Reactions of 3-Acetyltropolone Methyl Ethers with *o*-Phenylenediamine. Formation of Cyclohepta[*b*][1,5]benzodiazepine

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Reactions of 3-acetyltropolone methyl ethers with *o*-phenylenediamine are described. 3-Acetyl-2-methoxytropone (**2a**) with *o*-phenylenediamine in ethanol under reflux condition to afford 11-hydroxy-6-methylcyclohepta[*b*][1,5]benzodiazepine (**4**), 10-acetyl-6*H*-cyclohepta[*b*]quinoxaline (**5**), and 6-acetyl-5*H*-cyclohepta[*b*]-quinoxaline (**6**). The same reaction of 7-acetyl-2-methoxytropone (**2b**) gave 7-acetyl-2-(2-aminoanilino)-tropone (*3b*) besides **4**, **5**, and **6**. The compound **4** has a 1,4-diazaheptalene skeleton.

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It is well known that the reactions of 2-methoxytropones or 2-chlorotropones with *o*-phenylenediamine and *o*-aminobenzenethiol give 6*H*-cyclohepta[*b*]quinoxalines (1,2) and cyclohepta[*b*][1,4]benzothiazines (3), respectively, which are heterocyclic compounds containing two heteroatoms. Furthermore, the formation of cyclohepta[*b*][1,4]-benzoxazines by the reactions of reactive troponoids with *o*-aminophenol was also reported (4).

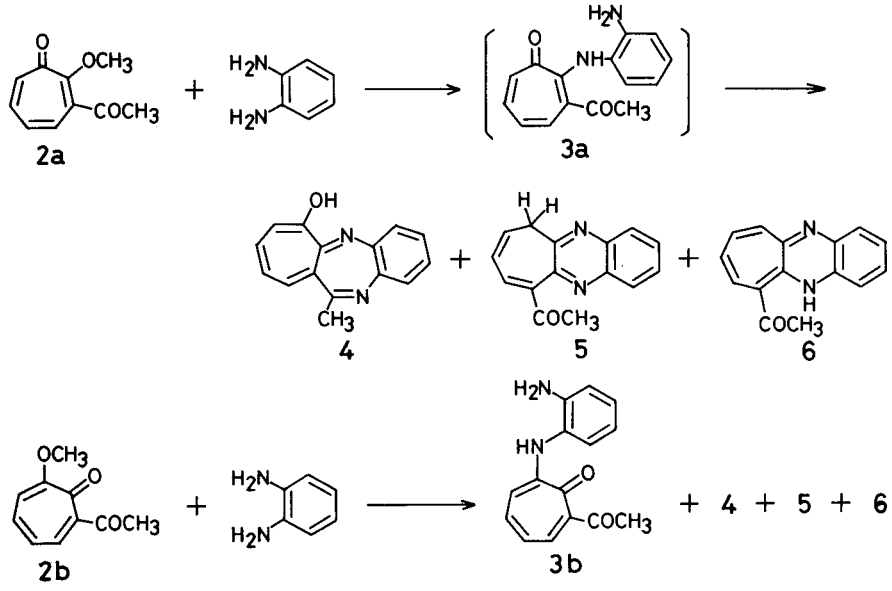
Recently, we obtained 3-acetyltropolone (**1**) by the treatment of 3-isopropenyltropolone with hydrazoic acid (5). This 3-acetyltropolone (**1**) is very useful as starting material for synthesis of heterocycle-condensed troponoid compounds. Thus, previously we reported that the reactions of 3-acetyltropolone (**1**) and its methyl ethers (**2a** and **2b**) with hydrazine (5), methylhydrazine (6), and phenylhydrazine (7) gave some cycloheptapyrazole derivatives.

Now, we wish to report the reactions of 3-acetyltropolone methyl ethers (**2a** and **2b**) with *o*-phenylenediamine.

Results and Discussion.

Reaction of 3-Acetyl-2-methoxytropone (**2a**) with *o*-Phenylenediamine.

