Synthesis and Biological Activities of 1-[2-(Dimethylamino)ethyl]- and 1-[3-(Dimethylamino)propyl]-substituted 3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones and Related Compounds

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3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones (2a—c), prepared from 3-acetyltropolones (1a—c), were treated with diazomethane, methyl iodide, dimethyl sulfate, and diethyl sulfate to give 1- and 2-alkylated compounds. The 1,8-dihydrocycloheptapyrazol-8-one (2a) also reacted with 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 3-(dimethylamino)propyl, and 2,3-dihydroxypropyl chloride to afford the corresponding 1-substituted products. A preliminary study was made of the biological activities of some of the obtained compounds.

Keywords synthesis; biological activity; 3-acetyltropolone; 1,8-dihydrocycloheptapyrazol-8-one; *N*-alkylation

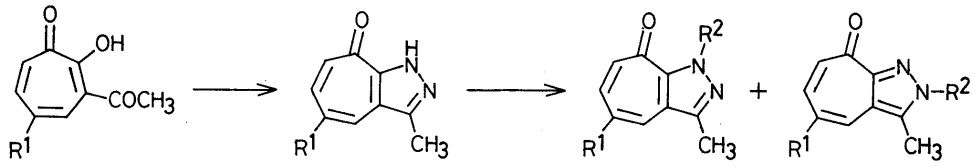
Many heterocyclic compounds are biologically active. Over a period of ten years, one of the authors (K.I.) has synthesized a variety of heterocycle-fused troponoid compounds from 3-acetyltropolone by utilizing positional features of its acetyl group.[2)] This communication deals with syntheses of some 1,8-dihydrocycloheptapyrazol-8-one derivatives for biological evaluation, and presents the results of preliminary screening for the biological activities.

Results and Discussion

Synthesis Previously, we found that 3-acetyltropolone (**1a**) reacted with hydrazine to afford 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**2a**) in a high yield.[3)] In a similar manner, the reactions of 3-acetyl-5-methyl- and -5-isopropyltropolones (**1b, c**)[4)] with hydrazine gave the corresponding 5-alkyl-substituted 3-methyl-1,8-dihydrocycloheptapyrazol-8-ones (**2b, c**) in 93 and 84% yields. These 1,8-dihydrocycloheptapyrazol-8-ones (**2a—c**) were methylated with diazomethane or methyl iodide to give two isomeric compounds, 5-alkyl-substituted 1,3-dimethyl-1,8-dihydrocycloheptapyrazol-8-ones (**3a**,[5)] **b, c**) as major products and 2,3-dimethyl-2,8-dihydrocycloheptapyrazol-8-ones (**4a**,[5)] **b, c**) as minor ones. Compounds **2a—c** reacted with diethyl sulfate to give 5-alkyl-substituted 1-ethyl-3-methyl-1,8-dihydrocycloheptapyrazol-8-ones (**3d**,[6)] **e, f**) and 2-ethyl-3-methyl-2,8-dihydrocycloheptapyrazol-8-ones (**4d**,[6)] **e, f**).

In order to examine the structure–activity profile, a nitrogen- or oxygen-containing side-chain was introduced into 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**2a**) at the 1-position. A solution of the 1,8-dihydrocycloheptapyrazol-8-one (**2a**) and two molar equivalents of 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, or 3-(dimethylamino)propyl chloride in acetone was refluxed for 6—8 h in the presence of potassium carbonate to afford the corresponding 1-[2-(dimethylamino)ethyl]-, 1-[2-(diethylamino)ethyl]-, or 1-[3-(dimethylamino)propyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-ones (**3g—i**) as an orange yellow oil in 88, 100, or 50% yield, respectively. However, isomeric 2-alkyl-substituted products were not isolated from these reactions.

