Reactions of 3-Acetyl-2-aminotropones and 2-Acetyl-7-aminotropones with Hydrazine

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3-Acetyl-2-aminotropone (**1a**) reacted with hydrazine to afford its hydrazone (**3a**) and 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**), while methylamino- and pyrrolidinyl-substituted compounds **1b** and **1c** gave only the cyclized compound (**4**). Reactions of 2-acetyl-7-aminotropones **2a-d** gave their hydrazones **5a-d** and the hydrazone **6**. The hydrazones **3a** and **5b** were heated in acetic acid to give **4** and 3-methyl-8-methylamino-1,2-diazaazulene (**7**), respectively. Several reactions of **4** and **6** were also described.

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3-Acetyltropolone is very useful as a starting material for synthesis of heterocycle-condensed troponoid compounds, because it has a β-diketone structure. Previously, we have reported the reactions of 3-acetyltropolone and its two isomeric methyl ethers - 3-acetyl-2-methoxytropone and 2-acetyl-7-methoxytropone - with hydrazines [1-3], hydroxylamine [4], guanidine and amidines [5], *o*-phenylenediamine [6], and *o*-aminophenol [7]. On the other hand, 3-acetyltropolone readily reacted with amines to afford acetyl-substituted aminotropones [8]. Although tropolones do not show any indication to react with nucleophilic reagents, the reactivity of 3-acetyltropolone would be based on the electron-withdrawing effect of the acetyl group as well as nitro and nitroso-groups [9]. We now describe the reactions of acetyl-substituted aminotropones with hydrazine and some reactions of the products.

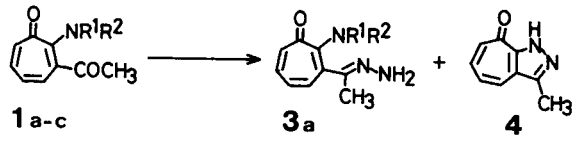
Results and Discussion.

Reactions of Acetyl-substituted Aminotropones with Hydrazine.

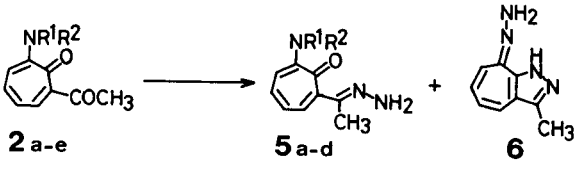
In general, the amino group of 2-aminotropones may be replaced by a variety of nucleophilic reagents. Dialkyl-amino groups are more easily replaceable than monosubstituted or unsubstituted amino group [10]. Thus, it was reported that 2-aminotropone and 2-methylaminotropone did not react with hydrazine, while 2-dimethylaminotropone readily reacted with hydrazine to afford 2-hydrazinotropone in 97% yield [11].

When a mixture of 3-acetyl-2-aminotropone (**1a**) and two equivalents of hydrazine in methanol was refluxed for 2 hours, **1a** was mostly recovered. Then, refluxing with three equivalents of hydrazine for 3 hours gave 3-acetyl-2-aminotropone hydrazone (**3a**) and 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) [1] in 18 and 30% yields, respectively, and **1a** (15%) was recovered. The yields of **3a** and **4** after 6 hours were 26 and 60%, respectively, being 13 and 70% after 9 hours, respectively. The structure of **3a** was determined by its elemental analysis and spectral data. Both the reactions of 3-acetyl-2-methylaminotropone (**1b**) and 3-acetyl-2-(1-pyrrolidinyl)tropone (**1c**) with two equivalents of hydrazine gave **4** in 83 and 91% yields, respectively, without hydrazones.

Scheme 1



a $R^1 = R^2 = H$
b $R^1 = CH_3$, $R^2 = H$
c $R^1, R^2 = -(CH_2)_4-$



a $R^1 = R^2 = H$
b $R^1 = CH_3$, $R^2 = H$
c $R^1 = CH_2CH_3$, $R^2 = H$
d $R^1 = CH_2Ph$, $R^2 = H$
e $R^1, R^2 = -(CH_2)_4-$

