

Synthesis of 3-(4-Thiazolyl)tropolones

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3-Acetyltropolone was brominated with phenyltrimethylammonium tribromide to afford 3-(2-bromoacetyl)tropolone (**2**), whose reactions with thiourea, thioformamide, and ammonium dithiocarbamate gave respectively 3-(2-amino-4-thiazolyl)-, 3-(4-thiazolyl)-, and 3-(2-mercapto-4-thiazolyl)tropolone. In a similar manner, compound **2** was treated with six 1-substituted 2-thioureas and three thioamides to give the corresponding 3-(4-thiazolyl)tropolone derivatives.

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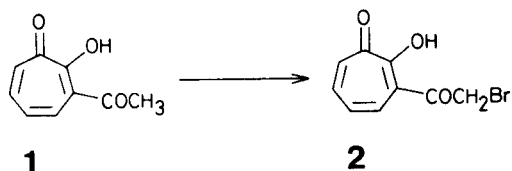
In the pharmacology, 2-aminothiazoles are one of the most important materials as precursors to synthetic drugs, such as sulphathiazole (antibiotic), thiabedazol (anthelmintic), etc. The 2-aminothiazoles are prepared by Hantzsch reaction, which is the reactions of α -haloketones with thioureas [1,2]. As an extension of 3-acetyltropolone chemistry [3], now we wish to report the preparation of 3-(2-bromoacetyl)tropolone as new synthon and the synthesis of 3-(4-thiazolyl)tropolones by its reactions with thioureas, thioamides, and ammonium dithiocarbamate.

Results and Discussion.

Preparation of 3-(2-Bromoacetyl)tropolone (**2**).

3-(2-Bromoacetyl)tropolone (**2**) is expected to be a very useful compound for the synthesis of a various heterocycle-substituted tropolones. However, its preparation by using bromine is difficult, since the tropolone nucleus is very susceptible to electrophilic substitution [4-7]. For example, 3-acetyltropolone was treated with bromine to afford 5,7-dibromo-3-acetyltropolone [8], while 4-acetyltropolone similarly gave substitution products at the tropolone nucleus as a major product and 7-bromo-4-(2-bromoacetyl)tropolone as a minor product [9]. Then, we carried out bromination by using phenyltrimethylammonium tribromide [10,11], which is a useful reagent for α -bromination of ketones and acetals.

Scheme 1



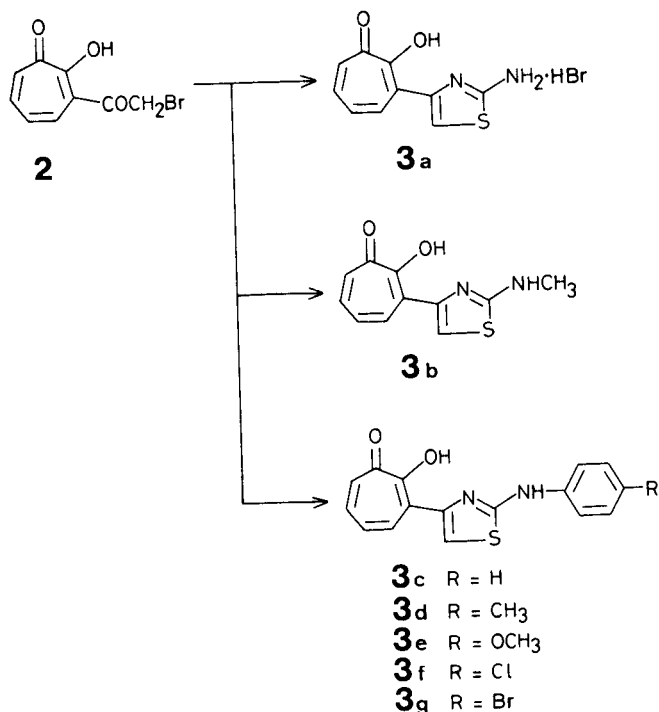
When 3-acetyltropolone (**1**) was treated with phenyltrimethylammonium tribromide in tetrahydrofuran to give 3-(2-bromoacetyl)tropolone (**2**) as greenish yellow scales

(mp 97-98°). Its structure was determined from the spectral data as well as elemental analysis ($C_9H_7BrO_3$). In the ir spectrum, three characteristic absorptions were observed at 3110 (OH), 1725 (bromoacetyl C=O), and 1630 cm^{-1} (tropolone C=O). The 1H nmr spectrum shows a singlet peak at δ 4.81 (2H) for CH_2 and multiplet peaks at δ 7.09-7.78 (4H) for ring protons.

