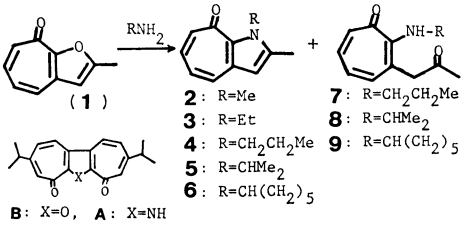
The Preparation of Pyrrolotropones from Furotropones

Hitoshi TAKESHITA,* Atsuko CHISAKA, and Hiroaki MAMETSUKA
Research Institute of Industrial Science, 86, Kyushu University, Hakozaki, Fukuoka 812
(Received March 18, 1980)

Synopsis. Furotropones were transformed into a series of pyrrolotropones by heating with amines. The methine proton of 1-isopropyl-2-methylcyclohepta[1,2-*b*]-pyrrol-8-one was found to appear at an unusually low field.

Recently, we have developed a new method of synthesizing furotropones, 8*H*-cyclohepta[1,2-*b*]furan-8-ones,[1] and difurotropones, 6*H*-cyclohepta[1,2-b:3,4-b']difuran-6-ones.[2] This prompted us to investigate a new method of synthesizing pyrrolotropones,[3,4] 8*H*-cylohepta[1,2-*b*]pyrrol-8-ones, by condensation with amines.[5]

2-Methyl-8*H*-cyclohepta[1,2-*b*]furan-8-one (**1**)[6] was heated with methylamine in a sealed tube to give a single product (**2**). The NMR spectra of **2** clearly showed it to be 1,2-dimethyl-8*H*-cyclohepta[1,2-*b*]pyrrol-8-one. Similarly, products (**3**, **4**, **5**, and **6**) were obtained from reaction with ethylamine, propylamine, isopropylamine, and cyclohexylamine respectively. When bulky amines were used, 2-alkylamino-3-(2-oxopropyl)tropones (**7**, **8**, and **9**) were obtained as by-products. However, **1** did not react with ammonia or *t*-butylamine under comparable conditions.



The structures of these products were deduced from their NMR spectra. The signal arising from the methine proton of the isopropyl group of 1-isopropyl-2-methyl-8*H*-cyclohepta[1,2-*b*]pyrrol-8-one (**5**) was found to appear at an unusually low field (δ[7]: 6.33).

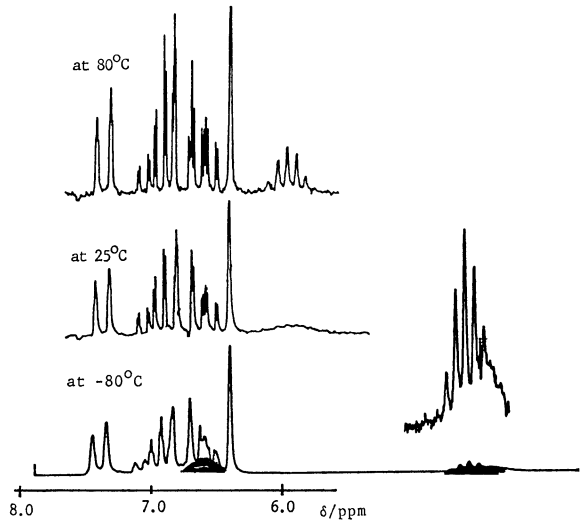
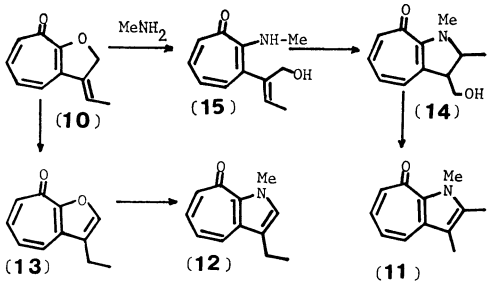


Fig. 1. The temperature dependent NMR spectrum of **5**.