At first, a mixture of 3-acetyltropolone (**1**) and *o*-phenylenediamine was refluxed, but no product was isolated. Heating of 3-acetyl-2-methoxytropone (**2a**) with *o*-phenylenediamine in ethanol under reflux for 1 hour gave two isomeric compounds **4** (m.p. 125-128°) and **5** (m.p. 122-123°) in 14 and 8% yields, respectively. From elemental analysis ($C_{15}H_{12}N_2O$), the mass-spectral determination of molecular weight (m/e M^+ 236), and other spectral data, the compound (**4**) was determined to be 11-hydroxy-6-methylcyclohepta[*b*][1,5]benzodiazepine. The ir spectrum shows no acetyl carbonyl absorption at near 1700 cm^{-1}. The ^1H nmr spectrum shows peaks at δ 2.20 (s, 3H) for CH_3, 4.96 (ddd, 1H, J = 12, 6, 3 Hz) for 9-H, 5.59 (d, 1H, J = 3 Hz) for 7-H, 5.61 (d, 1H, J = 6 Hz) for 10-H, 5.95 (d, 1H, J = 12 Hz) for 8-H, 6.5-7.0 (m, 4H) for 1- to 4-H, and



Scheme I

0022-152X/81/020335-04$02.25

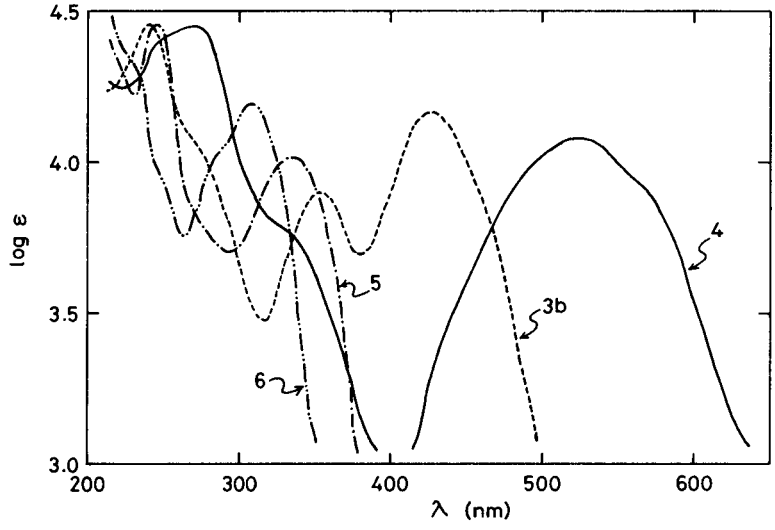
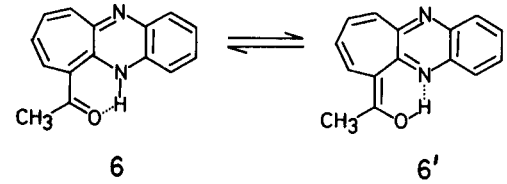


Fig. 1. Electronic Spectra in CH_3OH

15.9 ppm (br, s, 1H) for OH. The uv spectrum shows a band at very long wavelength region (Figure 1). Consequently, it is thought that the compound **4** has a diazaheptalene moiety. On the other hand, the compound (**5**) was assigned to 10-acetyl-6*H*-cyclohepta[*b*]quinoxaline from its elemental analysis ($C_{15}H_{12}N_2O$) and spectral data. The ir spectrum shows strong absorption at 1705 cm^{-1} for the acetyl carbonyl group. The ^1H nmr spectrum shows peaks at δ 2.51 (s, 3H) for $COCH_3$, 3.6-3.7 (m, 2H) for 6-CH_2, 6.2-6.8 (m, 2H) for 7- and 8-H, and 7.4-8.2 ppm (m, 5H) for 1- to 4-H and 9-H. The uv spectrum is very similar to that of 6*H*-cyclohepta[*b*]quinoxaline (1,2).

The prolonged reaction (24 hours) of **2a** with *o*-phenylenediamine afforded 6-acetyl-5*H*-cyclohepta[*b*]quinoxaline (**6**) (m.p. 233-234°) as a major product (yield 33%) together with traces of **4** and **5**. The ir spectrum of the product (**6**) shows absorption at 3200 for NH and 1710 cm^{-1} for the acetyl group. The ^1H nmr spectrum in deuteriochloroform shows two singlet peaks at δ 1.91 and 2.44 ppm for $=\underset{\underset{OH}{|}}{C}\text{-}CH_3$ and $\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_3$ protons, respectively, and multiplet at δ 6.8-7.6 ppm for six- and seven-membered ring protons. The two singlet peaks indicate that the compound **6** exists as a tautomer between structures **6** and **6′**. The ratio of **6′** to **6** is *ca.* 3:1 in deuteriochloroform, *ca.* 2:1 in methanol-d_4, and *ca.* 3:4 in DMSO-d_6 as shown in Figure 2. Furthermore, the ^{13}C nmr spectrum of **6** in DMSO-d_6 shows a peak at δ 202 ppm for the acetyl C=O group, whereas the spectrum in deuteriochloroform shows no peak for the acetyl C=O group. These results reveal that the enol-form (**6′**) is predominant in less polar solvents and the keto-form (**6**) is predominant in more polar solvent. The compound **6** has



the tautomeric structure of the compound **5**. However, we cannot observe the tautomerism between them.

