 7.15-7.95 (5H, m).

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.76; H, 4.86.

Conversion of the Compound 2 to 3.

A solution of the compound **2** (2.0 g) in absolute ethanol (30 ml) was refluxed for 36 hours. After evaporation to a volume of 10 ml, the residue was heated for 3 hours at 40 mm Hg in the presence of iron powder (trace) and purified by distillation at reduced pressure to give 3-ethoxycarbonylisochroman-4-one (**3**), yield 1.15 g (65%), bp 138-145°/0.1 mm Hg (lit [9] bp 145-150°/0.1 mm Hg).

3-Ethoxycarbonyl-2*H*-isochromano[4,3-*c*]pyrazole (4).

A solution of 3-ethoxyoxalylisochroman-4-one (**2**) (300 mg, 1.2 mmoles) and 98% hydrazine hydrate (2 ml) in acetic acid (10 ml) was refluxed for 3 hours. The reaction mixture was triturated with ice (15 g) and allowed to stand overnight. A precipitate was collected and recrystallized from ethanol to afford 3-ethoxycarbonyl-2*H*-isochromano[4,3-*c*]pyrazole (**4**) as colorless needles, yield 210 mg (72%), mp 170-171°; ir (potassium bromide): ν max 3415 (NH), 1720 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.32 (3H, t, J = 7.0 Hz, CH_3), 4.30 (2H, q, J = 7.0 Hz, $COOCH_2$), 5.27 (2H, s, 5-CH_2), 7.0-7.7 (4H, m), 10.15 (1H, brs, NH).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.93; H, 4.79; N, 11.28.

3,3a-Dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (5).

a) A mixture of 3-ethoxyoxalylisochroman-4-one (**2**) (1.73 g, 7.0

mmoles) and 50% hydrazine hydrate (2.1 g, 21 mmoles) in 5% sodium hydroxide solution (15 ml) was stirred for 4.5 hours at 75°. The solution was acidified with acetic acid to deposit crystals, which were collected, washed with water, and recyrstallized from 80% acetic acid to give 3,3a-dihydroisochromano[4,3-*c*]-pyrazol-3(2*H*)-one (**5**) as red plates, yield 1.00 g (76%), mp 222-224° (lit [6,7] mp 220-221°).

b) A mixture of 3-ethoxycarbonylisochroman-4-one (**3**) (1.5 g, 7.0 mmoles) and 50% hydrazine hydrate (2.1 g, 21 mmoles) was treated and worked up, as mentioned above, to give **5**, yield 1.14 g (86%).

2-Aryl-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-ones **6a-c**.

A solution of compound **3** (1.1 g, 5.0 mmoles) and arylhydrazine (1.5 mmoles) in absolute ethanol (10 ml) was refluxed for 10 hours. The reaction mixture was allowed to stand overnight at room temperature to deposit yellow crystals, which were collected and recrystallized from ethanol to afford 2-aryl-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-ones **6a-c**.

2-Phenyl-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**6a**).

This compound was obtained in a yield of 860 mg (65%), mp 164-165°; ir (potassium bromide): ν max 1726 cm^{-1} (C=O); ^1H nmr (deuteriodimenthyl sulfoxide): δ 5.12 (2H, s, CH_2), 7.3-7.35 (10H, m).

Anal. Calcd. for $C_{16}H_{11}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.59; H, 4.36; N, 10.48.

2-(4-Chlorophenyl)-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**6b**).

This compound was obtained in a yield of 1.09 g (73%), mp 183-184°; ir (potassium bromide): ν max 1718 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 5.15 (2H, s, CH_2), 7.3-7.6 (9H, m).

Anal. Calcd. for $C_{16}H_{11}N_2O_2Cl$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.48; H, 3.83; N, 9.59.

2-(4-Bromophenyl)-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**6c**).

This compound was obtained in a yield of 1.37 g (80%), mp 162-163°; ir (potassium bromide): ν max 1729 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 5.15 (2H, s, CH_2), 7.35-7.75 (9H, m).

Anal. Calcd. for $C_{16}H_{11}N_2O_2Br$: C, 56.00; H, 3.23; N, 8.17. Found: C, 56.21; H, 2.93; N, 8.07.

2-(2-Benzothiazolyl)-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-ones **7a-f**.

A solution of compound **3** (1.1 g, 5.0 mmoles) and 4- or 6-substituted 2-hydrazinobenzothiazole (6.0 mmoles) in absolute ethanol (15 ml) was refluxed for 27 hours. After cooling, the yellow crystals were collected, washed twice with ethanol, and recrystallized from dimethylformamide to afford 2-(2-benzothiazolyl)-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one **7a-f**.

2-(2-Benzothiazolyl)-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**7a**).

This compound was obtained in a yield of 1.38 g (86%), mp 173-174°; ir (potassium bromide): ν max 1684 cm^{-1} (C=O); ^1H (deuteriodimethyl sulfoxide): δ 5.14 (2H, s, CH_2), 7.3-7.9 (9H, m).