Moreover, although the methine proton appeared as a broad and unsolved signal at room temperature, it became a sharp septet (J=7 Hz) at 80 and 120 °C with almost the same chemical shift (Fig. 1). This extraordinary low-field shift can be explained in terms of the anisotropy of the carbonyl group, which is in the near vicinity of the methine group. This was further confirmed by a low-temperature measurement of the NMR spectrum; although above −40 °C, the NMR features were not very different, at −80 °C, the NMR disclosing the presence of the isomerism by showing pairs of signals, isopropyl methyl doublets, vinyl methyl singlets, and the methine broad multiplets [$\delta^{(CD_3)_2CO}$: 4.7 and 6.6], in a ratio of *ca.* 1:2.[8]

On the other hand, although the methine proton of the 1-cyclohexyl derivative (**6**) could not be identified in the room-temperature NMR spectrum, it was observed as a very broad multiplet at δ *ca.* 5.9 by heating the sample over 80 to 120 °C. Furthermore, a pair of broad, methine-proton signals due to the occurrence of rotational isomerism, as well as other signals, began to appear at $\delta^{(CD_3)_2CO}$: 4.6 and 6.4 (1:2) at −80 °C. The behavior is thus the same as that of **5**.

As we have mentioned, **1** was unreactive with ethanolic ammonia. However, we thought that a dihydrofurotropone, 3-ethylidene-2,3-dihydro-8*H*-cyclohepta[1,2-*b*]furan-8-one (**10**), might be more reactive than the fully conjugated furans such as **1**. Again, no reaction took place when **10** was heated with ethanolic ammonia in a sealed tube, but we found that, with methylamine, **10** yielded, when heating at 100 °C, 1,2,3-trimethylcyclohepta[1,2-*b*]pyrrol-8-one (**11**), 3-ethyl-1-methylcyclohepta[1,2-*b*]pyrrol-8-one (**12**), 3-ethylcyclohepta[1,2-*b*]furan-8-one (**13**), and two other by-products, 3-hydroxymethyl-1,2-dimethyl-2,3-dihydrocyclohepta[1,2-*b*]pyrrol-8-one and 2-methylamino-3(1-hydroxymethylpropen-1-yl)tropone (**14** and **15**). The **11**, product which was also obtained by the thermolysis of **14**, may be formed by the sequence depicted in Scheme 2.



Experimental

Reaction of **1** *with Methylamine.* A mixture of **1**[6] (80 mg) and methylamine (30% in water, 4 cm³) was heated in a sealed tube at 160 °C for 6 h. The mixture was then chromatographed on a silica-gel column, using hexane–

ethyl acetate as the eluent. The sole product identified was **2**; colorless needles; mp 76—77 °C (from hexane–benzene); 66 mg (76%) [Found: C, 76.29; H, 6.35; N, 8.00%. Calcd for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.00%. δ: 2.32 (3H, d, J=1 Hz), 4.14 (3H, s), 6.25 (1H, qm, J=1 Hz), 6.58 (1H, ddd, J=10.5, 5.5, 3.5 Hz), 6.97 (1H, dd, J=3.5, 1 Hz), 6.98 (1H, dd, J=5.5, 1 Hz), and 7.33 (1H, dt, J=10.5, 1 Hz)].

*Reaction of **1** with Ethylamine.* Similarly, a mixture of **1** (75 mg) and ethylamine (70% in water, 4 cm³) was heated in a sealed tube at 120 °C for 14 h to give **3** (colorless needles; mp 85—87 °C (from hexane–benzene); 57 mg (65%) [Found: C, 76.95; H, 7.08; N, 7.45%. Calcd for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48%. δ: 1.37 (3H, t, J=7 Hz), 2.41 (3H, s), 4.71 (2H, q, J=7 Hz), 6.33 (1H, s), 6.62 (1H, ddd, J=10.5, 5.5, 4.5 Hz), 7.0 (2H, m), and 7.36 (1H, dt, J=10.5, 1 Hz)]), together with a colorless oil (≈1 mg) which showed spectral features similar to those of uncyclized products, but no further characterization was carried out.