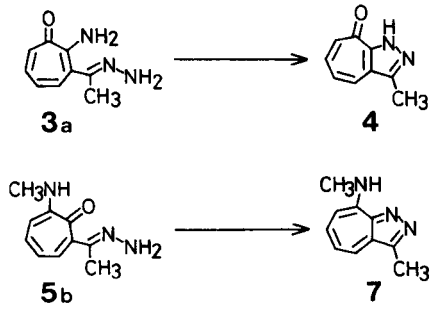
The reaction of 2-acetyl-7-aminotropone (**2a**) with hydrazine gave 2-acetyl-7-aminotropone hydrazone (**5a**) (6%) and 3-methyl-1,8-dihydrocycloheptapyrazol-8-one hydrazone (**6**) (43%), but not an expected 1,2-diazaazulene. The reactions of *N*-methyl-*N*-ethyl-, and *N*-benzyl-substituted derivatives **2b**, **2c**, and **2d** also gave their hydrazones [**5b** (66%), **5c** (44%), and **5d** (51%)] and **6** (8, 5, and 2%), respectively, while the reaction of 2-acetyl-7-(1-pyrrolidinyl)-tropone (**2e**) gave **6** (40%) as the sole product.

It was revealed that the amino and dialkylamino (*i.e.*, pyrrolidinyl) groups at the 7-position in 2-acetyl-7-aminotropones were readily displaced with hydrazine, while the monoalkylamino (*i.e.*, methylamino) group was not displaced.

Cyclization of the Hydrazones.

A solution of 3-acetyl-2-aminotropone hydrazone (**3a**) in methanol was refluxed for 5 hours but no reaction occurred. The hydrazone **3a** in acetic acid was heated on a water bath for 1 hour to cyclize to **4** (19%). Although 2-acetyl-7-methylaminotropone hydrazone (**5b**) did not cyclize by refluxing in methanol, the hydrazone (**5b**) in acetic acid was heated on a water bath for 1 hour to afford 3-methyl-8-methylamino-1,2-diazaazulene (**7**) (40%). These results were previously reported [12]. Little is known about the chemistry of 1,2-diazaazulene derivatives, except for two reports by Matsumoto [13] and by Treibs [14].

Scheme 2

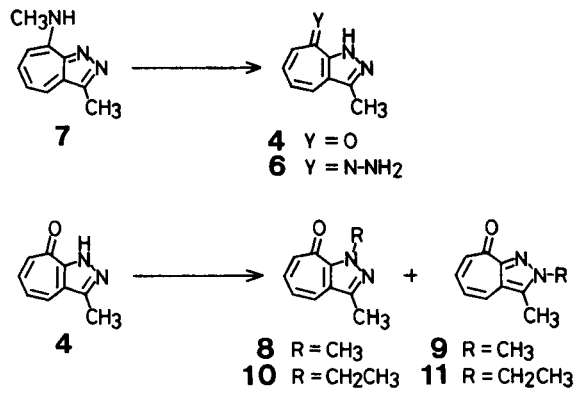


Furthermore, the 1,2-diazaazulene (**7**) was hydrolyzed with alkaline solution to give **4** and reacted with hydrazine to give **6**.

Reactions of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**).

The methylation of the compound **4** with diazomethane did not give *O*-methylated compound but gave two isomeric *N*-methylated compounds [2] - 1,3-dimethyl-1,8-dihydrocycloheptapyrazol-8-one (**8**) and 2,3-dimethyl-2,8-dihydrocycloheptapyrazol-8-one (**9**) - in 70 and 2% yields, respectively. The reaction with methyl iodide gave **8** and **9** in 76 and 17% yields, respectively. The methylation with dimethyl sulfate also gave **8** and **9** in 52 and 15% yields, respectively. The compound **4** was treated with diethyl sulfate to afford 1-ethyl-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**10**) and 2-ethyl-3-methyl-2,3-dihydrocycloheptapyrazol-8-one (**11**) in 51 and 28% yields, respectively, identified by their elemental analyses and spectral data.

Scheme 3



EXPERIMENTAL

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The ir spectra were taken on a JASCO IRA-1 spectrophotometer. The ^{1}H nmr spectra were recorded with a Hitachi Perkin-Elmer R-24 spectrometer (60 MHz).

Reaction of 3-Acetyl-2-aminotropone (**1a**) with Hydrazine.