Synthesis of 3-(4-Thiazolyl)tropolones.

Treatment of 3-(2-bromoacetyl)tropolone (**2**) with thiourea in refluxing ethanol for 30 minutes gave 3-(2-amino-4-thiazolyl)tropolone hydrobromide (**3a**) as yellow needles (mp 251-252°) in a 61% yield. Its structure was determin-

Scheme 2



ed on the basis of the spectral data as well as on elemental analysis ($C_{10}H_8N_2O_2S.HBr$). The ir spectrum shows three characteristic absorptions at 3166 (OH), 3122 (NH), and 1623 cm^{-1} (C=O). In the 1H nmr spectrum, two isolated signals are observed at δ 7.55 (s) for H-5' and 8.11 (d, $J = 10.0$ Hz) for H-4, besides multiplet peaks at δ 7.09-7.45 (3H) for H-5,6,7 protons. Compound **3a** also gave positive coloration with iron(III) chloride solution.

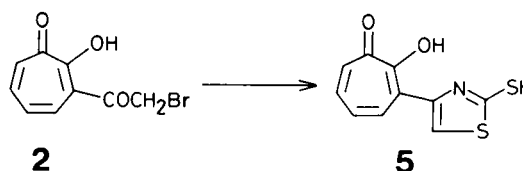
The reaction of **2** with 1-(methyl)thiourea also gave 3-(2-methylamino-4-thiazolyl)tropolone (**3b**) in 65% yield. The methylamino group was confirmed from the 1H nmr spectral data, which shows a singlet peak at δ 2.99 (3H, s) for CH_3 and a broad peak at δ 8.27 (1H) for NH protons. In a similar manner, treatment of **2** with five 1-(aryl)thiourea gave the corresponding 3-(2-aryl-4-thiazolyl)tropolones **3c-g** in 60-87% yields. These structures were also determined from the spectral data and elemental analysis (see: Experimental).

When a mixture of **2** and thioformamide in ethanol was refluxed for 20 minutes, 3-(4-thiazolyl)tropolone (**4a**) was isolated as orange needles in a 79% yield. Its structure was determined from the spectral data and elemental analysis ($C_{10}H_7NO_2S$). In the ir spectrum, two characteristic absorptions were observed at 3147 (OH) and 1610 cm^{-1} (C=O). The 1H nmr spectrum shows two singlet peaks at δ 8.89 (1H) for H-5' and 9.00 (1H) for H-2', a doublet peak at δ 9.21 (1H, $J = 9.9$ Hz) for H-4 and

multiplet peaks at δ 7.16-7.62 (3H) for H-5,6,7 in the tropolone ring.

Compound **2** was also reacted with thioacetamide, (phenyl)thioacetamide, and thiobenzamide afforded the corresponding 3-(2-methyl-4-thiazolyl)- (**4b**), 3-(2-benzyl-4-thiazolyl)- (**4c**), and 3-(2-phenyl-4-thiazolyl)tropolone (**4d**) in 80, 74, 69% yields, respectively. These products were confirmed from their spectral data and elemental analysis (See: Experimental).

Scheme 4



Furthermore, compound **2** was heated with ammonium dithiocarbamate in refluxing ethanol to give 3-(2-mercapto-4-thiazolyl)tropolone (**5**) as yellow needles (mp 216-218°) in a 73% yield. In its 1H nmr spectrum, the SH and H-4 protons were observed at δ 3.40 (s) and 7.84 (d, $J = 9.9$ Hz), respectively, and the signal for H-5' proton was overlapped in those of protons in the tropolone ring. The elemental analysis ($C_{10}H_7NO_2S_2$) also supported the structure.

In summary, it is found that 3-(2-bromoacetyl)tropolone (**2**) is a useful material for the synthesis of heterocycle-substituted troponoid compounds. Some of 3-(4-thiazolyl)tropolone derivatives are readily prepared and expected to be pharmaceutical precursors.

EXPERIMENTAL

Measurements.