Anal. Calcd. for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.80; H, 3.56; N, 13.32.

2-[2-(4-Methylbenzothiazolyl)]-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**7b**).

This compound was obtained in a yield of 1.07 g, (64%), mp 246° dec; ir (potassium bromide): ν max 1691 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 2.60 (3H, s, CH_3), 5.28 (2H, s, CH_2), 7.15-8.0 (8H, m).

Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53. Found: C, 64.58; H, 3.94; N, 12.56.

2-[2-(6-Methylbenzothiazolyl)]-1,3-dihydroisochromano[4,3-*c*]-pyrazol-3(2*H*)-one (**7c**).

This compound was obtained in a yield of 1.29 g (77%), mp 235° dec; ir (potassium bromide): ν max 1699 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide) δ: 2.38 (3H, s, CH_3), 5.16 (2H, s, CH_2), 7.15-7.7 (8H, m).

Anal. Calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53. Found: C, 64.75; H, 3.80; N, 12.53.

2-[2-(6-Methoxybenzothiazolyl)]-1,3-dihydroisochromano[4,3-*c*]-pyrazol-3(2*H*)-one (**7d**).

This compound was obtained in a yield of 1.23 g (70%), mp 212-213°; ir (potassium bromide): ν max 1690 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 3.82 (3H, s, OCH_3), 5.37 (2H, s, CH_2), 6.9-7.95 (8H, m).

Anal. Calcd. for $C_{18}H_{13}N_3O_3S$: C, 61.53; H, 3.73; N, 11.96. Found: C, 61.67; H, 3.81; N, 12.24.

2-[2-(6-Chlorobenzothiazolyl)]-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**7e**).

This compound was obtained in a yield of 1.05 g (59%), mp 264° dec; ir (potassium bromide): ν max 1698 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 5.14 (2H, s, CH_2), 6.75-7.6 (8H, m).

Anal. Calcd. for $C_{17}H_{10}N_3O_2ClS$: C, 57.39; H, 2.83; N, 11.81. Found: C, 57.64; H, 2.76; N, 11.89.

2-[2-(6-Bromobenzothiazolyl)]-1,3-dihydroisochromano[4,3-*c*]pyrazol-3(2*H*)-one (**7f**).

This compound was obtained in a yield of 1.04 g (52%), mp 250° dec; ir (potassium bromide): ν max 1702 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 5.17 (2H, s, CH_2), 6.9-7.9 (8H, m).

Anal. Calcd. for $C_{17}H_{10}N_3O_2BrS$: C, 51.01; H, 2.52; N, 10.50. Found: C, 50.96; H, 2.51; N, 10.80.

4-Hydroxyisochromano[4,3-*d*]pyrimidines **8a-c**.

A mixture of compound **3** (1.5 g, 7.0 mmoles) and amidine or glycocyamine (10 mmoles) in sodium butoxide solution, prepared from sodium (460 mg, 20 mmoles) and butanol (15 ml), was stirred for 4.5 hours at 110° and triturated with water. After removal of the precipitate, the filtrate was acidified with acetic acid and allowed to stand overnight. A yellow precipitate was collected and recrystallized from dimethylformamide to afford 4-hydroxyisochromano[4,3-*d*]pyrimidines **8a-c**.

4-Hydroxy-2-methylisochromano[4,3-*d*]pyrimidine (**8a**).

This compound was obtained by using acetamidine hydrochloride (950 mg, 10 mmoles) in a yield of 1.19 g (80%), mp 163-164°; ir (potassium bromide): ν max 3420 cm^{-1} (OH); ^1H nmr (deuteriodimethyl sulfoxide): δ 2.28 (3H, s, CH_3), 5.15 (2H, s, CH_2), 7.15-7.9 (5H, m, H arom + OH).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.47; H, 4.82; N, 13.03.

4-Hydroxy-2-phenylisochromano[4,3-*d*]pyrimidine (**8b**).

This compound was obtained by using benzamidine hydrochloride (1.6 g, 10 mmoles) in a yield of 1.59 g (82%), mp 180-181°; ir (potassium bromide): ν max 3435 cm^{-1} (OH), ^1H nmr (deuteriodimethyl sulfoxide): δ 5.16 (2H, s, CH_2), 7.15-7.75 (10H, m, H arom + OH).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.79; H, 4.39; N, 10.21.

2-[(Carboxymethyl)amino]-4-hydroxyisochromano[4,3-*d*]pyrimidine (**8c**).

This compound was obtained by using glycocyamine (1.2 g, 10 mmoles) in a yield of 1.32 g (69%), mp 201-202°; ir (potassium bromide): ν max 3431 cm^{-1} (OH); ^1H nmr (deuteriodimethyl sulfoxide): δ 4.01 (2H, s, NCH_2), 5.01 (2H, s, 1-CH_2), 7.0-7.85 (4H, m, H arom).

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.41; H, 4.00; N, 15.66.

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