(a) A mixture of 3-acetyl-2-aminotropone (**1a**) (245 mg, 1.5 mmoles) and 80% hydrazine hydrate (188 mg, 3.0 mmoles) in methanol (10 ml) was allowed to stand at room temperature for 24 hours. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate. The first fraction was recrystallized from benzene to give 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) (22 mg, 8%), mp 182-183° (lit [1], 183-184°). The third fraction was recrystallized from benzene-hexane to give 3-acetyl-2-aminotropone hydrazone (**3a**) as yellow needles (6 mg, 2%), mp 87-88°; ir (chloroform): ν max 3400 (NH), 1610 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 2.18 (s, 3H, CH_3), 5.00 (br, 2H, N-NH_2), 6.4-7.3 (m, 4H), 8.15 (br, 2H, C-NH_2).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 61.05; H, 6.27; N, 23.68.

(b) A mixture of **1a** (245 mg, 1.5 mmoles) and 80% hydrazine hydrate (188 mg, 3.0 mmoles) in methanol (10 ml) was refluxed for 2 hours on a water bath and worked up, as mentioned above, to afford **3a** (trace) and **4** (trace). Compound **1a** (188 mg, 77%) was recovered.

(c) A mixture of **1a** (245 mg, 1.5 mmoles) and 80% hydrazine hydrate (282 mg, 4.5 mmoles) in methanol (10 ml) was refluxed for 3 hours and worked up, as mentioned above, to afford **3a** (49 mg, 18%) and **4** (72 mg, 30%). Compound **1a** (36 mg, 15%) was recovered.

(d) A mixture of **1a** (245 mg, 1.5 mmoles) and 80% hydrazine hydrate (282 mg, 4.5 mmoles) in methanol (10 ml) was refluxed for 6 hours and worked up, as mentioned above, to afford **3a** (69 mg, 26%) and **4** (144 mg, 60%). Compound **1a** (5 mg, 2%) was recovered.

(e) A mixture of **1a** (245 mg, 1.5 mmoles) and 80% hydrazine hydrate (282 mg, 4.5 mmoles) in methanol (10 ml) was refluxed for 9 hours and worked up, as mentioned above, to afford **3a** (35 mg, 13%) and **4** (168 mg, 70%).

Reaction of 3-Acetyl-2-methylaminotropone (**1b**) with Hydrazine.

A mixture of 3-acetyl-2-methylaminotropone (**1b**) (354 mg, 2.0 mmoles) and 80% hydrazine hydrate (250 mg, 4.0 mmoles) in methanol (20 ml) was refluxed for 1 hour. After removal of the solvent, the residue was chromatographed on two Wakogel B-10 plates (30 × 30 cm^2) with ethyl acetate to afford **4** (266 mg, 83%).

Reaction of 3-Acetyl-2-(1-pyrrolidinyl)tropone (**1c**) with Hydrazine.

A mixture of 3-acetyl-2-(1-pyrrolidinyl)tropone (**1c**) (435 mg, 2.0 mmoles) and 80% hydrazine hydrate (250 mg, 4.0 mmoles) in methanol (20 ml) was refluxed for 2 hours and worked up, as mentioned above, to afford **4** (292 mg, 91%).

Reaction of 2-Acetyl-7-aminotropone (**2a**) with Hydrazine.

A mixture of 2-acetyl-7-aminotropone (**2a**) (326 mg, 2.0 mmoles) and 80% hydrazine hydrate (250 mmoles) in methanol (20 ml) was refluxed for 1 hour. After removal of the solvent, the residue was recrystallized from methanol to give 3-methyl-1,8-dihydrocycloheptapyrazol-8-one hydrazone (**6**) (150 mg, 43%); mp 199-201° (lit [1] 199-201°). The mother liquor was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate to afford 2-acetyl-7-aminotropone hydrazone (**5a**) as yellow prisms (21 mg, 6%), mp 149-152°; ir (chloroform): ν

max 3500 (NH), 3340 (NH), 1600 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.07 (s, 3H, CH_3), 5.10 (br, 2H, N-NH_2), 6.30 (br, 2H, C-NH_2), 6.4-7.6 (m, 4H).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.72. Found: C, 60.87; H, 6.32; N, 23.59.

Reaction of 2-Acetyl-7-methylaminotropone (**2b**) with Hydrazine.