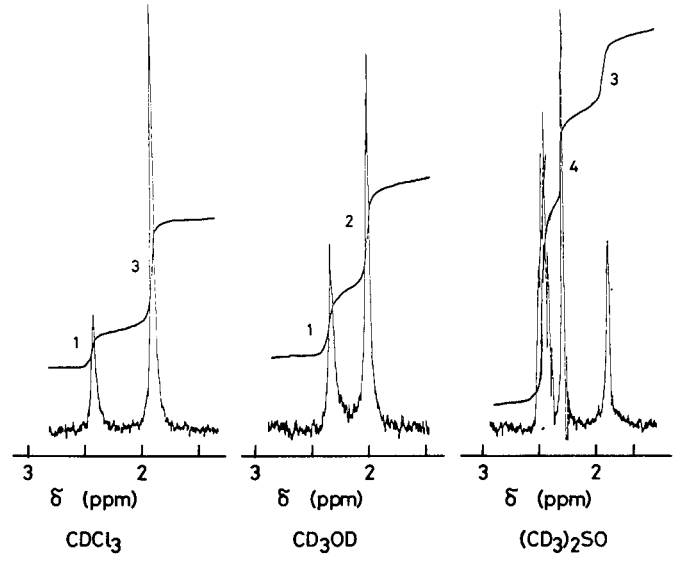


Fig. 2. ^1H-NMR Spectra of **6** in Various Solvents

It is considered that the compounds **4**, **5**, and **6** are formed *via* 3-acetyl-2-(2-aminoanilino)tropone (**3a**). However, **3a** was not isolated because the *o*-aminoanilino

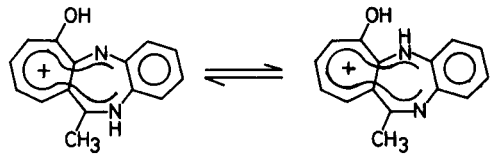
group exists at the C_2-position and immediately reacts with the acetyl group to afford **4**, and the tropone carbonyl group at the C_1-position to afford **5** and **6**.

Reaction of 7-Acetyl-2-methoxytropone (**2b**) with *o*-Phenylenediamine.

Refluxing of a mixture of 7-acetyl-2-methoxytropone (**2b**) and *o*-phenylenediamine in ethanol for 1 hour gave 7-acetyl-2-(2-aminoanilino)tropone (**3b**) together with trace amounts of **4** and **5**. The ir spectrum of **3b** shows absorptions at 3460 and 3380 for NH_2, 1700 for $COCH_3$, and 1598 cm^{-1} for the tropone carbonyl group. The uv spectrum is very similar to that of 2-anilinotropone (8). The reaction was continued for 24 hours to afford **3b**, **4**, **5**, and **6** in 7, 7, 11, and 24% yields, respectively. Thus, it is thought that the product (**3b**) is a precursor to **4**, **5**, and **6**. In fact, a solution of **3b** in ethanol was refluxed for 24 hours to give **4**, **5**, and **6** in 4, 9, and 29% yields, respectively. These yields are almost comparable to those of the reaction of the methyl ether (**2b**) with *o*-phenylenediamine.

^1H Nmr Spectra in Trifluoroacetic Acid.

The ^1H nmr spectrum of the compound (**4**) in trifluoroacetic acid, which exists as a cation, shows peaks at δ 2.54 (s, 3H) for CH_3, 5.7-6.1 (m, 2H) for 8- and 9-H, 6.4-7.0 (m, 5H) for 1- to 4-H and 7-H, and 7.26 ppm (d, 1H, J = 11 Hz) for 10-H. These data indicate shifts of the seven-membered ring protons by 0.8-1.3 ppm and that of the methyl protons by 0.34 ppm towards lower magnetic field. The benzene ring protons hardly show any shift. Thus, the positive charge of the cation is delocalized over both the seven-membered ring and the diazepine ring and is not delocalized over the benzene ring.



4′ 4″

The spectrum of **5** in trifluoroacetic acid is identical with that of **4** in the same solvent. Then, a trifluoroacetic acid solution of **5** was diluted with water and extracted with chloroform to give dark violet crystals, whose spectrum in deuteriochloroform is also consistent with that of an authentic substance (**4**).