*Reaction of **1** with Propylamine.* A mixture of **1** (83 mg) and propylamine (33% in water, 4 cm³) was heated in a sealed tube at 160 °C for 24 h. Subsequently, silica gel chromatography of the mixture gave **7** (a colorless oil; 4.5 mg (4%) [Found: *m/e*, 219(M^+). δ: 1.05 (3H, t, J=7 Hz), 1.77 (2H, m), 2.28 (3H, s), 3.26 (2H, tm, J=7 Hz), 3.80 (2H, s), 6.54 (1H, dd, J=10, 1 Hz), 6.62 (1H, td, J=9.5, 1 Hz), 7.21 (1H, ddd, J=10, 8.5, 1 Hz), and 7.34 (1H, dd, J=9.5, 1 Hz)]) and **4** (colorless needles; mp 57—58 °C (from hexane–benzene); 89 mg (85%) [Found: C, 77.47; H, 7.53; N, 6.94%. Calcd for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96%. δ: 0.96 (3H, t, J=7 Hz), 1.77 (2H, m), 2.39 (3H, s), 4.59 (2H, t, J=7 Hz), 6.32 (1H, s), 6.61 (1H, ddd, J=10.5, 5.5, 4 Hz), 6.99 (2H, m), and 7.35 (1H, dt, J=10.5, 1 Hz)]).

*Reaction of **1** with Isopropylamine.* A mixture of **1** (85 mg) and isopropylamine (33% in water, 4 cm³) was heated in a sealed tube at 160 °C for 23 h to give **8** (a colorless oil; 21 mg (18%) [Found: *m/e*, 219 (M^+). δ: 1.30 (6H, d, J=7 Hz), 2.27 (3H, s), 3.77 (2H, s), 3.80 (1H, m), 6.52 (1H, dd, J=10.5, 1 Hz), 6.60 (1H, td, J=8, 1 Hz), 7.20 (1H, td, J=10.5, 1 Hz), and 7.33 (1H, dd, J=8, 1 Hz)]) and **5** (colorless needles; mp 78—79 °C (from hexane); 48 mg (45%) [Found: C, 77.17; H, 7.61; N, 6.55%. δ: 1.37 (6H, d, J=7 Hz), 2.51 (3H, d, J=1 Hz), 6.3 (1H, qm, J=1 Hz), 6.1—6.4 (1H, br. m), 6.60 (1H, ddd, J=10.5, 5, 4 Hz), 6.97 (2H, m), and 7.33 (1H, dt, J=10.5, 1 Hz)]).

*Reaction of **1** with Cyclohexylamine.* A neat mixture of **1** (96 mg) and cyclohexylamine (200 mg) was heated in a sealed tube at 160 °C for 6 h to give **9** (a colorless oil; 18 mg (12%) [Found: *m/e*, 259(M^+). δ: 1.1—2.2 (10H, m), 2.28 (3H, s), 3.45 (1H, m), 3.78 (2H, s), 6.57 (1H, dt, J=9, 1 Hz), 6.59 (1H, td, J=9, 1 Hz), 7.18 (1H, td, J=9, 1 Hz), 7.32 (1H, dd, J=9, 1 Hz), and 7.2—7.5 (1H, br., N*H*)]) and **6** (a colorless oil; 20 mg (14%) [Found: M.W., 241.1471. Calcd for $C_{16}H_{19}ON$: 241.1567. δ: 1.1—2.4 (11H, m), 2.53 (3H, d, J=1 Hz), 6.30 (1H, qm, J=1 Hz), 6.60 (1H, ddd, J=10.5, 5, 4.5 Hz), 6.98 (2H, m), and 7.33 (1H, dt, J=10.5, 1 Hz)]).