On the other hand, **2a** reacted with 2,3-dihydroxypropyl chloride in the presence of potassium carbonate to give two isomeric products, 1-(2,3-dihydroxypropyl)-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**3j**) and 2-(2,3-dihydroxypropyl)-3-methyl-2,8-dihydrocycloheptapyrazol-8-one (**4j**),



1a—c 2a—c 3a—j 4a—f,j

a : R = H
b : R = CH_3
c : R = $CH(CH_3)_2$

a : R = H
b : R = CH_3
c : R = $CH(CH_3)_2$

a : R^1 = H, R^2 = CH_3
b : R^1 = R^2 = CH_3
c : R^1 = $CH(CH_3)_2$, R^2 = CH_3
d : R^1 = H, R^2 = CH_2CH_3
e : R^1 = CH_3, R^2 = CH_2CH_3
f : R^1 = $CH(CH_3)_2$, R^2 = CH_2CH_3
g : R^1 = H, R^2 = $CH_2CH_2N(CH_3)_2$
h : R^1 = H, R^2 = $CH_2CH_2N(CH_2CH_3)_2$
i : R^1 = H, R^2 = $CH_2CH_2CH_2N(CH_3)_2$
j : R^1 = H, R^2 = $CH_2CH(OH)CH_2OH$

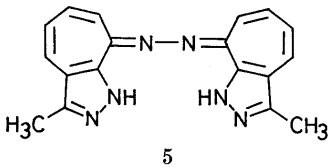


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Chart 1

TABLE I. Properties of Products

Compound	Yield (%)	Appearance	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Found (Calcd)		
						C	H	N
2b	93	Orange needles	Methanol	245—246	$C_{10}H_{10}N_2O$	68.75 (68.95	6.03 5.79	15.98 16.08)
2c	84	Orange needles	Cyclohexane	148—149	$C_{12}H_{14}N_2O$	71.04 (71.26	7.12 6.98	14.13 13.85)
3b	83,[a] 44,[b] 51[c]	Pale yellow prisms	Hexane	87—88	$C_{11}H_{12}N_2O$	70.12 (70.18	6.47 6.43	15.17 14.88)
3c	58,[a] 44,[b] 46[c]	Yellow needles	Hexane	49—50	$C_{13}H_{16}N_2O$	72.26 (72.19	7.48 7.46	13.01 12.95)
3e	35	Yellow needles	Hexane	75—76	$C_{12}H_{14}N_2O$	71.22 (71.26	7.12 6.98	13.65 13.85)
3f	23	Orange prisms	Hexane	62—63	$C_{14}H_{18}N_2O$	72.88 (73.01	8.06 7.88	12.18 12.17)
3g	88	Orange yellow oil			$C_{13}H_{17}N_3O \cdot HCl \cdot 1/2H_2O$	56.43 (56.42	7.04 6.92	15.22 15.18)
3h	100	Orange yellow oil			$C_{15}H_{21}N_3O \cdot HCl \cdot 1/2H_2O$	58.95 (59.11	7.45 7.61	13.67 13.79)
3i	50	Orange oil			$C_{14}H_{19}N_3O \cdot HCl \cdot H_2O$	56.09 (56.23	7.40 7.50	14.02 14.18)
3j	73	Pale yellow crystals	Chloroform–ligroin	199—200.5	$C_{12}H_{14}N_2O_3$	61.70 (61.53	6.17 6.02	11.96 11.96)
4b	14,[a] 17,[b] 41[c]	Pale yellow prisms	Benzene–hexane	163—164	$C_{11}H_{12}N_2O$	69.86 (70.18)	6.51 6.43	14.62 14.88)
4c	38,[a] 45,[b] 32[c]	Yellow needles	Benzene–hexane	162—163	$C_{13}H_{16}N_2O$	72.19 (72.19	7.54 7.46	13.12 12.95)
4e	18	Yellow needles	Benzene–hexane	124—125	$C_{12}H_{14}N_2O$	70.97 (71.26	7.16 6.98	14.11 13.85)
4f	38	Yellow needles	Benzene–hexane	92—93	$C_{14}H_{18}N_2O$	72.96 (73.01	8.13 7.88	12.18 12.17)
4j	14	Pale orange yellow crystals	Chloroform–ligroin	—[d]	$C_{12}H_{14}N_2O_3$	61.79 (61.53	6.03 6.02	12.09 11.96)

a) Reaction with diazomethane. *b*) Reaction with methyl iodide/silver oxide. *c*) Reaction with dimethyl sulfate. *d*) The melting point for this compound was not determined.

in 73 and 14% yields, respectively.

The solubilities in water (>10 mg/ml) of compounds **3g—j** were increased in comparison with those of the parent compounds **2a** and **3a**. Compound **3j** and the hydrochlorides of **3g—i** sublime.