UV Spectra.

The uv spectra of **3b**, **4**, **5** and **6** are shown in Figure 1, those in acidic medium being shown in Figure 3. The spectra of both **3b** and **5** in acidic medium agree perfectly with that of **4** in the same solvent. This indicates that **3b** and **5** are readily converted into **4**.

EXPERIMENTAL

The melting points 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 ^1H nmr spectra were recorded with a Hitachi R-24 spectrometer (60 MHz) and the ^{13}C nmr spectra with a JEOL JNM-FX-100 spectrometer (100 MHz). The mass spectra were run on a JEOL JMS-01-SG-2 spectrometer.

Reaction of 3-Acetyl-2-methoxytropone (**2b**) with *o*-Phenylenediamine. a)

A mixture of 3-acetyl-2-methoxytropone (**2a**) (720 mg. 4 mmoles) and *o*-phenylenediamine (860 mg., 8 mmoles) in absolute ethanol (40 ml.) was

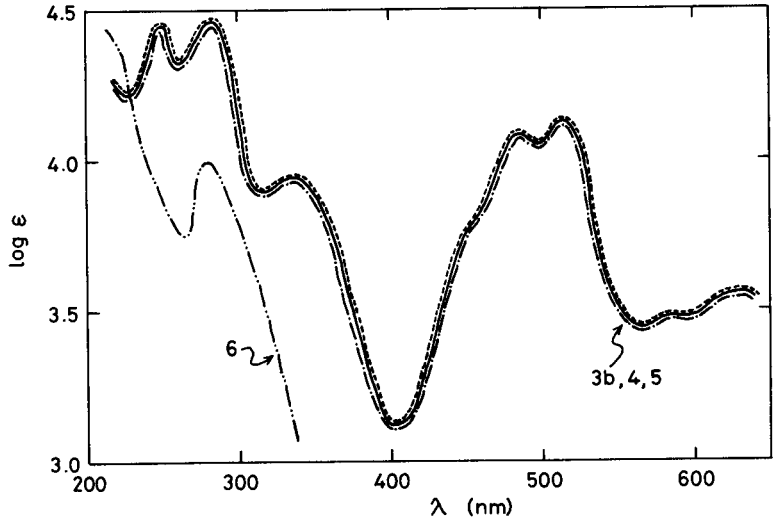


Fig. 3. Electronic Spectra in HCl/CH_3OH

refluxed for 1 hour. After evaporation of the solvent, the residue was chromatographed of five Wakogel B-10 plates (30 x 30 cm^2) with chloroform to afford two fractions. Crystals from the upper band was recrystallized from hexane to give 11-hydroxy-6-methylcyclohepta[*b*][1,5]-benzodiazepine (**4**) as dark red crystals (137 mg., 14%), m.p. 125-128°; ir (chloroform): ν max 1605, 1585 cm^{-1}; uv (methanol): λ max 265 (log ϵ 4.45), 330 sh (3.79), 526 (4.08), 564 sh nm (3.76); ^{1}H nmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3) 4.96 (ddd, H, J = 12, 6, 3 Hz, 9-H), 5.59 (d, 1H, J = 3 Hz, 7-H), 5.61 (d, 1H, J = 6 Hz, 10-H), 5.95 (d, 1H, J = 12 Hz, 8-H), 6.5-7.0 (m, 4H, 1- to 4-H), 15.9 ppm (br, 1H, OH); m/e 236 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.02; H, 5.03; N, 11.94.

A fraction from the lower band was rechromatographed on a Wakogel B-10 plate (30 x 30 cm^2) with ether and recrystallized from hexane to give 10-acetyl-6*H*-cyclohepta[*b*]quinoxaline (**5**) as colorless crystals (75 mg., 8%), m.p. 122-123°; ir (chloroform): ν max 1705 cm^{-1}; uv (methanol) λ max 247 (log ϵ 4.46), 280 sh (3.77), 338 nm (4.03); ^{1}H nmr (deuteriochloroform): δ 2.51 (s, 3H, CH_3), 3.6-3.7 (m, 2H, 6-CH_2), 6.2-6.8 (m, 2H, 7- and 8-H), 7.4-8.2 ppm (m, 5H).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.31; H, 5.04; N, 11.65.

b).