*Reaction of 3-Ethylidene-8H-2,3-dihydrocyclohepta[1,2-b]furan-8-one (**10**) with Methylamine.* A mixture of **10** (90 mg) and methylamine (30% in water, 4 cm³) was heated in a sealed tube at 100 °C for 4 h. The mixture was then diluted with water and extracted with ether. Subsequent silica gel column chromatography of the extracts gave **11** (pale yellow prisms; mp 106—107.5 °C (from hexane–methanol); 9.6 mg (9.9%) [Found: C, 76.85; H, 7.22; N, 7.33%. Calcd for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48%. δ: 2.23 (3H, s), 2.34 (3H, s), 4.20 (3H, s), 6.65 (1H, ddd, J=10.7, 6, 3 Hz), 6.9—7.1 (2H, m), and 7.43 (1H, dt, J=10.7, 1 Hz)]), **12** (pale yellow needles; mp 73—74 °C (from hexane–benzene); 5.2 mg (5.4%) [Found: 76.72; H, 6.90; N, 7.59%. δ: 1.26 (3H, t, J=7 Hz), 2.68 (2H, q, J=7 Hz), 4.20 (3H, s), 6.60 (1H, ddd, J=11, 7, 2.5 Hz), 6.85 (1H, s), 7.00 (2H, m), and 7.42 (1H, dt, J=11, 1 Hz)]), **14** (a yellow liquid; 75 mg (70%) [Found: M.W., 205.1103. Calcd for $C_{12}H_{15}O_2N$: 205.1103. δ: 1.28 (3H, d, J=6 Hz), 2.89 (1H, q, J=6 Hz), 3.16 (1H, br. m), 3.51 (3H, s), 3.70 (2H, d, J=6 Hz), 6.44 (1H, ddd, J=10, 8, 2 Hz), and 6.8—7.1 (3H, m)]), and **15** (a yellow liquid; 5.5 mg (5.3%) [Found: *m/e*, 205 (M^+). δ: 1.92 (3H, d, J=7 Hz), 3.06 (3H, d, J=5.5 Hz), 4.2 (2H, m), 4.5—4.8 (1H, br. s), 5.76 (1H, q, J=7 Hz), 6.57 (1H, d, J=10 Hz), 6.67 (1H, td, J=10, 1 Hz), 7.25 (1H, td, J=10, 1 Hz), 7.39 (1H, dd, J=10, 1 Hz), and 7.2—7.6 (1H, br., N*H*))].

*Thermal Dehydration of **14** to **11**.* A dimethyl sulfoxide solution (0.3 cm³) of **14** (20 mg) was heated in a sealed tube at 185 °C for 4 h. The NMR analysis indicated the formation of **11** in a 60% yield, together with unchanged **14** (40%).

*Reaction of 3-Ethyl-8H-cyclohepta[1,2-b]furan-8-one (**13**)*[1] *with Methylamine.* A mixture of **13** (45 mg) and an aqueous solution of methylamine (30%, 4 cm³) was heated in a sealed tube at 120 °C for 7 h. Subsequent silica gel chromatography of the mixture afforded **12** (40 mg; 83%).

References

1) a) H. Takeshita, I. Kouno, and K. Miyake, *Kyushu Daigaku Seisan Kagaku Kenkyusho Hokoku*, **66**, 1 (1977); b) H. Takeshita, K. Tajiri, and I. Kouno, *Bull. Chem. Soc. Jpn.*, **52**, 223 (1979).

2) a) H. Takeshita, K. Tajiri, and I. Kouno, *Heterocycles*, **6**, 1101 (1977); b) H. Takeshita, K. Tajiri, and I. Kouno, *Kyushu Daigaku Seisan Kagaku Kenkyusho Hokoku*, **70**, 65 (1979).

3) T. Nozoe, Y. Kitahara, and T. Arai, *Proc. Jpn. Acad.*, **30**, 478 (1954).

4) M. Muhlstadt and W. Treibs, *Ann. Chem.*, **608**, 38 (1957).

5) Previously, a dicycloheptapyrroledione (**A**) was obtained by the amination of the corresponding dicycloheptafurandione(**B**); see T. Nozoe, K. Doi, and Y. Kitahara, *Proc. Jpn. Acad.*, **32**, 480 (1956).

6) A. Pryde, J. Zsindely, and H. Schmid, *Helv. Chim. Acta*, **57**, 1598 (1974).

7) The NMR spectra were obtained in $CDCl_3$ solutions unless otherwise stated, and the chemical shifts were expressed in terms of the δ value (Me_4Si as the internal standard).

8) Assuming the coalescent temperature as *ca.* 30 °C, the observed $\Delta\delta$=190 led to an estimation for the activation barrier of rotatomers as 13.7 kcal/mol.