Reactions of 3-Acetyltropolone Methyl Ethers † with Guanidine and Amidines

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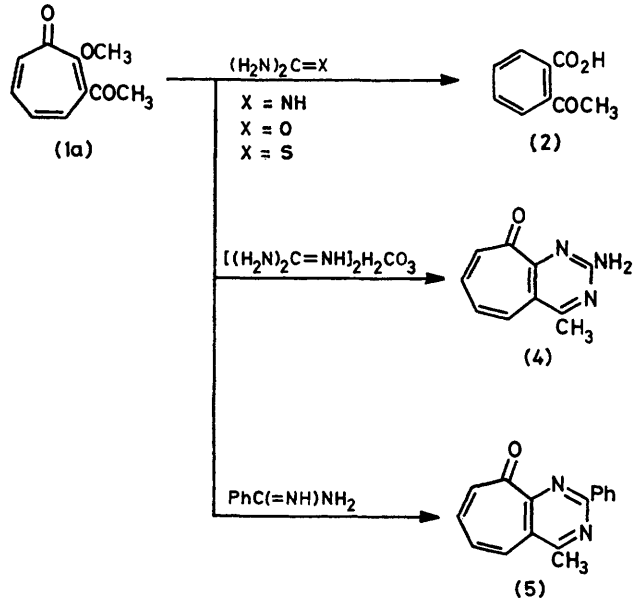
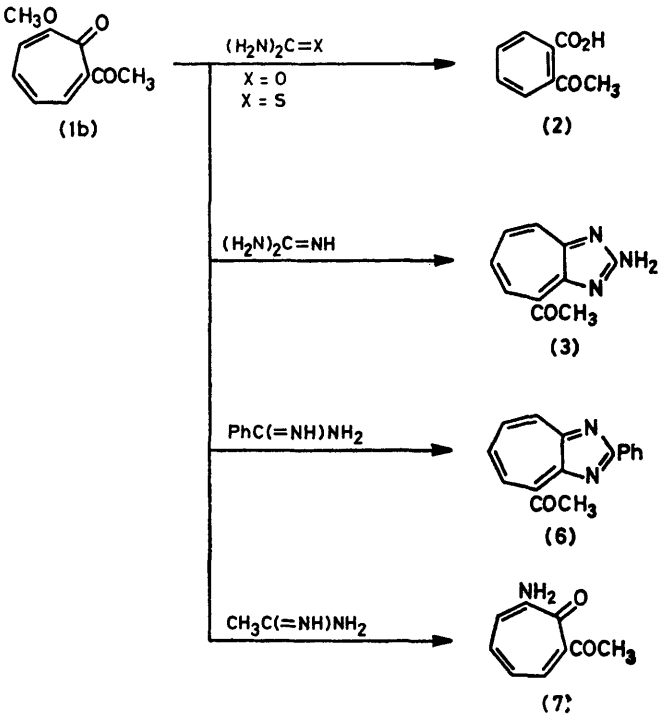
3-Acetyl-2-methoxytropone (1a) rearranged to 2-acetylbenzoic acid (2) on treatment with guanidine in the presence of sodium ethoxide, and reacted with benzamidine to give 4-methyl-2-phenyl-9*H*-cyclohepta[*d*]-pyrimidin-9-one (5). Reaction with guanidine carbonate in the absence of sodium ethoxide gave 2-amino-4-methyl-9*H*-cyclohepta[*d*]pyrimidin-9-one (4). 2-Acetyl-7-methoxytropone (1b) reacted with guanidine, benzamidine, and acetamidine to afford 4-acetyl-2-aminocycloheptimidazole (3), 4-acetyl-2-phenylcycloheptimidazole (6), and 2-acetyl-7-aminotropone (7), respectively.

SINCE 3-acetyltropolone has a β-diketone structure, it is useful as starting material for synthesis of fused heterocyclic troponoid compounds. Previously, we have reported the reactions of 3-acetyltropolone and its two isomeric methyl ethers with hydrazines,[1-3] semicarbazide,[4] and *o*-phenylenediamine.[5] It is well known that 2-methoxytropones react with guanidine and thiourea to afford cycloheptimidazole derivatives;[6,7] however with urea these reactions do not give cycloheptimidazoles but yield molecular compounds, except in the case of 4-(*p*-nitrostyryl)tropolone methyl ethers.[8] The reactions of amidines, such as benzamidine,[9,10] and acetamidine,[11] with reactive troponoids gave cycloheptimidazoles.

We now describe the reactions of 3-acetyl-2-methoxy- and 2-acetyl-7-methoxy-tropones (1a and b) with guanidine and amidines.