Biological Activities A preliminary study of the biological activities of several compounds was made using general methods. The results are listed in Table III.

The parent compound **2a** has various biological activities, such as inotropic, diuretic, antiedema, *etc.* However, it caused gastric irritation. Compound **3a** bearing the methyl group at the 1-position also exhibited histamine H_2 inhibition and antihistamine activity. However, the azine **5**[3] without the tropone carbonyl oxygen atom lacked these activities. The 2-(dimethylamino)ethyl-substituted compound **3g** exhibited antiallergy and antihistamine activities. The 3-(dimethylamino)propyl-substituted compound **3i** exhibited diuretic activity. On the other hand, compound **3j** having the 2,3-dihydroxypropyl side-chain was ineffective.

In conclusion, these compounds have no remarkable activities and do not appear to be suitable as lead compounds.

Experimental

General Methods Melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. Infrared (IR) spectra were taken on a JASCO A-102 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded with JEOL JNM-PMX60SI, JEOL JNM-FX100, and Varian XL-200 spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a JEOL JMS-01-SG2 spectrometer.

Preparation of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones (2b, c). General Procedure A solution of 5-methyl- or 5-isopropyl-3-acetyltropolone (**1b, c**) (10 mmol) and hydrazine hydrate (750 mg, 15 mmol) in methanol (40 ml) was refluxed for 5 h. After removal of the solvent, the residue was recrystallized to yield 5-alkyl-substituted 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**2b, c**).

Reaction of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones (2b, c) with Diazomethane. General Procedure An excess of diazomethane ethereal solution was added to a solution of a 1,8-dihydrocycloheptapyrazol-8-one (**2b, c**) (1.0 mmol) in chloroform (10 ml). The mixture was allowed to stand overnight. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30×30 cm) with ethyl acetate to give 1-methyl-substituted 1,8-dihydrocycloheptapyrazol-8-one (**3b, c**) and 2-methyl-substituted 2,8-dihydrocycloheptapyrazol-8-one (**4b, c**).

Reaction of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones (2b, c) with Methyl Iodide. General Procedure A solution of a 1,8-dihydrocycloheptapyrazol-8-one (**2b, c**) (1.0 mmol) and methyl iodide (2 ml) in acetone (20 ml) was refluxed for 8 h in the presence of silver oxide (467 mg, 2.0 mmol). The reaction mixture was filtered and the filtrate was diluted with water and extracted with chloroform. The extract was washed twice with water and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed, as described above, to give 1-methyl-substituted 1,8-dihydrocycloheptapyrazol-8-one (**3b, c**) and 2-methyl-substituted 2,8-dihydrocycloheptapyrazol-8-one (**4b, c**).

Reaction of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones (2b, c) with Dimethyl Sulfate. General Procedure A solution of a 1,8-dihydrocycloheptapyrazol-8-one (**2b, c**) (1.0 mmol) and dimethyl sulfate (252 mg, 2.0 mmol) in acetone (20 ml) was refluxed for 24 h in the presence of potassium carbonate (275 mg, 2.0 mmol). The reaction mixture was worked up and chromatographed as described above, to give 1-methyl-substituted 1,8-dihydrocycloheptapyrazol-8-one (**3b, c**) and 2-methyl-substituted

