Reactions of 3-Acetyltropolone Methyl Ethers with 1,2-Cyclohexanediamine

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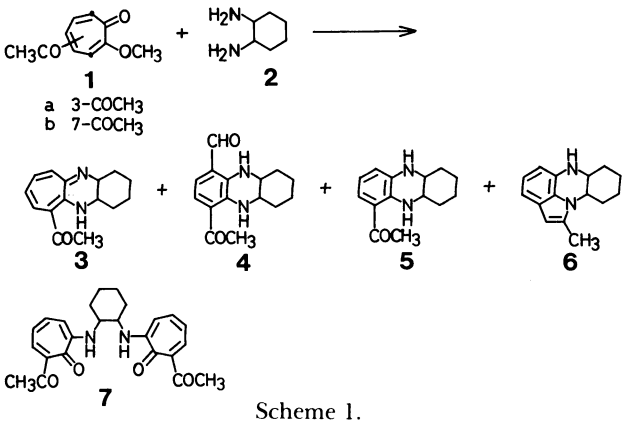
Synopsis. 3-Acetyl-2-methoxytropone reacted with 1,2-cyclohexanediamine (**2**) (a mixture of *cis* 60% and *trans* 40%) to give four *cis-trans* pairs of 6-acetyl-5*H*-1,2,3,4,4a,11a-hexahydrocyclohepta[*b*]quinoxaline (**3**), 6-acetyl-9-formyl-1,2,3,4,4a,5,10,10a-octahydrophenazine (**4**), 6-acetyl-1,2,3,4,-4a,5,10,10a-octahydrophenazine (**5**), and 1-methyl-6*H*-6a,7,8,-9,10,10a-hexahydropyrrolo[3,2,1-*de*]phenazine (**6**). The reaction of 2-acetyl-7-methoxytropone with **2** gave *cis*- and *trans*-*N,N'*-bis(6-acetyl-7-oxo-1,3,5-cycloheptatrienyl)-1,2-cyclohexanediamine, besides the above products. The *cis*- and *trans*-isomers of **4**, **5**, and **6** were secondary products from the *cis*- and *trans*-isomers of **3**, respectively.

Recently, we found and reviewed that 3-acetyltropolone and its methyl ethers reacted with a variety of nucleophilic reagents having two functional groups to give heterocycle-fused troponoid compounds.[1] On the extension of this series, we carried out the reactions with 1,2-alkanediamines in order to obtain diazaheptalene derivatives.[2] However, the desired compounds were not isolated, but 1*H*-2,3-dihydrocyclohepta[*b*]pyrazine derivatives and some rearrangement products were obtained.[2] In this paper, we describe the reactions of 3-acetyltropolone methyl ethers with 1,2-cyclohexanediamine.



Scheme 1.

A solution of 3-acetyl-2-methoxytropone (**1a**) and an equimolar amount of 1,2-cyclohexanediamine (**2**) (a mixture of *cis* 60% and *trans* 40%) in methanol was refluxed for 2 h to afford *cis*- and *trans*-6-acetyl-5*H*-1,2,3,4,4a,11a-hexahydrocyclohepta[*b*]quinoxaline [**3a** (44%) and **3b** (27%)], *cis*- and *trans*-6-acetyl-9-formyl-1,2,3,4,4a,5,10,10a-octahydrophenazine [**4a** and **4b** (mix. 1%)], *cis*- and *trans*-6-acetyl-1,2,3,4,4a,5,10,10a-octahydrophenazine [**5a** and **5b** (mix. 1%)], and *cis*- and *trans*-1-methyl-6*H*-6a,7,8,9,10,10a-hexahydropyrrolo[3,2,1-*de*]phenazine [**6a** (5%) and **6b** (3%)]. The structures were determined by their elemental analyses and spectral data, which were analogous with those of previously reported compounds.[2]

Refluxing of **1a** with five molar amounts of the diamine (**2**) caused remarkable decreases of the yields of **3a** (19%) and **3b** (3%). Instead, the yields of the by-products increased [**4a** (8%), **4b** (5%), **5a** (3%), **5b** (2%), **6a** (12%), and **6b** (7%)]. This result suggested that the compounds (**4a**, **4b**, **5a**, **5b**, **6a**, and **6b**) were secondary products from the compounds (**3a** and **3b**).