Reactions with Guanidine and Related Compounds.—A mixture of (1a) and guanidine hydrochloride in absolute ethanol refluxed for 2 h in the presence of sodium ethoxide afforded the rearrangement product 2-acetylbenzoic acid (2);[12] however the reaction of (1b) with guanidine gave 4-acetyl-2-aminocycloheptimidazole (3), identified by elemental analysis and spectral data. The u.v. spectrum is very similar to that of 2-aminocycloheptimidazole.[13] The n.m.r. spectrum shows a singlet at



δ 2.80 ($COCH_3$) and a multiplet at δ 7.4—8.3 for the seven-membered-ring protons. The i.r. spectrum shows absorptions at 3 410 and 1 706 cm^{-1} for the amino and acetyl carbonyl groups, respectively.

Matsumoto has reported that the reaction of 3-formyl-6-isopropyltropolone with guanidine carbonate affords 2-amino-6-isopropyl-9*H*-cyclohepta[*d*]pyrimidin-9-one.[14] We therefore carried out the reactions of the 3-acetyltropolone methyl ethers (1a and b) with guanidine carbonate. The reaction of (1a) gave 2-amino-4-9*H*-cyclohepta[*d*]pyrimidin-9-one (4), identified by elemental analysis and spectral data. The u.v. spectrum

† 3-Acetyl-2-methoxycyclohepta-2,4,6-trien-1-one and 2-acetyl-7-methoxycyclohepta-2,4,6-trien-1-one.

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is very similar to that of Matsumoto's cyclohepta[*d*]-pyrimidin-9-one. The n.m.r. spectrum shows a singlet at δ 2.74 (CH_3), a broad peak at 6.21 (NH_2), and a multiplet at 6.8—7.6 for the seven-membered-ring protons. The i.r. spectrum shows absorptions at 3 410 and 1 610 cm^{-1} for the amino and tropone carbonyl groups, respectively. The reaction of (1b) with guanidine carbonate gave the cycloheptimidazole (3).

The difference between the reactions of (1a and b) may be explicable as follows. As the methoxy-group of (1a) is sterically hindered, guanidine attacks at the acetyl group, and cyclization then occurs at C-2. On the other hand, in the reaction of (1b), guanidine attacks at the carbon atom bearing the methoxy-group, to afford the cycloheptimidazole.

The reactions of the methyl ethers (1a and b) with urea and thiourea gave the rearrangement product (2), which was also formed when (1a) or (1b) was heated in the presence of sodium ethoxide. Rearrangement of this type on heating with alkali or alkoxide are well known.[15,16]

Reactions with Benzamidine.—A mixture of the methyl ether (1a) and benzamidine in dry benzene was refluxed for 1 h in the presence of potassium hydroxide to give the cycloheptapyrimidinone (5). The i.r. spectrum shows no acetyl carbonyl signal near 1 700 cm^{-1}. The n.m.r. spectrum shows peaks at δ 2.90 (s, 3 H, CH_3), 6.6—7.2 (m, 3 H, H-5, -6, -7), 7.3—7.6 (m, 4 H, H-3′, -4′, -5′, -8), and 8.4—8.7 (m, 2 H, H-2′, -6′). The u.v. spectrum differs from that of cycloheptimidazole.

The isomer (1b) with benzamidine under the same conditions gave the cycloheptimidazole (6). Its i.r. spectrum shows a characteristic band at 1 710 cm^{-1} for the acetyl carbonyl group and its u.v. spectrum is very similar to that of 2-phenylcycloheptimidazole.[17]

These reactions with benzamidine are thus similar to those with guanidine carbonate.

Reactions with Acetamidine.—No product was isolated on treatment of the methyl ethers (1a and b) with acetamidine in dry benzene in the presence of potassium hydroxide. However, the reaction of (1b) with acetamidine in methanol in the presence of potassium hydroxide under reflux gave the aminotropone (7). The i.r. spectrum shows the amino absorption at 3 505 and 3 348, the acetyl carbonyl at 1 698, and the tropone carbonyl signal at 1 600 cm^{-1}. The n.m.r. spectrum shows peaks at δ 2.60 (s, 3 H, $COCH_3$), 6.4 (br, 2 H, NH_2), 6.7—7.4 (m, 3 H, H-4, -5, -6), and 7.61 (dd, 1 H, *J* 8.1 and 1.4 Hz, H-3). Compound (7) was also obtained readily by the reaction of 3-acetyltropolone with ammonia.[18] The production of ammonia from decomposition of the acetamidine by alkali accounts for the formation of (7) from (1b).