TABLE II. Spectral Data

Compd.	IR ($CHCl_3$) ν (cm^{-1})	NMR Instr.[a]	^{1}H-NMR ($CDCl_3$) δ (J, Hz)	^{13}C-NMR ($CDCl_3$) δ	MS m/z (rel. intensity)
2a	1640 (C=O)	A	2.62 (3H, s, 3-CH_3), 6.87 (1H, dd, 10.7, 8.6, 5-H), 7.19 (1H, d, 12.2, 7-H), 7.45 (1H, ddd, 12.2, 8.6, 0.7, 5-H), 7.59 (1H, d, 10.7, 4-H), 12.89 (1H, br, NH)	11.79 (3-CH_3), 121.9 (3a-C), 123.70 (5-C), 130.27 (4-C), 134.27 (7-C), 138.48 (6-C), 143.91 (8a-C), 150.24 (3-C), 176.78 (8-C)	160 (M^+, 100), 132 (55), 131 (89)
2b	1643 (C=O)	A	2.45 (3H, d, 1.0, 5-CH_3), 2.59 (3H, s, 3-CH_3), 7.07 (1H, d, 12.8, 7-H), 7.35 (1H, dd, 12.8, 1.8, 6-H), 7.38—7.42 (1H, m, 4-H)	11.86 (3-CH_3), 26.32 (5-CH_3), 121.22 (3a-C), 127.97 (4-C), 133.36 (5-C), 133.61 (7-C), 142.12 (6-C), 143.08 (8a-C), 149.77 (3-C), 176.18 (8-C)	174 (M^+, 100), 146 (50), 145 (75)
2c	1640 (C=O)	A	1.30 [6H, d, 6.9, 5-C(CH_3)$_2$], 2.62 (3H, s, 3-CH_3), 2.92 (1H, septet, 6.9, 5-CH), 7.18 (1H, d, 13.0, 7-H), 7.40 (1H, dd, 13.0, 1.8, 6-H), 7.41 (1H, d, 1.8, 4-H), 12.6 (1H, br, NH)	11.90 (3-CH_3), 23.53 [5-C(CH_3)], 38.01 (5-CH), 121.19 (3a-C), 125.78 (4-C), 134.25 (7-C), 139.97 (6-C), 142.97 (8a-C), 143.81 (5-C), 149.93 (3-C), 176.18 (8-C)	202 (M^+, 94), 188 (14), 187 (100)
3a	1643 (C=O)	A	2.51 (3H, s, 3-CH_3), 4.41 (3H, s, 1-CH_3), 6.67 (1H, ddd, 10.8, 8.3, 0.8, 5-H), 6.95 (1H, dd, 12.5, 0.8, 7-H), 7.19 (1H, ddd, 12.5, 8.3, 1.0, 6-H), 7.38 (1H, dd, 10.8, 1.0, 4-H)	11.55 (3-CH_3), 40.60 (1-CH_3), 122.51 (3a-C), 122.72 (5-C), 129.55 (4-C), 136.01 (7-C), 136.68 (6-C), 141.25 (8a-C), 147.56 (3-C), 178.13 (8-C)	174 (M^+, 100), 173 (87), 146 (15), 145 (33)
3b	1642 (C=O)	A	2.36 (3H, d, 1.1, 5-CH_3), 2.51 (3H, s, 3-CH_3), 4.39 (3H, s, 1-CH_3), 6.88 (1H, d, 12.8, 7-H), 7.10 (1H, dd, 12.8, 0.8, 6-H), 7.18—7.24 (1H, m, 4-H)	11.60 (3-CH_3), 25.73 (5-CH_3), 40.44 (1-CH_3), 122.66 (3a-C), 127.26 (4-C), 132.02 (5-C), 135.25 (7-C), 140.35 (6-C), 140.49 (8a-C), 146.67 (3-C), 177.63 (8-C)	188 (M^+, 100), 187 (93), 160 (17), 159 (36)
3c	1639 (C=O)	C	1.23 [6H, d, 7.0, 5-C(CH_3)$_2$], 2.42 (3H, s, 3-CH_3), 2.81 (1H, septet, 7.0, 5-CH), 4.30 (3H, s, 1-CH_3), 6.6—7.2 (3H, m)		
3d	1645 (C=O)	C	1.44 [3H, t, 7.0, 1-C(CH_3)], 2.45 (3H, s, 3-CH_3), 4.81 (2H, q, 7.0, 1-CH_2), 6.4—7.5 (4H, m)		
3e	1640 (C=O)	C	1.43 [3H, t, 7.0, 1-C(CH_3)], 2.35 (3H, s, 5-CH_3), 2.48 (3H, s, 3-CH_3), 4.85 (2H, q, 7.0 1-CH_2), 6.7—7.4 (3H, m)		
3f	1643 (C=O)	C	1.27 [6H, d, 7.0, 5-C(CH_3)$_2$], 1.43 [3H, t, 7.0, 1-C(CH_3)], 2.53 (3H, s, 3-CH_3), 2.83 (1H, septet, 7.0, 5-CH), 4.90 (2H, q, 7.0, 1-CH_2), 6.9—7.4 (3H, m)		
