Synthesis of 3-[[(2-Benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptapyrazol-8-ones

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3-(Bromoacetyl)tropolone was reacted with five 2-mercaptobenzimidazoles to give 3-[[(2-benzimidazolyl)thio]acetyl]tropolones. These products were heated with methylhydrazine to afford 3-[[(2-benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptapyrazol-8-ones. In these reactions, 1-methyl-3-[(1-methylhydrazino)methyl]-1,8-dihydrocycloheptapyrazol-8-one was isolated as a minor product.

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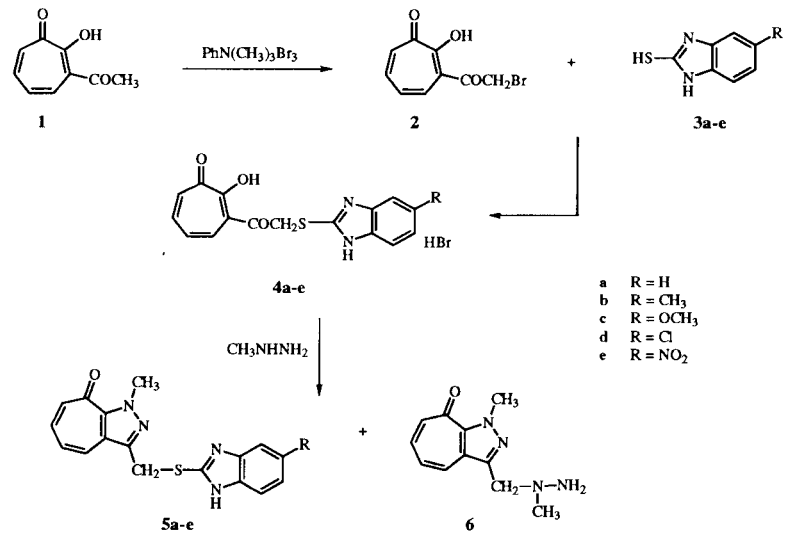
3-Acetyltropolone (**1**) is an important starting material for synthesis of heterocycle-fused troponoid compounds [1,2], because it has a reactive acetyl group at the 3-position and β-diketone structure. As an example, compound **1** reacted with hydrazine to afford 3-methyl-1,8-dihydrocycloheptapyrazol-8-one in a good yield [3]. On the other hand, 3-acetyltropolone (**1**) was treated with phenyltrimethylammonium tribromide to give 3-(bromoacetyl)-tropolone (**2**) as a new synthon [4].

Recently, gastric antisecreting effect has been found in 2-(heteroarylmethylthio)cycloheptimidazoles [5], which have the five-membered diazaheterocycle-fused tropoid structure. Their partial structure is very similar to that of omeprazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]-1*H*-benzimidazole [6], which has been put on the market as an antiulcer agent [7].

It is well known that treatment of α-haloketone with thiols gives α-alkylthio or α-arylthio ketones [8]. Thus, we prepared 1,8-dihydrocycloheptapyrazol-8-ones bearing various heteroarylthiomethyl group at the 3-position by using 3-(bromoacetyl)tropolone (**2**) [9]. These structures are similar to those of cycloheptimidazoles. Of them, it was found that [(2-benzimidazolyl)thio]methyl-substituted 1,8-dihydrocycloheptapyrazol-8-one have antiulcer H^+/K^+-ATPase activity [10]. In order to enhance biological activity, we studied introduction of a substituent into the benzimidazole ring. In this paper, these synthetic results will be described.