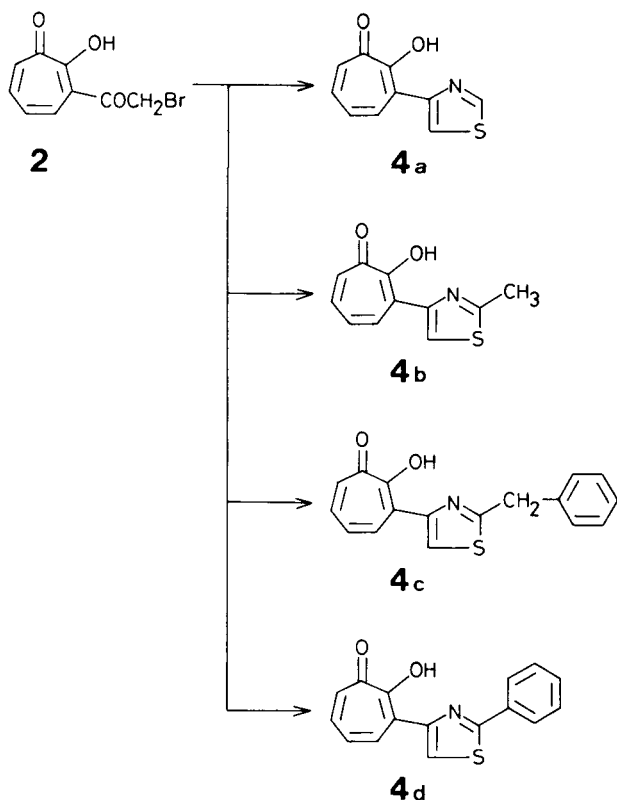
The melting points are uncorrected. The ir and uv spectra were taken on a Perkin-Elmer 1730 spectrophotometer and a Shimadzu UV-250 spectrophotometer, respectively. The 1H nmr spectra were measured with a JEOL JNM-PMX60 spectrometer. Chemical shifts are recorded as δ values relative to tetramethylsilane as the internal standard.

3-(2-Bromoacetyl)tropolone (**2**).

To a solution of 3-acetyltropolone (**1**) (2.05 g, 12.5 mmoles) in tetrahydrofuran (40 ml) was added phenyltrimethylammonium tribromide (4.7 g, 12.5 mmoles) in a period of 15 minutes. A precipitate was deposited from the solution, and the color of the solution changed into pale yellow. After stirring for 20 minutes and standing for 30 minutes, cold water (120 ml) was added to the reaction mixture. The precipitate was collected, washed with water, and recrystallized from petroleum ether to afford 3-(2-bromoacetyl)tropolone (**2**) as greenish yellow scales, yield 1.52 g (50%), mp 97-98°; ir (potassium bromide): ν max 3110 (OH), 1725 (C=O), 1630 cm^{-1} (C=O); uv (methanol): λ max 201 (log ϵ 4.46), 226 (4.40), 292 nm (4.32); 1H nmr (deuteriochloroform): δ 4.81 (2H, s, CH_2), 7.09-7.79 (4H, m).

Anal. Calcd. for $C_9H_7BrO_2$: C, 44.47; H, 2.90. Found: C, 44.69; H, 3.02.

Scheme 3



Reactions of 3-(2-Bromoacetyl)tropolone (2) with Thioureas.

To a solution of 3-(2-bromoacetyl)tropolone (2) (243 mg, 1.0 mmole) in absolute ethanol (30 ml) was added thiourea (1.0 mmole). The mixture was refluxed for 20-30 minutes. After cooling, the precipitate was collected and recrystallized to give 3-(4-thiazolyl)tropolones 3a-g.

3-(2-Amino-4-thiazolyl)tropolone Hydrobromide (3a).

This compound was obtained from the reaction with thiourea as yellow needles (from 95% ethanol) in a yield of 184 mg (61%), mp 251-252°; ir (potassium bromide): ν max 3166 (OH), 3122 (NH), 1623 cm^{-1} (C=O); uv (methanol): λ max 203 (log ϵ 4.43), 246 (4.53), 323 (4.19), 399 nm (4.20); ^1H nmr (deuteriochloroform): δ 7.09-7.45 (3H, m), 7.55 (1H, s, H-5'), 8.11 (1H, d, J = 10.0 Hz, H-4).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}\cdot\text{HBr}$: C, 39.87; H, 3.01; N, 9.33. Found: C, 40.12; H, 2.92; N, 9.33.

3-(2-Methylamino-4-thiazolyl)tropolone (3b).

This compound was obtained from the reaction with 1-(methyl)thiourea as yellow needles (from ethanol) in a yield of 152 mg (65%), mp 212-214°; ir (potassium bromide): ν max 3155 (OH), 3116 (NH), 1623 cm^{-1} (C=O); uv (methanol): λ max 217 (log ϵ 4.43), 261 (4.40), 324 (3.70), 369 nm (3.84); ^1H nmr (deuteriochloroform): δ 2.99 (3H, s, CH_3), 7.09-7.69 (5H, m), 8.27 (1H, br, NH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 56.39; H, 4.30; N, 11.96. Found: C, 56.60; H, 4.05; N, 11.86.