3g	1630 (C=O)	B	2.34 [6H, s, N(CH_3)$_2$], 2.52 (3H, s, 3-CH_3), 2.79 (2H, t, 7.1, 2′-CH_2), 4.96 (2H, t, 7.1, 1′-CH_2), 6.66 (1H, ddd, 10.7, 7.9, 1.2, 5-H), 6.92 (1H, dd, 12.0, 1.2, 7-H), 7.19 (1H, ddd, 12.0, 7.9, 1.2, 6-H), 7.37 (1H, dd, 10.7, 1.2, 4-H)	11.66 (3-CH_3), 45.63 (N-CH_3), 50.17 (2′-C), 59.94 (1′-C), 122.80 (3a-C, 5-C), 129.50 (4-C), 135.93 (7-C), 136.46 (6-C), 140.87 (8a-C), 147.92 (3-C), 177.61 (8-C)	231 (M^+, 21), 187 (5), 161 (13), 71 (100)
3h	1630 (C=O)	B	1.04 [6H, t, 7.1, NC(CH_3)$_2$], 2.52 (3H, s, 3-CH_3), 2.62 [4H, t, 7.1, N(CH_2)$_2$], 2.88 (2H, t, 7.4, 2′-CH_2), 4.90 (2H, t, 7.4, 1′-CH_2), 6.64 (1H, ddd, 10.7, 7.9, 1.2, 5-H), 6.92 (1H, dd, 12.2, 1.2, 7-H), 7.18 (1H, ddd, 12.2, 7.9, 1.2, 6-H), 7.36 (1H, dd, 10.7, 1.2, 4-H)	11.61 (3-CH_3), 12.23 (NC-CH_3), 47.48 (N-CH_2), 50.34 (2′-C), 53.65 (1′-C), 122.68 (3a-C, 5-C), 129.44 (4-C), 135.84 (7-C), 136.40 (6-C), 140.96 (8a-C), 147.87 (3-C), 177.61 (8-C)	259 (M^+, 27), 187 (25), 161 (9), 99 (97), 86 (100)
3i	1626 (C=O)	B	1.9—2.15 (2H, m, 2′-CH_2), 2.24 [6H, s, N(CH_3)$_2$], 2.37 (2H, t, 7.1, 3′-CH_2), 2.52 (3H, s, 3-CH_3), 4.86 (2H, t, 7.1, 1′-CH_2), 6.59 (1H, ddd, 10.7, 7.9, 1.2, 5-H), 6.91 (1H, dd, 12.2, 1.2, 7-H), 7.17 (1H, ddd, 12.2, 7.9, 1.2, 6-H), 7.36 (1H, dd, 10.7, 1.2, 4-H)	11.61 (3-CH_3), 29.54 (2′-C), 45.37 (N-CH_2), 51.04 (3′-C), 56.66 (1′-C), 122.69 (3a-C, 5-C), 129.41 (4-C), 135.98 (7-C), 136.37 (6-C), 140.61 (8a-C), 147.66 (3-C), 177.53 (8-C)	246 (M+1, 10), 201 (10), 187 (12), 174 (25), 173 (69), 161 (54)
3j	3400 (OH) 3280 (OH) 1630 (C=O)	B	1.83 (1H, br, 3′-OH), 2.55 (3H, s, 3-CH_3), 3.05 (1H, br, 2′-OH), 3.59 (2H, m, 3′-CH_2), 4.05—4.15 (1H, m, 2′-CH), 5.00 (2H, d, 5.1, 1′-CH_2), 6.79 (1H, ddd, 10.5, 8.1, 1.2, 5-H), 7.02 (1H, dd, 12.2, 1.2, 7-H), 7.31 (1H, ddd, 12.2, 8.1, 1.2, 6-H), 7.47 (1H, dd, 10.5, 1.2, 4-H)	11.64 (3-CH_3), 53.97 (3′-C), 63.74 (1′-C), 71.87 (2′-C), 123.29 (3a-C), 123.78 (5-C), 129.93 (4-C), 135.61 (7-C), 137.63 (6-C), 141.65 (8a-C), 148.68 (3-C), 178.35 (8-C)	234 (M^+, 15), 216 (43), 203 (78), 174 (64), 173 (100), 161 (83)
4a	1650 (C=O)	A	2.55 (3H, s, 3-CH_3), 4.07 (3H, s, 2-CH_3), 6.55 (1H, ddd, 10.9, 8.3, 0.7, 5-H), 6.92 (1H, dd, 12.6, 0.7, 7-H), 7.16 (1H, ddd, 12.6, 8.3, 0.9, 6-H), 7.25 (1H, dd, 10.9, 0.9, 4-H)	9.84 (3-CH_3), 37.88 (2-CH_3), 120.44 (3a-C), 121.91 (5-C), 128.82 (4-C), 134.21 (7-C), 136.73 (6-C), 140.30 (8a-C), 149.51 (3-C), 181.80 (8-C)	174 (M^+, 100), 146 (99), 145 (75), 103 (65)
4b	1648 (C=O)	A	2.33 (3H, d, 1.1, 5-CH_3), 2.53 (3H, s, 3-CH_3), 4.06 (3H, s, 2-CH_3), 6.87 (1H, d, 13.2, 7-H), 7.05—7.50 (1H, m, 4-H), 7.06 (1H, dd, 13.2, 1.7, 6-H)	9.74 (3-CH_3), 25.98 (5-CH_3), 37.80 (2-CH_3), 120.54 (3a-C), 126.09 (4-C), 130.75 (5-C), 133.49 (7-C), 139.06 (8a-C), 140.56 (6-C), 148.99 (3-C), 181.49 (8-C)	188 (M^+, 100), 160 (92), 159 (74), 145 (29)
4c	1649 (C=O)	C	1.23 [6H, d, 7.0, 5-C(CH_3)$_2$], 2.52 (3H, s, 3-CH_3), 2.86 (1H, septet, 7.0, 5-CH), 4.03 (3H, s, 2-CH_3), 6.7—7.4 (3H, m)		