A solution of **3a** in methanol was refluxed for 21 h in the presence of the diamine (**2**) gave **4a** (26%), **5a** (7%), and **6a** (36%). The same treatment of **3b** with the diamine (**2**) also gave **4b** (16%), **5b** (10%), and **6b** (24%).

When a mixture of 2-acetyl-7-methoxytropone (**1b**) and an equimolar amount of **2** was refluxed for 2 h, dimeric products—*cis*- and *trans*-*N,N'*-bis(6-acetyl-7-oxo-1,3,5-cycloheptatrienyl)-1,2-cyclohexanediamine (**7a** and **7b**) were obtained in 10 and 7% yields, respectively, besides **3a** (13%) and **3b** (10%). Furtheremore, the prolonged reaction (24 h) gave five pairs of *cis*- and *trans*-isomers [**3a** (55%), **3b** (15%), **4a** and **4b** (mix. 2%), **5a** and **5b** (mix. trace), **6a** (1%), and **6b** (0.5%)].

Experimental

Measurements. The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The HPLC separations were performed on an Altex 330/110A/153 apparatus with a HY-ODS column. The IR and UV spectra were taken on a JASCO IRA-1 and a Hitachi EPS-3T spectrophotometer, respectively. The ^{1}H NMR spectra were recorded with a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz). The high-resolution mass spectra were obtained with a JEOL JMS-DX-300 apparatus.

Material. 1,2-Cyclohexanediamine (purchased from Tokyo Kasei Co., Ltd.) is a mixture of approximately 60% of *cis*- and 40% of *trans*-isomer.

*Reaction of 3-Acetyl-2-methoxytropone (**1a**) with 1,2-Cyclohexanediamine (**2**).* A mixture of 3-acetyl-2-methoxytropone (**1a**) (178 mg, 1.0 mmol) and 1,2-cyclohexanediamine (**2**) (0.1 ml, 1.0 mmol) in methanol (10 ml) was refluxed for 2 h. After removal of the solvent, the residue was four times chromatographed on a Wakogel B-10 plate (30×30 cm^2) with benzene. The first fraction was collected and recrystallized from hexane to give 12 mg (5%) of *cis*-1-methyl-6*H*-6a,7,8,9,10,10a-hexahydropyrrolo[3,2,4-*de*]-phenazine (**6a**) as colorless plates; mp 149—150°C; IR ($CHCl_3$) 3380 cm^{-1} (NH); UV (CH_3OH) 226 (log ε 4.47), 283 (3.94), 295 nm (sh, 3.91); NMR ($CDCl_3$) δ=1.1—2.2 (8H, m, CH_2×4), 2.37 (3H, s, CH_3), 3.20 (1H, br, NH), 3.5—3.8 (1H, m, CH), 3.8—4.4 (1H, m, CH), 6.02 (1H, s, H-2), 6.18 (1H, dd, *J*=6, 3 Hz, H-5), 6.78 (1H, dd, *J*=8, 6 Hz, H-4), 6.84 (1H, dd, *J*=8, 3 Hz, H-3). Found: *m/e* 226.1446 (M$^+$). Calcd for $C_{15}H_{18}N_2$: M, 226.1470. The third fraction was recrystallized from hexane to give 8 mg (3%) of *trans*-1-methyl-6*H*-6a,7,8,9,10,10a-hexahydropyrrolo[3,2,1-*de*]phenazine (**6b**) as colorless prisms; mp 195—196°C; IR ($CHCl_3$) 3370 cm^{-1} (NH); UV (CH_3OH) 227 (log ε 4.41), 280 nm (3.91); NMR ($CDCl_3$) δ=1.1—2.2 (8H, m, CH_2×4), 2.43 (3H, s, CH_3), 2.6—3.4 (1H, m, CH), 3.45 (1H, br, NH), 3.4—4.1 (1H, m, CH), 6.07 (1H, s, H-2), 6.23 (1H, dd, *J*=5, 3 Hz, H-5), 6.82 (1H, dd, *J*=8.5, 5 Hz, H-4), 6.87 (1H, dd, *J*=8.5, 3 Hz, H-3). Found: *m/e* 226.1458 (M$^+$). Calcd for $C_{15}H_{18}N_2$: M,