3-(2-Anilino-4-thiazolyl)tropolone (3c).

This compound was obtained from the reaction with 1-(phenyl)thiourea as yellow needles (from 95% ethanol) in a yield of 207 mg (70%), mp 191-192°; ir (potassium bromide): ν max 3488 (NH), 3262 (OH), 1599 cm^{-1} (C=O); uv (methanol): λ max 202 (log ϵ 4.48), 275 (4.51), 337 (4.04), 405 nm (4.09); ^1H nmr (deuteriochloroform): δ 6.90-7.74 (8H, m), 8.31 (1H, s, H-5'), 8.91 (1H, d, J = 10.0 Hz, H-4), 10.15 (1H, br, NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.06; H, 4.12; N, 9.43.

3-[2-(4-Methylanilino)-4-thiazolyl]tropolone (3d).

This compound was obtained from the reaction with 1-(4-methylphenyl)thiourea as yellow needles (from ethanol) in a yield of 230 mg (74%), mp 182-183°; ir (potassium bromide): ν max 3287 (OH), 3174 (NH), 1591 cm^{-1} (C=O); uv (methanol): λ max 202 (log ϵ 4.57), 277 (4.53), 338 (4.06), 407 nm (4.09); ^1H nmr (deuteriochloroform): δ 2.27 (3H, s, CH_3), 7.12-7.63 (7H, m), 8.30 (1H, s, H-5'), 8.91 (1H, d, J = 10.0 Hz, H-4), 10.17 (1H, br, NH).

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 65.78; H, 4.55; N, 9.03. Found: C, 66.03; H, 4.45; N, 9.05.

3-[2-(4-Methoxyanilino)-4-thiazolyl]tropolone (3e).

This compound was obtained from the reaction with 1-(4-methoxyphenyl)thiourea as pale orange yellow needles (from ethanol) in a yield of 196 mg (60%), mp 170-171°; ir (potassium bromide): ν max 3482 (NH), 3353 (OH), 1624 cm^{-1} (C=O); uv (methanol): λ max 202 (log ϵ 4.69), 279 (4.68), 361 (4.20), 408 nm (4.20); ^1H nmr (deuteriochloroform): δ 3.85 (3H, s, OCH_3), 6.84-7.66 (7H, m), 8.26 (1H, s, H-5'), 8.90 (1H, d, J = 10.0 Hz, H-4), 10.07 (1H, br, NH).

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$: C, 62.55; H, 4.32; N, 8.59. Found: C, 62.38; H, 4.12; N, 8.43.

3-[2-(4-Chloroanilino)-4-thiazolyl]tropolone (3f).

This compound was obtained from the reaction with 1-(4-chlorophenyl)thiourea as yellow needles (from 95% ethanol) in a yield of 255 mg (77%), mp 198-199°; ir (potassium bromide): ν max 3285 (NH), 3200 (OH), 1603 cm^{-1} (C=O); uv (methanol): λ max 202 (log ϵ 4.61), 276 (4.62), 297 (4.56), 406 nm (4.23); ^1H nmr (deuteriochloroform): δ 7.30-7.79 (7H, m), 8.34 (1H, s, H-5'), 8.88 (1H, d, J = 10.1 Hz, H-4), 10.41 (1H, br, NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}$: C, 58.09; H, 3.35; N, 8.47. Found: C, 58.27; H, 3.11; N, 8.24.

3-[2-(4-Bromoanilino)-4-thiazolyl]tropolone (3g).

This compound was obtained from the reaction with 1-(4-bromophenyl)thiourea as pale yellow needles (from ethanol) in a yield of 326 mg (87%), mp 211-212°; ir (potassium bromide): ν max 3358 (OH), 3320 (NH), 1600 cm^{-1} (C=O); uv (methanol): λ max 202 (log ϵ 4.47), 277 (4.49), 299 (4.44), 405 nm (4.08); ^1H nmr (deuteriochloroform): δ 7.27-7.75 (7H, m), 8.34 (1H, s, H-5'), 8.89 (1H, d, J = 10.0 Hz, H-4), 10.43 (1H, br, NH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{BrN}_2\text{O}_2\text{S}$: C, 51.20; H, 2.96; N, 7.46. Found: C, 51.48; H, 2.89; N, 7.41.

Reaction of 3-(2-Bromoacetyl)tropolone (2) with Thioamides.