TABLE II. (continued)

Compd.	IR ($CHCl_3$) ν (cm^{-1})	NMR Instr.[a]	^{1}H-NMR ($CDCl_3$) δ (J, Hz)	^{13}C-NMR ($CDCl_3$) δ	MS m/z (rel. intensity)
4d	1640 (C=O)	C	1.50 [3H, t, 7.0, 2-C(CH_3)], 2.52 (3H, s, 3-CH_3), 4.35 (2H, q, 7.0, 2-CH_2), 6.3—7.4 (4H, m)		
4e	1644 (C=O)	C	1.50 [3H, t, 7.0, 2-C(CH_3)], 2.32 (3H, s, 5-CH_3), 2.53 (3H, s, 3-CH_3), 4.40 (2H, q, 7.0, 2-CH_2), 6.7—7.4 (3H, m)		
4f	1643 (C=O)	C	1.27 [6H, d, 7.0, 5-C(CH_3)$_2$], 1.52 [3H, t, 7.0, 2-C(CH_3)], 2.58 (3H, s, 3-CH_3), 2.84 (1H, septet, 7.0, 5-CH), 4.45 (2H, q, 7.0, 2-CH_2), 6.8—7.5 (3H, m)		
4j	3350 (OH) 1625 (C=O)	B	[CD_3OD] 3.58 (2H, d, 4.9, 3′-CH_2), 4.1—4.3 (1H, m, 2′-CH), 4.42 (2H, d, 5.0, 1′-CH_2), 6.66 (1H, dd, 11.0, 8.6, 5-H), 6.83 (1H, d, 12.6, 7-H), 7.31 (1H, ddd, 12.6, 8.6, 1.0, 6-H), 7.52 (1H, dd, 11.0, 1.0, 4-H)	[CD_3OD] 10.00 (3-CH_3), 54.47 (3′-C), 64.65 (1′-C), 72.40 (2′-C), 122.07 (3a-C), 123.12 (5-C), 131.54 (4-C), 133.59 (7-C), 139.91 (6-C), 144.71 (8a-C), 150.22 (3-C), 183.52 (8-C)	234 (M^+, 53), 203 (27), 174 (100), 173 (60), 161 (71)

a) ^{1}H- and ^{13}C-NMR spectrometers: A, Varian XL-200; B, JEOL JNM-FX100; C, JEOL JNM-PMX60SI.