A mixture of 3-(bromoacetyl)tropolone (**2**) and 2-mercaptobenzimidazole (**3a**) in absolute ethanol was heated under reflux for 30 minutes to afford 3-[[(2-benzimidazolyl)thio]acetyl]tropolone hydrobromide (**4a**) in 75% yield. 2-Mercaptobenzimidazoles **3b-e** also reacted with α-bromo compound **2** to give the corresponding 3-[[(2-benzimidazolyl)thio]acetyl]tropolone hydrobromide **4b-e**. Heating a methanolic solution of these compounds **4a-e** and methylhydrazine for 2 hours gave 5'-substituted 3-[[(2-benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptimidazol-8-ones **5a-e** and 1-methyl-3-[(1-methylhydrazino)methyl]-1,8-dihydrocycloheptimidazol-8-one (**6**) in 31-58% and 18-35% yield, respectively. The former compounds **5a-e** would be yielded from tautomeric β-dike-

Scheme 1



to form of compound **4a-e** with methylhydrazine. It is thought that hydrazino-substituted compound **6** was produced from the reaction of compounds **5a-e** with methylhydrazine. Thus, when the reaction of compound **5a** with methylhydrazine was tried, the compound **6** was obtained.

EXPERIMENTAL

Measurements.

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer. The ^{1}H nmr spectra were recorded with a JEOL JNM-PMX60SI spectrometer (60 MHz). The mass spectra were obtained with a JEOL JMS-01-SG2 apparatus.

Materials.

2-Mercaptobenzimidazole (**3a**) was purchased from Tokyo Kasei Kogyo Co. Ltd. and 5-methyl- and 5-nitro-2-mercaptobenzimidazole **3b,e** were purchased from Aldrich Chemical Co. Ltd. 5-Methoxy-2-mercaptobenzimidazole (**3c**) [mp 263° (lit [11] 263-264°) and 5-chloro-2-mercaptobenzimidazole (**3d**) [mp 298-300° (lit [11] 301-303°] were prepared according to the literature [12].

Reactions of 3-(Bromoacetyl)tropolone (**2**) with 2-Mercaptobenzimidazoles **3a-e**.

A solution of **2** (2.53 g, 10 mmoles) and 2-mercaptobenzimidazole (10 mmoles) in absolute ethanol (80 ml) was refluxed for 30 minutes. After cooling, a precipitate was collected and recrystallized to give 3-[[(2-benzimidazolyl)thio]acetyl]-tropolone hydrobromides **4a-e**.

3-[[(2-Benzimidazolyl)thio]acetyl]tropolone Hydrobromide (**4a**).

This compound was obtained in a yield of 2.94 g (75%) as yellow prisms (from ethanol), mp 184-185°; ir (potassium bromide): ν max 3420 (OH), 1700 ($COCH_2$), 1620 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 5.06 (2H, s, CH_2), 7.15-7.9 (10H, m).

Anal. Calcd. for $C_{16}H_{12}N_2O_3S$•HBr: C, 48.86; H, 3.33; N, 7.13. Found: C, 48.89; H, 3.35; N, 7.13.

3-[[(5-Methyl-2-benzimidazolyl)thio]acetyl]tropolone Hydrobromide (**4b**).

This compound was obtained in a yield of 3.50 g (86%) as pale yellow prisms (from ethanol), mp 189-191°; ir (potassium bromide): ν max 3420 (OH), 1720 ($COCH_2$), 1620 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.47 (3H, s, CH_3), 5.09 (2H, s, CH_2), 6.95-7.9 (9H, m); ms: m/z 327 [(M+1) as $C_{17}H_{14}N_2O_3S$].

Anal. Calcd. for $C_{17}H_{14}N_2O_3S$•HBr: C, 50.13; H, 3.71; N, 6.88. Found: C, 50.14; H, 3.70; N, 6.71.

3-[[(5-Methoxyl-2-benzimidazolyl)thio]acetyl]tropolone Hydrobromide (**4c**).

This compound was obtained in a yield of 3.60 g (85%) as pale yellow prisms (from ethanol), mp 170-171°; ir (potassium bromide): ν max 3420 (OH), 1710 ($COCH_2$), 1630 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.87 (3H, s, OCH_3), 5.10 (2H, s, CH_2), 6.95-7.95 (9H, m); ms: m/z 343 [(M+1) as $C_{17}H_{14}N_2O_4S$].

Anal. Calcd. for $C_{17}H_{14}N_2O_4S$•HBr: C, 48.24; H, 3.57; N, 6.62. Found: C, 48.40; H, 3.51; N, 6.55.

3-[[(5-Chloro-2-benzimidazolyl)thio]acetyl]tropolone Hydrobromide (**4d**).