EXPERIMENTAL

M.p.s were determined with a Yanagimoto MP-S2 apparatus. I.r. spectra were taken with a JASCO IRA-1 spectrophotometer and u.v. spectra with a Hitachi EPS-3T spectrophotometer. ^1H N.m.r. spectra were recorded with a Hitachi–Perkin-Elmer R-24 spectrometer (60 MHz).

Reaction of 3-Acetyl-2-methoxytropone (1a) *with Guanidine.*—(*a*) To a solution of (1a) (178 mg, 1 mmol) in absolute ethanol (8 ml) was added a solution of guanidine hydrochloride (150 mg, 1.5 mmol) and sodium ethoxide [from sodium (35 mg, 1.5 mmol)] in absolute ethanol (2 ml). The mixture was refluxed for 2 h on a water-bath. The solvent was removed and the residue was diluted with water, made slightly acidic with 0.1M-hydrochloric acid, and extracted with chloroform. Evaporation and recrystallization from benzene gave 2-acetylbenzoic acid (2) (100 mg, 61%); m.p. 113—114 °C (lit.,[12] 114—115 °C).

(*b*) A mixture of (1a) (100 mg, 0.56 mmol) and guanidine carbonate (110 mg, 1.2 mmol) in absolute ethanol (10 ml) was refluxed for 2 h on a water-bath, then evaporated. The residue was diluted with water and extracted with chloroform. The extract was evaporated and the residue was recrystallized from benzene–hexane to afford 2-*amino*-4-*methyl*-9H-*cyclohepta*[d]*pyrimidin*-9-*one* (4) as yellow microcrystals (85 mg, 80%); m.p. 211—213 °C; $\nu_{max.}$ ($CHCl_3$) 3 410 (NH) and 1 610 cm^{-1} (C=O); $\lambda_{max.}$ (CH_3OH) 250 (log ε 4.17), 267 (4.02), 275 (4.03), 305 (3.38), 342 (3.84), 375 (3.57), 410 (3.74), and 470 nm (2.34); δ ($CDCl_3$) 2.74 (s, 3 H, CH_3), 6.21 (br, 2 H, NH_2), and 6.8—7.6 (m, 4 H) (Found: C, 64.25; H, 4.98; N, 22.85. $C_{10}H_9N_3O$ requires C, 64.15; H, 4.85; N, 22.45%).

Reactions of the Methyl Ether (1a) *with Urea and Thiourea.*—The reaction of (1a) (356 mg, 2 mmol) with urea (240 mg, 4 mmol) was carried out in the presence of sodium ethoxide. The solvent was removed and the residue was diluted with water, made slightly acidic with 0.1M-hydrochloric acid, and extracted with chloroform. Evaporation of the extract and recrystallization from benzene gave the acid (2) (250 mg, 78%). The reaction of (1a) (712 mg, 4 mmol) with thiourea (456 mg, 6 mmol) also gave the acid (2) (320 mg, 53%).

Rearrangement of the Methyl Ether (1a) *with Sodium Ethoxide.*—To sodium ethoxide solution [from sodium (21 mg, 1 mmol) and absolute ethanol (10 ml)] was added (1a) (178 mg, 1 mmol). The mixture was heated for 2 h on a water-bath and worked up, as above, to give the acid (2) (105 mg, 63%).

Reaction of 2-Acetyl-7-methoxytropone (1b) *with Guanidine.*—(*a*) To a solution of (1b) (356 mg, 2 mmol) in absolute ethanol (8 ml) was added a solution of guanidine hydrochloride (300 mg, 3 mmol) and sodium ethoxide [from sodium (70 mg, 3 mmol)] in absolute ethanol (2 ml). The mixture was refluxed for 2 h on a water-bath. The solvent was removed and the residue was treated with water to give a precipitate, which was recrystallized from benzene–hexane to yield 4-*acetyl*-2-*aminocycloheptimidazole* (3) as yellow needles (160 mg, 43%); m.p. 213—215 °C; $\nu_{max.}$ ($CHCl_3$) 3 410 (NH) and 1 706 cm^{-1} (C=O); $\lambda_{max.}$ (CH_3OH) 265 (log ε 4.06) and 370 nm (3.78); δ [$(CD_3)_2SO$] 2.80 (s, 3 H, CH_3) and 7.4—8.3 (m, 4 H, H-5, -6, -7, -8) (Found: C, 63.85; H, 4.9; N, 22.15. $C_{10}H_9N_3O$ requires C, 64.15; H, 4.85; N, 22.45%).

(*b*) A mixture of (1b) (178 mg, 1 mmol) and guanidine carbonate (180 mg, 2 mmol) in absolute ethanol (10 ml) was refluxed for 2 h on a water-bath. The solvent was removed and the residue was dissolved in water and extracted with chloroform. Evaporation and recrystallization from benzene–hexane gave the cycloheptimidazole (3) (160 g, 85%).