(a) A mixture of 2-acetyl-7-methylaminotropone (**2b**) (105 mg, 0.6 mmole) and 80% hydrazine hydrate (80 mg, 1.3 mmoles) in methanol (10 ml) was allowed to stand at room temperature for 24 hours. After removal of the solvent, the residue was recrystallized from methanol to give **6** (7 mg, 7%). The evaporation of the methanol from the mother liquor and the residue was recrystallized from benzene-hexane to afford 2-acetyl-7-methylaminotropone hydrazone (**5b**) as yellow plates (86 mg, 76%); mp 133-135°; ir (chloroform): ν max 3320 (NH), 1595 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.09 (s, 3H, C-CH_3), 3.00 (s, 3H, N-CH_3), 5.25 (br, 2H, NH_2), 6.3-7.7 (m, 5H).

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.98. Found: C, 62.81; H, 6.77; N, 22.14.

(b) A mixture of **2b** (119 mg, 0.7 mmole) and 80% hydrazine hydrate (85 mg, 1.4 mmoles) in methanol (10 ml) was refluxed for 2 hours and worked up, as mentioned above, to afford **5a** (85 mg, 66%) and **6** (9 mg, 8%).

Reaction of 2-Acetyl-7-ethylaminotropone (**2c**) with Hydrazine.

A mixture of 2-acetyl-7-ethylaminotropone (**2c**) (222 mg, 1.2 mmoles) and 80% hydrazine hydrate (115 mg, 1.8 mmoles) in methanol (10 ml) was refluxed for 1.5 hours. After removal of the solvent, the residue was recrystallized from benzene to give **6** (10 mg, 5%). The mother liquor was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate to afford 2-acetyl-7-ethylaminotropone hydrazone (**5c**) as orange prisms (104 mg, 44%), mp 125-126°; ir (chloroform): ν max 3300 (NH), 1590 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.32 (t, 3H, J = 6.5 Hz, CH_3), 1.98 (s, 3H, CH_3), 3.29 (m, 2H, CH_2), 5.10 (br, 2H, NH_2), 6.4-7.6 (m, 5H).

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.36; H, 7.37; N, 20.47. Found: C, 64.46; H, 7.41; N, 20.45.

Reaction of 2-Acetyl-7-benzylaminotropone (**2d**) with Hydrazine.

A mixture of 2-acetyl-7-benzylaminotropone (**2d**) (300 mg, 1.2 mmoles) and 80% hydrazine hydrate (150 mg, 2.4 mmoles) in methanol (20 ml) was refluxed for 1.5 hours and worked up, as mentioned above, to give **6** (5 mg, 2%) and 2-acetyl-7-benzylaminotropone hydrazone (**5d**) as yellow plates (161 mg, 51%), mp 111-112°; ir (chloroform): ν max 3300 (NH), 1590 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.06 (s, 3H, CH_3), 4.50 (d, 2H, J = 6.0 Hz, CH_2), 5.10 (br, 2H, NH_2), 6.4-7.6 (m, 4H), 7.30 (s, 5H, Ph), 7.70 (br, 2H, NH_2).

Reaction of 2-Acetyl-7-(1-pyrrolidinyl)tropone (**2e**) with Hydrazine.

A mixture of 2-acetyl-7-(1-pyrrolidinyl)tropone (**2e**) (435 mg, 2.0 mmoles) and 80% hydrazine hydrate (250 mg, 4.0 mmoles) in methanol (20 ml) was refluxed for 2 hours. After removal of the solvent, the residue was recrystallized from benzene to give **6** (140 mg, 40%).

Cyclization of 3-Acetyl-2-aminotropone Hydrazone (**3a**).

A solution of 3-acetyl-2-aminotropone hydrazone (**3a**) (177 mg, 1.0 mmole) in acetic acid (5 ml) was heated on a water bath for 1 hour. After removal of the acetic acid under reduced pressure, the residue was chromatographed on two Wakogel B-10 plates (30 × 30 cm^2) with ethyl acetate to give **4** (31 mg, 19%).

Cyclization of 2-Acetyl-7-methylaminotropone Hydrazone (**5b**).

A solution of 2-acetyl-7-methylaminotropone hydrazone (**5b**) (191 mg, 1.0 mmole) in acetic acid (5 ml) was heated on a water bath for 1 hour and worked up, as mentioned above, to afford 3-methyl-8-methylamino-1,2-diazaazulene (**7**) (69 mg, 40%), mp 174-176° [12].