This compound was obtained in a yield of 2.99 g (70%) as pale yellow prisms (from ethanol), mp 178-179°; ir (potassium bromide): ν max 3430 (OH), 1705 ($COCH_2$), 1610 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 4.87 (2H, s, CH_2), 7.1-7.9 (9H, m); ms: m/z 347 [(M+1) as $C_{16}H_{11}ClN_2O_3S$].

Anal. Calcd. for $C_{16}H_{11}ClN_2O_3S$•HBr: C, 44.93; H, 2.83; N, 6.55. Found: C, 45.12; H, 2.76; N, 6.49.

3-[[(5-Nitro-2-benzimidazolyl)thio]acetyl]tropolone Hydrobromide (**4e**).

This compound was obtained in a yield of 3.37 g (70%) as yellow needles (from ethanol), mp 135-136°; ir (potassium bromide): ν max 3420 (OH), 1705 ($COCH_2$), 1605 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 4.83 (2H, s, CH_2), 7.1-7.9 (6H, m), 7.59 (1H, d, J = 10 Hz, 7'-H), 8.09 (1H, dd, J = 10, 2.5 Hz, 6'-H), 8.30 (1H, d, J = 2.5 Hz, 4'-H); ms m/z 358 [(M+1) as $C_{16}H_{11}N_3O_5S$].

Anal. Calcd. for $C_{16}H_{11}N_3O_5S$•HBr: C, 43.85; H, 2.76; N, 9.59. Found: C, 44.08; H, 2.86; N, 9.74.

Reactions of the Compounds **4a-e** with Methylhydrazine.

A mixture of compound **4a-e** (2.0 mmoles) and methylhydrazine (138 mg, 3.0 mmoles) in methanol (20 ml) was heated for 2 hours under refluxing. After removal of the solvent the residue was chromatographed on two Wakogel B-10 plates (30 x 30 cm) with ethyl acetate to give 3-[[(2-benzimidazolyl)-thio]methyl-1-methyl-1,8-dihydrocycloheptapyrazol-8-ones **5a-e** and 1-methyl-3-[(1-methylhydrazino)methyl]-1,8-dihydrocycloheptapyrazol-8-one (**6**).

3-[[(2-Benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptapyrazol-8-one (**5a**).

This compound was obtained in a yield of 290 mg (45%), mp 106-107° (lit [9], mp 107-108°).

1-Methyl-3-[[(5-methyl-2-benzimidazolyl)thio]methyl]-1,8-dihydrocycloheptapyrazol-8-one (**5b**).

This compound was obtained in a yield of 310 mg (46%) as orange prisms (from cyclohexane), mp 97-98°; ir (potassium bromide): ν max 1630 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.42 (3H, s, 5'-CH_3), 4.20 (3H, s, 1-CH_3), 4.72 (2H, s, CH_2), 6.3-7.55 (8H, m).

Anal. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.66. Found: C, 63.98; H, 5.01; N, 16.57.

3-[[(5-Methoxy-2-benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptapyrazol-8-one (**5c**).

This compound was obtained in a yield of 218 mg (31%) as orange prisms (from benzene-carbon tetrachloride), mp 83-84°; ir (potassium bromide): ν max 1630 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.80 (3H, s, OCH_3), 4.27 (3H, s, CH_3), 4.72 (2H, s, CH_2), 6.6-7.9 (8H, m).

Anal. Calcd. for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.22; H, 4.81; N, 15.93.

3-[[(5-Chloro-2-benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptapyrazol-8-one (**5d**).

This compound was obtained in a yield of 278 mg (39%) as pale orange prisms (from benzene-carbon tetrachloride), mp 97-99°; ir (potassium bromide): ν max 1630 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 4.30 (3H, s, CH_3), 4.90 (2H, s, CH_2), 6.65-7.9 (8H, m).

Anal. Calcd. for $C_{17}H_{13}ClN_4OS$: C, 57.22; H, 3.67; N, 15.70. Found: C, 57.50; H, 3.64; N, 15.51.

3-[[(5-Nitro-2-benzimidazolyl)thio]methyl]-1-methyl-1,8-dihydrocycloheptapyrazol-8-one (**5e**).

