HETEROCYCLES, Vol 16, No 6, 1981

REACTIONS OF 3- AND 7-ACETYL-2-CHLOROTROPONES WITH HYDRAZINES. FORMATION OF 1(2*H*)-PHTHALAZINONES

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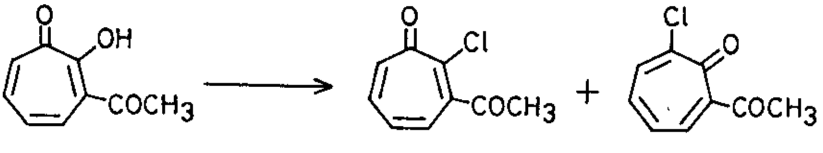
Abstract —— 3-Acetyl- and 7-acetyl-2-chlorotropones (2a and 2b) reacted with hydrazine to afford a rearrangement product, 4-methyl-1(2*H*)-phthalazinone (3). In the reactions with methylhydrazine, 2a and 2b gave 1,3-dimethyl-7-methylamino-1,8-dihydrocycloheptapyrazol-8-one (4) and 2,4-dimethyl-1(2*H*)-phthalazinone (5), respectively.

As a series of studies on the chemistry of 3-acetyltropolone (1), recently we have described the reactions of 1 and its two isomeric methyl ethers with hydrazine,[1] methylhydrazine,[2] and phenylhydrazine.[3] These reactions gave 1,8- and 2,8-dihydrocycloheptapyrazol-8-ones —— pyrazolo[3,4-*b*]tropones. The present communication reports the synthesis of 3- and 7-acetyl-2-chlorotropones (2a and 2b) as another reactive troponoids and their reactions with hydrazine and methylhydrazine. On the other hand, it is well known that ciné substitution at the 7-position and rearrangement to benzenoid compounds very often occur besides normal substitution at the 2-position in the reactions of 2-chlorotropones with hydrazine.[4]



1 2a 2b

3-Acetyltropolone (1) was chlorinated with thionyl chloride to give two isomeric chlorotropones (2a and 2b).[#] Their structure was determined by the ele-

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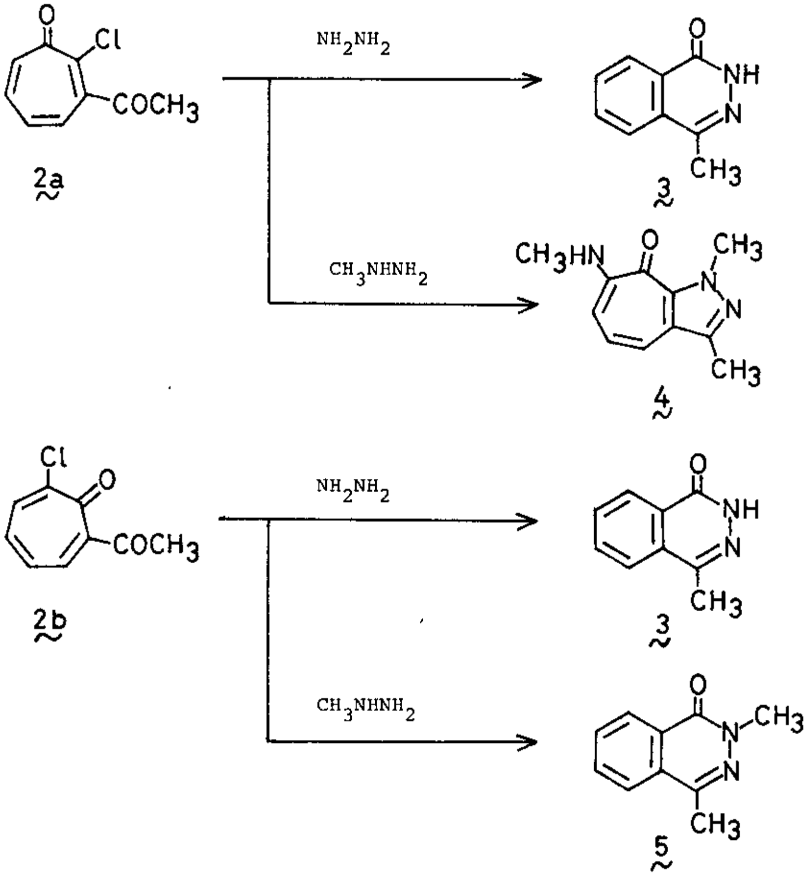
[#] Caution: These 3- and 7-acetyl-2-chlorotropones (2a and 2b) irritate and inflame the skin similarly to other halotropones.