Reactions of the Methyl Ether (1b) *with Urea and Thiourea.*

—The reaction of (1b) (356 mg, 2 mmol) with urea (240 mg, 4 mmol) was carried out in the presence of sodium ethoxide. The solvent was removed and the residue was diluted with water, acidified with 0.1M-hydrochloric acid, and extracted with chloroform. Evaporation and recrystallization from benzene gave (2) (200 mg, 65%). The reaction of (1b) (178 mg, 1 mmol) with thiourea (152 mg, 2 mmol) also gave the acid (2) (90 mg, 59%).

Rearrangement of the Methyl Ether (1b) *with Sodium Ethoxide.*—To sodium ethoxide solution [from sodium (21 mg, 1 mmol) and absolute ethanol (10 ml)] was added (1b) (178 mg, 1 mmol). The mixture was heated for 2 h on a water-bath and worked up, as above, to give the acid (2) (98 mg, 59%).

Reaction of the Methyl Ether (1a) *with Benzamidine.*—A mixture of (1a) (178 mg, 1 mmol), benzamidine hydrochloride (156 mg, 1 mmol), and potassium hydroxide (56 mg, 1 mmol) in dry benzene (10 ml) was refluxed for 1 h. The solvent was removed and the residue was diluted with water, neutralized with 0.1M-hydrochloric acid, and extracted with chloroform. The residue from evaporation of the extract was chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate to give yellow crystals, which were recrystallized from cyclohexane to give *4-methyl-2-phenyl-9H-cyclohepta*[d]*pyrimidin-9-one* (5) as yellow needles (90 mg, 36%); m.p. 137—138 °C; $\nu_{max.}$ ($CHCl_3$) 1 650 cm^{-1}; $\lambda_{max.}$ (CH_3OH) 273 (log ε 4.28) and 330 nm (4.17); δ ($CDCl_3$) 2.90 (s, 3 H, CH_3), 6.6—7.2 (m, 3 H, H-5, -6, -7), 7.3—7.6 (m, 4 H, H-3′, -4′, -5′, -8), and 8.4—8.7 (m, 2 H, H-2′, -6′) (Found: C, 77.45; H, 4.9; N, 11.0. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.85; N, 11.3%).

Reaction of the Methyl Ether (1b) *with Benzamidine.*—A mixture of (1b) (178 mg, 1 mmol), benzamidine hydrochloride (156 mg, 1 mmol), and potassium hydroxide (56 mg, 1 mmol) in dry benzene (10 ml) was refluxed for 1 h. The solvent was removed and the residue was diluted with water, neutralized with 0.1M-hydrochloric acid, and extracted with chloroform. The extract was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ether to afford crystals, which were recrystallized from hexane to give *4-acetyl-2-phenylcycloheptimidazole* (6) as yellow needles (95 mg, 38%); m.p. 142—143 °C; $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (C=O); $\lambda_{max.}$ (CH_3OH) 260 (log ε 4.04) and 370 nm (3.95); δ ($CDCl_3$) 3.15 (s, 3 H, CH_3), 7.35—7.75 (m, 3 H, H-3′, -4′, -5′), 7.85—8.25 (m, 3 H, H-6, -7, -8), and 8.45—8.94 (m, 3 H, H-2′, -5, -6′) (Found: C, 77.15; H, 5.15; N, 10.95. $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.85; N, 11.3%).

Reaction of the Methyl Ether (1b) *with Acetamidine.*—To a solution of (1b) (178 mg, 1 mmol) and acetamidine hydrochloride (188 mg, 2 mmol) in methanol (15 ml) was added potassium hydroxide (112 mg, 2 mmol). The mixture was refluxed for 2 h on a water-bath, then evaporated. The residue was diluted with water, neutralized with 0.1M-hydrochloric acid, and extracted with chloroform. The extract was concentrated and chromatographed on a Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate to give crystals, which were recrystallized from benzene to give *2-acetyl-7-aminotropone* (7) as yellow needles (90 mg 60%); m.p. 126—127 °C; $\nu_{max.}$ ($CHCl_3$) 3 505, 3 348 (NH_4), 1 698 ($COCH_3$), and 1 600 cm^{-1} (tropone C=O); δ ($CDCl_3$) 2.60 (s, 3 H, CH_3), 6.4 (br, 2 H, NH_2), 6.5—7.4 (m, 3 H, H-4, -5, -6), and 7.61 (dd, 1 H, *J* 8.1 and 1.4 Hz, H-3) (Found: C, 66.25; H, 5.7; N, 8.6. C_9H_9NO requires C, 66.25; H, 5.55; N, 8.6%).

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