This compound was obtained in a yield of 426 mg (58%) as orange prisms (from benzene), mp 124-125°; ir (potassium bromide): ν max 1630 cm^{-1} (C=O); ^1H nmr (deuteriodimethyl sulfoxide): δ 4.30 (3H, s, CH_3), 4.97 (2H, s, CH_2), 6.65-7.95 (5H, m), 7.67 (1H, d, J = 9.5 Hz, 7'-H), 8.18 (1H, dd, J = 9.5, 2.5 Hz, 6'-H), 8.39 (1H, d, J = 2.5 Hz, 4'-H).

Anal. Calcd. for $C_{17}H_{13}N_5O_3S$: C, 55.58; H, 3.57; N, 19.07. Found: C, 55.62; H, 3.49; N, 19.36.

1-Methyl-3-[(1-methylhydrazino)methyl]-1,8-dihydrocycloheptapyrazol-8-one (**6**).

This compound was isolated in a yield of 130 mg (30%), 139 mg (32%), 153 mg (35%), 140 mg (30%), and 79 mg (18%) from the reaction with **3a**, **3b**, **3c**, **3d** and **3e**, respectively, as orange prisms (from benzene-cyclohexane), mp 59-61°; ir (potassium bromide): ν max 1630 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.55 (3H, s, N-CH_3), 3.54 (2H, br, NH_2), 3.92 (2H, s, CH_2), 4.42 (3H, s, 1-CH_3), 5.6-7.8 (4H, m).

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.48; H, 6.59; N, 25.77.

Reaction of Compound **5a** with Methylhydrazine.

A solution of **5a** (161 mg, 0.5 mmole) and methylhydrazine (46 mg, 1.0 mmole) in methanol (5 ml) was refluxed for 2 hours. The evaporation residue was recrystallized from benzene to give compound **6** in a yield of 75 mg (69%).

REFERENCES AND NOTES

[1] K. Imafuku, *Kumamoto Daigaku Kyoyobu Kiyo, Shizen Kagaku Hen*, **25**, 47 (1990).

[2] K. Imafuku, Trends in Heterocyclic Chemistry, A. Kumar, ed, Research Trends, Vol **1**, Trivandrum, India, 1990, pp 137-153.

[3] A. Yamane, M. Nagayoshi, K. Imafuku and H. Matsumura, *Bull. Chem. Soc. Japan*, **52**, 1972 (1979).

[4] C. -Y. Qian, Z. -T. Jin, B. -Z. Yin and K. Imafuku, *J. Heterocyclic Chem.*, **26**, 601 (1989).

[5] K. Kawai, N. Tsuchiya, M. Yokota, M. Sonegawa, R. Hasegawa, H. Sekiguchi, T. Shirai and T. Tomiyama, the 109th National Meeting of the Pharmaceutical Society of Japan, Nagoya, 1989, No. 4B3-2.

[6] S. Gustavsson, L. Loof, H. O. Adami and O. Nyberg, *Lancet, (II)*, 124 (1983).

[7] *E.g.* [a] Omeprazon (Yoshitomi Pharmaceutical Co. Ltd., Japan); [b] Omepral (Fujisawa Pharmaceutical Co. Ltd., Japan).

[8] R. Verhe and N. de Kempe, The Chemistry of Halides, Pseudohalides and Azides, Supplement, D. S. Patai and A. Rappoport, eds, John Wiley & Sons, Chichester, 1983, p 813.

[9] I. Kishi, K. Imafuku, K. Ogawa and Y. Matsushita, *Heterocycles*, **31**, 677 (1990).

[10] K. Imafuku, unpublished.

[11] M. Uchida, S. Morita, M. Chihiro, T. Kanbe, Y. Yamasaki, Y. Yabuuchi and K. Nakagawa, *Chem. Pharm. Bull.*, **37**, 1517 (1989).

[12] J. A. Van Allan and B. D. Deacon, Oraganic Syntheses, Coll Vol **IV**, N. Rabjohn, ed, John Wiley & Sons, Inc, 1963, p 569.