A mixture of 3-(2-bromoacetyl)tropolone (2) (243 mg, 1.0 mmole) and thioamide (1.0 mmole) in absolute ethanol (30 ml) was heated for 20-30 minutes under refluxing. After cooling, the precipitate was collected and recrystallized to give 3-(4-thiazolyl)tropolone 4a-d.

3-(4-Thiazolyl)tropolone (4a).

This compound was obtained from the reaction with thioformamide as orange needles (from 95% ethanol) in a yield of 162 mg (79%), mp 107-108°; ir (potassium bromide): ν max 3147 (OH), 1610 cm^{-1} (C=O); uv (methanol): λ max 214 (log ϵ 4.44), 261 (4.10), 351 (3.44), 395 nm (3.39); ^1H nmr (deuteriochloroform): δ 7.16-7.62 (3H, m), 8.89 (1H, s, H-5'), 9.00 (1H, s, H-2'), 9.21 (1H, d, J = 9.9 Hz, H-4).

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{NO}_2\text{S}$: C, 58.52; H, 3.44; N, 6.83. Found: C, 58.67; H, 3.24; N, 6.63.

3-(2-Methyl-4-thiazolyl)tropolone (4b).

This compound was obtained from the reaction with thioacetamide as greenish yellow needles (from 95% ethanol) in a yield of 175 mg (80%), mp 127-129°; ir (potassium bromide): ν max 3175 (OH), 1613 cm^{-1} (C=O); uv (methanol): λ max 216 (log ϵ 4.43), 261 (4.20), 356 (3.65), 396 nm (3.59); ^1H nmr (deuteriochloroform): δ 2.74 (3H, s, CH_3), 7.15-7.59 (3H, m), 8.70 (1H, s, H-5'), 8.92 (1H, d, J = 10.3 Hz, H-4).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NO}_2\text{S}$: C, 60.26; H, 4.14; N, 6.39. Found: C, 59.98; H, 4.44; N, 6.63.

3-(2-Benzyl-4-thiazolyl)tropolone (4c).

This compound was obtained from the reaction with (phenyl)thioacetamide as greenish yellow needles (from 95% ethanol) in a yield of 219 mg (74%), mp 152-153°; ir (potassium bromide): ν max 3152 (OH), 1606 cm^{-1} (C=O); uv (methanol): λ max 216 (log ϵ 4.80), 261 (4.57), 357 (4.06), 397 nm (4.00); ^1H nmr (deuteriochloroform): δ 4.41 (2H, s, CH_2), 7.18-7.59 (8H, m), 8.73 (1H, s,

H-5'), 8.93 (1H, d, J = 10.3 Hz, H-4).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.74. Found: C, 68.94; H, 4.65; N, 4.66.

3-(2-Phenyl-4-thiazolyl)tropolone (**4d**).

This compound was obtained from the reaction with thiobenzamide as greenish yellow needles (from ethanol) in a yield of 194 mg (69%), mp 148-149°; ir (potassium bromide): ν max 3151 (OH), 1611 cm^{-1} (C=O); uv (methanol): λ max 215 (log ϵ 4.58), 261 (4.28), 290 (3.75), 401 nm (3.18); 1H nmr (deuteriochloroform): δ 7.23-8.10 (8H, m), 8.90 (1H, s, H-5'), 9.08 (1H, d, J = 10.3 Hz, H-4).

Anal. Calcd. for $C_{16}H_{11}NO_2S$: C, 68.31; H, 3.94; N, 4.98. Found: C, 68.18; H, 3.86; N, 4.69.

Reaction of 3-(2-Bromoacetyl)tropolone (**2**) with Ammonium Dithiocarbamate.

A mixture of 3-(2-bromoacetyl)tropolone (**2**) (243 mg, 1.0 mmole) and ammonium dithiocarbamate (110 mg, 1.0 mmole) in absolute ethanol (30 ml) was heated for 30 minutes under refluxing. The precipitate was collected and recrystallized from 70% ethanol to afford 3-(2-mercapto-4-thiazolyl)tropolone (**5**) as yellow needles, yield 173 mg (73%), mp 216-218°; ir (potassium bromide): ν max 3455 (OH), 1609 cm^{-1} (C=O); uv (methanol): λ

max 213 (log ϵ 4.66), 247 (4.45), 319 (4.41), 402 nm (4.04); 1H nmr (deuteriochloroform): δ 3.40 (1H, s, SH), 6.98-7.59 (4H, m), 7.84 (1H, d, J = 9.9 Hz, H-4).

Anal. Calcd. for $C_{10}H_7NO_2S_2$: C, 50.61; H, 2.98; N, 5.90. Found: C, 50.43; H, 3.26; N, 5.75.

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