Alkaline Hydrolysis of 3-Methyl-8-methylamino-1,2-diazaazulene (**7**).

A suspended solution of **7** (87 mg, 0.5 mmole) in 10% sodium hydroxide aqueous solution (5 ml) and methanol (5 ml) was heated on a water bath for 4 hours. After removal of the solvents under reduced pressure, the residue was triturated with water, neutralized with 1*M* hydrochloric acid, and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. The evaporation residue from the extract was recrystallized from benzene to give **4** (48 mg, 60%).

Reaction of 3-Methyl-8-methylamino-1,2-diazaazulene (**7**) with Hydrazine.

A mixture of the 1,2-diazaazulene (**7**) (87 mg, 0.5 mmole) and 80% hydrazine hydrate (63 mg, 1.0 mmole) in methanol (10 ml) was refluxed for 4 hours on a water bath. After removal of the solvent, the residue was recrystallized from methanol to afford **6** (34 mg, 39%).

Methylation of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-one (**8**) with Diazomethane.

To a solution of 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) (160 mg, 1.0 mmole) in chloroform (5 ml) was added an excess of diazomethane ethereal solution. The mixture was allowed to stand for 2 days in a refrigerator. The solvents and excess of diazomethane were evaporated off and the residue was chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate. The upper fraction was recrystallized from hexane to give 1,3-dimethyl-1,8-dihydrocycloheptapyrazol-8-one (**8**) (122 mg, 70%), mp 97-98° (lit [2] 96-98°). The lower fraction was recrystallized from benzene-hexane to give 2,3-dimethyl-2,8-dihydrocycloheptapyrazol-8-one (**9**) (3 mg, 2%), mp 178-179° (lit [2] 178-179°).

Methylation of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) with Methyl Iodide.

A mixture of **4** (160 mg, 1.0 mmole) and methyl iodide (1 ml) in acetone (20 ml) was refluxed for 8 hours in the presence of silver oxide (231 mg, 1.0 mmole). The reaction mixture was filtered. The evaporation residue from the filtrate was worked up, as mentioned above, to give **8** (132 mg, 76%) and **9** (29 mg, 17%).

Methylation of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) with Dimethyl Sulfate.

A solution of **4** (160 mg, 1.0 mmole) and dimethyl sulfate (126 mg, 1.0 mmole) in acetone (20 ml) was refluxed for 4 hours in the presence of potassium carbonate (138 mg, 1.0 mmole). After filtration of the potassium carbonate, the evaporation residue from the filtrate was triturated with water and extracted with chloroform. The extract was washed with water and dried over sodium sulfate. The solvent was removed and the residue was worked up, as mentioned above, to afford **8** (90 mg, 52%) and **9** (21 mg, 12%).

Ethylation of 3-Methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) with Diethyl Sulfate.

A solution of 3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**4**) (320 mg, 2.0 mmoles) and diethyl sulfate (308 mg, 2.0 mmoles) in acetone (40 ml) was refluxed for 4 hours in the presence of potassium carbonate (276 mg, 2.0 mmoles). The reaction mixture was treated, as mentioned above, and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate. The upper fraction afforded 1-ethyl-3-methyl-1,8-dihydrocycloheptapyrazol-8-one (**10**) as pale yellow crystals (193 mg, 51%), mp 42-44°; ir (chloroform): ν max 1595 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.44 (t, 3H, J = 7.0 Hz, CH_3), 2.45 (s, 3H, CH_3), 4.81 (q, 2H, J = 7.0 Hz, CH_2), 6.4-7.5 (m, 4H).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.95; H, 6.36; N, 14.64.

The lower fraction was recrystallized from benzene-hexane to afford 2-ethyl-3-methyl-2,8-dihydrocycloheptapyrazol-8-one (**11**) as pale yellow prisms (105 mg, 28%), mp 97-99°; ir (chloroform): ν max 1640 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.50 (t, 3H, J = 7.0 Hz, CH_3), 2.52 (s, 3H, CH_3), 4.35 (q, 2H, J = 7.0 Hz, CH_2), 6.3-7.4 (m, 4H).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.26; H, 6.50; N, 14.65.

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