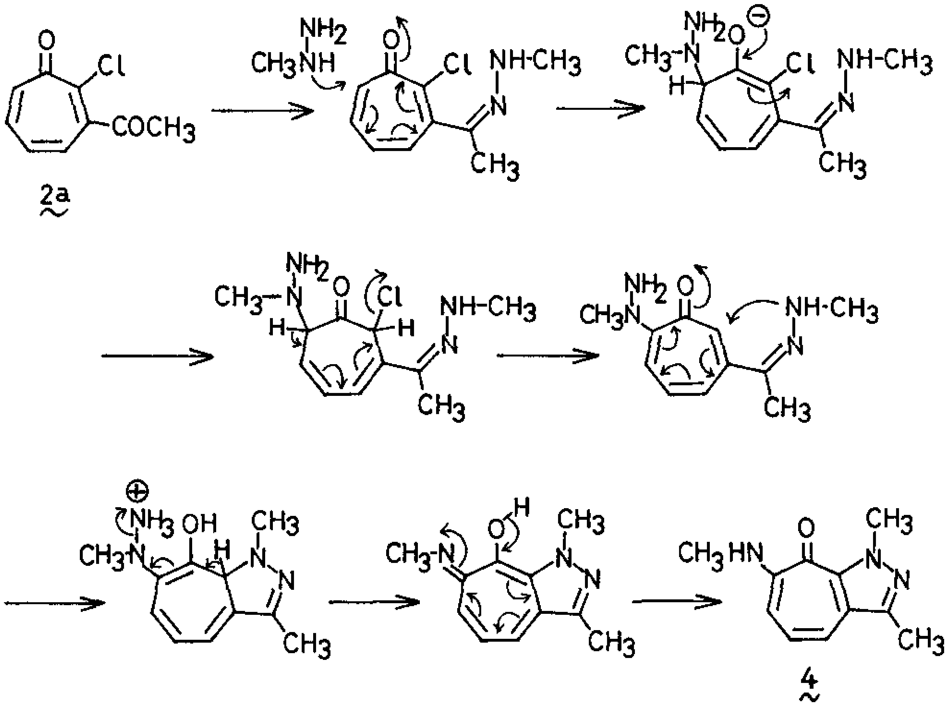
mental analyses and spectral data. The Nmr spectrum of **2a** shows a multiplet peak at δ 6.5-7.3 ppm for the seven-membered ring protons while that of **2b** shows peaks at lower magnetic field [δ 6.9-7.3 (m, 2H, H-4 and H-5), 7.4-7.6 (m, 1H, H-6), and 7.7-7.9 ppm (m, 1H, H-3)]. Thus, **2a** was assigned to 3-acetyl-2-chlorotropone and **2b** to 7-acetyl-2-chlorotropone.



Refluxing of **2a** and hydrazine in methanol gave the rearrangement product —— 4-methyl-1(2*H*)-phthalazinone (**3**). The isomer (**2b**) also reacted with hydrazine to give **3**. The product **3** was identified by comparison of its mp and spectral data with those of an authentic sample.[5]

When a solution of **2a** and methylhydrazine in methanol was refluxed, 1,3-dimethyl-7-methylamino-1,8-dihydrocycloheptapyrazol-8-one (**4**) was obtained. The structure was confirmed by its elemental analysis ($C_{11}H_{13}N_3O$) and spectral data.

The pattern of the Uv spectrum is very similar to that of 1,3-dimethyl-1,8-dihydrocycloheptapyrazol-8-one.[2] Each absorption band shifted toward the long wavelength region by the introduction of the methylamino group at the 7-position. The Nmr spectrum shows three methyl peaks at δ 2.48 (s, 3H, $C-CH_3$), 2.92 (d, 3H, J = 4.8 Hz, $NH-CH_3$), and 4.06 ppm (s, 3H, $N-CH_3$) and peaks at δ 6.0-6.8 ppm for the seven-membered ring protons. The spectrum in trifluoroacetic acid shows a shift of the seven-membered ring protons by ca. 1.0-1.2 ppm and one of the three methyl protons by ca. 0.25-0.40 ppm towards a lower magnetic field. These results support the structure of the product. On the other hand, the reaction of **2b** with methylhydrazine gave 2,4-dimethyl-1(2H)-phthalazinone (**5**), whose structure was determined by comparison of its mp and spectral data with those of an authentic matrial.[6] In addition, the formation of **4** from **2a** might be considered to proceed via methylhydrazone formation , ciné substitution, cyclization, and deamination as shown in the following scheme.



In conclusion, these 3- and 7-acetyl-2-chlorotropones (2a and 2b) are more *reactive than 3-acetyltropolone methyl ethers and reacted with hydrazine to give* 1(2H)-phthalazinone derivatives (3 and 5) by rearrangement process and to give 1,8-dihydrocycloheptapyrazol-8-one (4) by ciné substitution and cyclization reaction.