A solution of methyl ether (**2a**) (178 mg., 1 mmole) in absolute ethanol (20 ml.) was refluxed with *o*-phenylenediamine (211 mg., 2 mmoles) for 24 hours. After evaporation of the solvent, the residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm^2) with chloroform to afford **4** (trace) and **5** (trace) from the first and second fractions, respectively. The third fraction was recrystallized from benzene to give 6-acetyl-5*H*-cyclohepta[*b*]quinoxaline (**6**) as colorless needles (70 mg., 33%), m.p. 233-234°; ir (chloroform): ν max 3200, 1710 cm^{-1}; uv (methanol): λ max 232 sh (log ϵ 4.31), 248 sh (3.97), 257 sh (3.82), 312 (4.20), 325 nm (4.05); ^{1}H nmr (deuteriochloroform): δ 1.91 (s), 2.44 (s), 6.8-7.6 ppm (m); m/e 236 (M^+).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.29; H, 5.13; N, 11.89.

Reaction of 7-Acetyl-2-methoxytropone (**2b**) with *o*-Phenylenediamine.

a)

A mixture of 7-acetyl-2-methoxytropone (**2b**) (356 mg., 2 mmoles) and *o*-phenylenediamine (430 mg., 4 mmoles) in absolute ethanol (20 ml.) was heated under reflux for 1 hour. The evaporation residue was chromatographed on two Wakogel B-10 plates (30 x 30 cm^2) with chloroform to afford **4** (trace) and **5** (trace) from the first fraction. The second fraction was also rechromatographed on a Wakogel B-10 plate (30 x 30 cm^2) with ether and recrystallized from benzene-hexane to afford 7-acetyl-2-(2-aminoanilino)tropone (**3b**) as orange prisms (313 mg., 58%), m.p. 105-106°; ir (chloroform): ν max 3460, 3380, 3260, 1700, 1598 cm^{-1}; uv (methanol): λ max 240 (log ϵ 4.46), 273 sh 4.06), 353 (3.91), 247 nm (4.17); ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, CH_3), 3.58 (s, 2H, NH_2), 6.5-7.4 (m, 7H), 7.62 (dd, 1H, J = 10, 2 Hz, 3-H), 8.7 ppm (br, 1H, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.93; H, 5.63; N, 11.14.

b)

Methyl ether (**2b**) (720 mg., 4 mmoles) was treated with *o*-phenylenediamine (824 mg., 7.6 mmoles) in absolute ethanol (40 ml.) under reflux for 24 hours. The evaporation residue was chromatographed on four Wakogel B-10 plates (30 x 30 cm^2) with chloroform. The first and second fractions were recrystallized from hexane to give **4** (62 mg., 7%) and **5** (108 mg., 11%), respectively. The third fraction was rechromatographed on a Wakogel B-10 plate (30 x 30 cm^2) with ether to afford two fractions, which were recrystallized from benzene and benzene-hexane to afford **3b** (71 mg., 7%) and **6** (225 mg., 24%), respectively.

Cyclization of 7-Acetyl-2-(2-aminoanilino)tropone (**3b**).

A solution of **3b** (224 mg., 1 mmole) in absolute ethanol (15 ml.) was refluxed for 24 hours and worked up, as mentioned above, to afford **4** (10 mg., 4%), **5** (21 mg., 9%), and **6** (70 mg., 29%).

Acknowledgement.

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REFERENCES AND NOTES

(1) T. Nozoe, Y. Kitahara, K. Takase and M. Sasaki, *Proc. Jpn. Acad.*, **32**, 349 (1956).

(2) T. Fukunaga, 23 th IUPAC Congress, Boston (1971).

(3) T. Nozoe, T. Asao and K. Takahashi, *Bull. Chem. Soc. Japan* **34**, 146 (1961); *ibid.*, **39**, 1980 (1966).

(4a) A. Nozoe, H. Okai and T. Someya, *ibid.*, **51**, 2185 (1978); (b) T. Nozoe and T. Someya, *ibid.*, **51** 3316 (1978); (c) T. Nozoe, T. Someya, *ibid.*, **52**, 3123 (1979).

(5) A. Yamane, M. Nagayoshi, K. Imafuku and H. Matsumura, *ibid.*, **52**, 1972 (1979).

(6) A. Yamane, K. Imafuku and H. Matsumura, *ibid.*, **53**, 1461 (1980).

(7) K. Imafuku, A. Yamane and H. Matsumura, *J. Heterocyclic Chem.*, **17**, 1293 (1980).

(8) S. Iseda, *Bull. Chem. Soc. Japan*, **28**, 617 (1955).