TABLE III. Biological Activities

Activity	2a	3a	3g·HCl	3i·HCl	3j	5
(+)-Inotropic activity	+	+	−	−	−	−
Diuretic activity	+	+	−	+	−	−
Antiallergy activity	−	−	+	−	−	−
Anti-inflammatory activity	+	+	−	−	−	−
Bronchodilation	+	+	−	−	−	−
Histamine H_2 inhibition	−	+	−	−	−	−
Gastric irritation	+	+	NT	NT	NT	NT
Antihistamine activity	−	+	+	NT	NT	NT
Anticholinergic activity	+	+	NT	NT	NT	NT

NT, not tested.

2,8-dihydrocycloheptapyrazol-8-one (**4b**, **c**).

Reaction of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-ones (2b, c) with Diethyl Sulfate. General Procedure A solution of a 1,8-dihydrocycloheptapyrazol-8-one (**2b**, **c**) (1.0 mmol) and diethyl sulfate (308 mg, 2.0 mmol) in acetone (20 ml) was refluxed for 24 h in the presence of potassium carbonate (276 mg, 2.0 mmol). The reaction mixture was worked up and chromatographed as described above, the give 1-ethyl-substituted 1,8-dihydrocycloheptapyrazol-8-one (**3e**, **f**) and 2-ethyl-substituted 2,8-dihydrocycloheptapyrazol-8-one (**4e**, **f**).

Preparation of 1-[2-(Dimethylamino)ethyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (3g) A solution of 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**2a**) (1.30 g, 8.12 mmol) and 2-(dimethylamino)ethyl chloride hydrochloride (1.29 g, 8.93 mmol) in acetone (70 ml) was refluxed for 7 h in the presence of potassium carbonate (2.47 g, 17.9 mmol). The reaction mixture was filtered. The residue from evaporation of the filtrate was purified by column chromatography (silica gel, 75 g) with chloroform–methanol (15:1) to give 1-[2-(dimethylamino)ethyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**3g**) as an orange yellow oil (1.68 g, 88%).

Hydrochloride: Pale yellow crystals, mp 215—217 °C.

Preparation of 1-[2-(Diethylamino)ethyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (3h) A solution of the 1,8-dihydrocycloheptapyrazol-8-one (**2a**) (220 mg, 1.37 mmol) and 2-(diethylamino)ethyl chloride hydrochloride (260 mg, 1.51 mmol) in acetone (50 ml) was refluxed for 6 h in the presence of potassium carbonate (418 mg, 3.02 mmol). The reaction mixture was worked up as described above, and chromatographed on a column (silica gel, 30 g) with chloroform–methanol (20:1) to give 1-[2-(diethylamino)ethyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**3h**) as an orange yellow oil (358 mg, 100%).

Hydrochloride: Pale yellow crystals, mp 197—198 °C.

Preparation of 1-[3-(Dimethylamino)propyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (3i) A solution of the 1,8-dihydrocycloheptapyrazol-8-one (**2a**) (1.50 g, 9.36 mmol) and 3-(dimethylamino)propyl chloride hydrochloride (1.78 g, 11.2 mmol) in acetone (150 ml) was refluxed for 8 h in the the presence of potassium carbonate (3.10 g, 22.4 mmol). The reaction mixture was worked up as described above, and chromatographed on a column (silica gel, 75 g) with chloroform–methanol (12:1) to give 1-[3-(dimethylamino)propyl]-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**3i**) as an orange oil (1.15 g, 50%).

Hydrochloride: Pale yellow crystals, mp 202—204 °C.

Reaction of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-one (2a) with 2,3-Dihydroxypropyl Chloride A solution of the 1,8-dihydrocycloheptapyrazol-8-one (**2a**) (1.0 g, 6.24 mmol) and 2,3-dihydroxypropyl chloride (1.66 g, 15.0 mmol) in acetone (200 ml) was refluxed for 24 h in the presence of potassium carbonate (1.92 g, 15.0 mmol). The reaction mixture was worked up as described above, and chromatographed on a column (silica gel, 75 g) with chloroform–methanol (15:1). The first fraction gave 1-(2,3-dihydroxypropyl)-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**3j**) as pale yellow crystals (1.07 g, 73%). The second one gave 2-(2,3-dihydroxypropyl)-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**4j**) as pale yellow orange crystals (0.21 g 14%).

Screening of Biological Activities The screening was performed in Panlabs, Inc., Taiwan, using general methods.

References and Notes

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