Experimental

The mp's were determined with a Yanagimoto MP-S2 melting point measuring apparatus and are uncorrected. The Ir spectra were taken on a JASCO IRA-1 spectrophotometer and the Uv spectra on a Hitachi EPS-3T spectrophotometer. The Nmr spectra were recorded with a Hitachi R-24 spectrometer (60 MHz).

Chlorination of 3-Acetyltropolone (1). A mixture of 1 (1.64 g, 10 mM) and thionyl chloride (1,75 g, 15 mM) in dry benzene (25 ml) was gently refluxed for 8 h. The reaction mixture was brought to dryness by evaporation of the solvent and extracted with hot cyclohexane. Then, the cyclohexane was evaporated off and the residue was chromatographed on three Wakogel B-10 plates (30×30 cm^2) by using ethyl ether. The fraction from the lower band was recrystallized from cyclohexane to afford 3-acetyl-2-chlorotropone (2a) as pale yellow prisms. Yield: 205 mg (11 %); mp 91-93°C; Ir: ν(CHCl$_3$) 1734, 1634, 1596 cm^{-1}; Uv: λ_{max}(CH$_3$OH) 243 (log ε 4.22), 325 nm (3.77); Nmr: δ(CDCl$_3$) 2.52 (s, 3H, CH$_3$), 6.5-7.3 ppm (m, 4H). Found: C, 59.18; H, 3.90 %. Calcd for $C_9H_7ClO_2$: C, 59.20; H, 3.86 %. The upper fraction was also recrystallized from cyclohexane to afford 7-acetyl-2-chlorotropone (2b) as pale yellow needles. Yield: 720 mg (40 %); mp 77-78°C; Ir: ν(CHCl$_3$) 1706, 1618, 1596 cm^{-1}; Uv: λ_{max}(CH$_3$OH) 248 (log ε 4.20), 331 nm (3.77); Nmr: δ(CDCl$_3$) 2.46 (s, 3H, CH$_3$), 6.9-7.3 (m, 2H,H-4 and H-5), 7.4-7.6 (m, 1H, H-6), 7.7-7.9 ppm (m, 1H, H-3). Found: C, 59.19; H, 3.88 %. Calcd for $C_9H_7ClO_2$: C, 59.20; H, 3.86 %.

Reaction of 3-Acetyl-2-chlorotropone (2a) with Hydrazine. To a solution of 2a (183 mg, 1.0 mM) in methanol (10 ml) was added 80% hydrazine hydrate (125 mg, 2.0 mM). The mixture was refluxed for 2 h on a water bath. Then, the solvent was evaporated off and the residue was recrystallized from methanol to give 4-methyl-1(2H)-phthalazinone (3). Yield: 47 mg (29 %); mp 229-231°C (lit,[5] 222°C).

Reaction of 7-Acetyl-2-chlorotropone (2b) with Hydrazine. A solution of 2b (183 mg, 1.0 mM) and 80% hydrazine hydrate (125 mg, 2.0 mM) in methanol (10 ml) was refluxed for 2 h. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 X 30 cm^2) by using ethyl acetate to afford 1,3-dimethyl-7-methylamino-1,8-dihydrocycloheptapyrazol-8-one (**4**) as yellowish brown prisms (from benzene-hexane). Yield: 87 mg (43 %); mp 202-204°C; Ir: $\nu(CHCl_3)$ 3380, 1600, 1582 cm^{-1}; Uv: $\lambda_{max}(CH_3OH)$ 237 (log ε 4.13), 279 (4.21), 347 (4.06), 436 nm (3.88); Nmr: $\delta(CDCl_3)$ 2.48 (s, 3H, $C\text{-}CH_3$), 2.92 (d, 3H, J = 4.8 Hz, $NH\text{-}CH_3$), 4.06 (s, 3H, $N\text{-}CH_3$), 6.0-6.9 ppm (m, 5H); $\delta(CF_3COOH)$ 2.83 (s, 3H), 3.32 (s, 3H), 4.31 (s, 3H), 7.0-8.1 ppm (m, 4H). Found: C, 64.92; H. 6.47; N, 20.23 %. Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68 %.

Reaction of 7-Acetyl-2-chlorotropone (2b) with Methylhydrazine. A mixture of **2b** (183 mg, 1.0 mM) and methylhyrazine (92 mg, 2.0 mM) in methanol (10 ml) was refluxed for 2 h. The reaction mixture was concentrated to dryness and chromatographed on a Wakogel B-10 plate (30 X 30 cm^2) by using ethyl acetate to afford 2,4-dimethyl-1(2*H*)-phthalazinone (**5**). Yield: 93 mg (53 %); mp 110-112°C (lit,[6] 109-110°C).

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Received, 4th March, 1981