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226.1470. The second fraction gave 3 mg (1%) of a mixture of *cis*- and *trans*-6-acetyl-9-formyl-1,2,3,4,4a,5,10,10a-octahydrophenazine (**4a** and **4b**), which was separated by the HPLC method (eluent: 70% methanol) to *cis*- and *trans*-isomers (**4a**:**4b**=5:3). **4a**: Red needles (from methanol-water); mp 103—104.5 °C; IR ($CHCl_3$) 3280 (NH), 1655 (acetyl C=O), 1640 cm^{-1} (formyl C=O); UV (CH_3OH) 241 (log ε 4.24), 272 (sh, 3.96), 339 (4.05), 492 nm (3.78); NMR ($CDCl_3$) δ=1.1—2.2 (8H, m, $CH_2\times4$), 2.50 (3H, s, CH_3), 3.3—3.8 (2H, m, $CH\times2$), 6.64 (1H, d, J=8.5 Hz, H-7), 6.90 (1H, d, J=8.5 Hz, H-8), 8.54 (1H, br, NH-10), 9.03 (1H, br, NH-5), 9.73 (1H, s, CHO). Found: *m/e* 258.1363 (M^+). Calcd for $C_{15}H_{18}N_2O_2$: M, 258.1368. **4b**: Red needles (from methanol-water); mp 88—90 °C; IR ($CHCl_3$) 3280 (NH), 1655 (acetyl C=O), 1640 cm^{-1} (formyl C=O); UV (CH_3OH) 240 (log ε 4.21), 274 (3.96), 327 (3.99), 488 nm (3.72); NMR ($CDCl_3$) δ=1.0—2.3 (8H, m, $CH_2\times4$), 2.54 (3H, s, CH_3), 2.7—3.2 (2H, m, $CH\times2$), 6.70 (1H, d, J=8.5 Hz, H-7), 6.96 (1H, d, J=8.5 Hz, H-8), 8.42 (1H, br, NH-10), 8.94 (1H, br, NH-5), 9.73 (1H, s, CHO). Found: *m/e* 258.1389 (M^+). Calcd for $C_{15}H_{18}N_2O_2$: M, 258.1368. The fourth fraction gave 3 mg (1%) of a mixture of *cis*- and *trans*-6-acetyl-1,2,3,4,-4a,5,10,10a-octahydrophenazine (**5a** and **5b**), which was separated on a TLC plate with benzene to *cis*- and *trans*-isomers, (**5a**:**5b**=2:1). **5a**: A yellow oil; IR ($CHCl_3$) 3300 (NH), 1635 cm^{-1} (C=O); UV (CH_3OH) 264 (log ε 3.90), 422 nm (3.58); NMR ($CDCl_3$) δ=1.1—2.2 (8H, m, $CH_2\times4$), 2.51 (3H, s, CH_3), 3.40 (1H, br, NH-5), 3.2—3.8 (2H, m, $CH\times2$), 6.37 (1H, dd, J=8, 8 Hz, H-8), 6.50 (1H, dd, J=8, 2 Hz, H-9), 7.14 (1H, dd, J=8, 2 Hz, H-7), 8.75 (1H, br, NH-10). Found: *m/e* 230.1471 (M^+). Calcd for $C_{14}H_{18}N_2O$: M, 230.1419. **5b**: Yellow needles (from hexane); mp 95—96 °C; IR ($CHCl_3$) 3300 (NH), 1635 cm^{-1} (C=O); UV (CH_3OH) 262 (log ε 4.06), 417 nm (3.74); NMR ($CDCl_3$) δ=0.8—3.4 (10H, m, $CH_2\times4+CH\times2$), 2.51 (3H, s, CH_3), 3.50 (1H, br, NH-5), 6.37 (1H, dd, J=8, 8 Hz, H-8), 6.52 (1H, dd, J=8, 2.5 Hz, H-9), 7.15 (1H, dd, J=8, 2.5 Hz, H-7), 8.58 (1H, br, NH-10). Found: C, 72.95; H, 8.07; N, 12.21%. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16%. The fifth fraction was collected and rechromatographed on a TLC palte to give *cis*- and *trans*-6-acetyl-5*H*-1,2,3,4,4a, 11a-hexahydrocyclohepta[*b*]quinoxaline [**3a** (106 mg, 44%) and **3b** (66 mg, 27%)]. **3a**: Yellow prisms (from benzene-hexane); mp 117-119 °C; IR ($CHCl_3$) 3160 (NH), 1600 cm^{-1} (C=O); UV (CH_3OH) 255 (log ε 4.30), 390 (3.83), 454 nm (4.03): NMR ($CDCl_3$) δ=1.0—2.1 (8H, m, $CH_2\times4$), 2.48 (3H, s, CH_3), 3.3—4.0 (2H, m, $CH\times2$), 5.81 (1H, ddd, J=11, 5.5, 3 Hz, H-8), 6.2—6.8 (2H, m, H-9, 10), 6.90 (1H, d, J=11 Hz, H-7), 12.2 (1H, br, NH). Found: C, 74.54; H, 7.44; N, 11.68%. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56%. **3b**: A yellow semisolid; IR ($CHCl_3$) 3160 (NH), 1600 cm^{-1} (C=O); UV (CH_3OH) 255 (log ε 4.11), 390 (3.65), 448 nm (3.81); NMR ($CDCl_3$) δ=0.9—3.3 (10H, m, $CH_2\times4+CH\times2$), 2.42 (3H, s, CH_3), 5.87 (1H, ddd, J=11, 6, 2.5 Hz, H-8), 6.2—6.8 (2H, m, H-9,10), 6.89 (1H, d, J=11 Hz, H-7), 11.9 (1H, br, NH). Picrate: Mp 182—183 °C. Found: C, 53.89; H, 4.52; N, 14.82%. Calcd for $C_{21}H_{21}N_5O_8$: C, 53.50; H, 4.49; N, 14.86%.

*Reaction of 2-Acetyl-7-methoxytropone (**1b**) with 1,2-Cyclohexanediamine (**2**).* A solution of 2-acetyl-7-methoxytropone (**1b**) (178 mg, 1.0 mmol) and 1,2-cyclohexanediamine (**2**) (0.1 ml, 1.0 mmol) in methanol (10 ml) was refluxed for 2 h. After removal of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30×30 cm^2) with ethyl acetate. The first fraction gave 70 mg of *cis*- and *trans*-*N,N'*-bis(6-acetyl-7-oxo-1,3,5-cycloheptatrienyl)-1,2-cyclohexanediamine (**7a** and **7b**), which was separated by the HPLC method (eluent: 60% methanol) to *cis* and *trans*-isomers (**7a**:**7b**=7:5). **7a**: A yellow oil; IR ($CHCl_3$) 3250 (NH), 1695 (acetyl C=O), 1595 cm^{-1} (tropone C=O); UV (CH_3OH) 248 (log ε 4.43), 355 (4.05), 421 nm (4.21); NMR ($CDCl_3$) δ=1.3—2.2 (8H, m, $CH_2\times4$), 2.48 (6H, s, $CH_3\times2$), 3.9—4.4 (2H, m, $CH\times2$), 6.4—7.7 (8H, m, aromatic H), 7.76 (2H, br. d, J=8 Hz, $NH\times2$). Found: *m/e* 406.1883 (M^+). Calcd for $C_{24}H_{26}N_2O_4$: M, 406.1893. **7b**: Yellow brown crystals (from benzene-hexane); mp 111-113 °C; IR ($CHCl_3$) 3240 (NH), 1695 (acetyl C=O), 1595 cm^{-1} (tropone C=O); UV (CH_3OH) 249 (log ε 4.46), 358 (4.06), 421 nm (4.20); NMR ($CDCl_3$) δ =1.1—2.4 (8H, m, $CH_2\times4$), 2.44 (6H, s, $CH_3\times2$), 3.5—4.1 (2H, m, $CH\times2$), 6.3—7.6 (8H, m, aromatic H), 7.70 (2H, br. d, J=6 Hz, $NH\times2$). Found: *m/e* 406.1869 (M^+). Calcd for $C_{24}H_{26}N_2O_4$: M, 406.1893. The second and third fractions gave **3b** (23 mg, 10%) and **3a** (32 mg, 13%), respectively.

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