Reactions of 2,3-Dihydro-1*H*-cyclohepta[*b*]pyrazines with Acyl Halides

Yuuki Kawamata and Kimiaki Imafuku*

Department of Chemistry, Faculty of Science,
Kumamoto University, Kurokami, Kumamoto 860, Japan

Dong-Hao Li, Zhong-Tian Jin*, Zhi-Hong Li and Yan-Wen Xiao

Department of Chemistry, Yanbian University, Yanji, Jilin Province, People's Republic of China
Received May 31, 1994

When 2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**3**) was treated with acetyl chloride under the Friedel-Crafts conditions, its pyrazine ring opened to afford 2-[*N'*-acetyl-(2-aminoethyl)amino]tropone. Reactions with propionyl and butyryl chloride also gave similarly ring-opened products. On the other hand, aromatic benzoyl chlorides reacted with compound **3** to afford *N*-benzoyl-substituted 2,3-dihydro-1*H*-cyclohepta[*b*]pyrazines, in addition to ring-opened compounds.

J. Heterocyclic Chem., **31**, 1553 (1994).

Tropolones have aromatic character as well as benzene derivatives. It is well known that the tropolone nucleus is highly susceptible to many electrophilic substitution reactions such as halogenation, nitration, *etc.*, but does not undergo Friedel-Crafts type alkylation and acylation because of metal complex formation [1-4]. Attempts to facilitate the Friedel-Crafts acylation of 2-aminotropone were also unsuccessful [5].

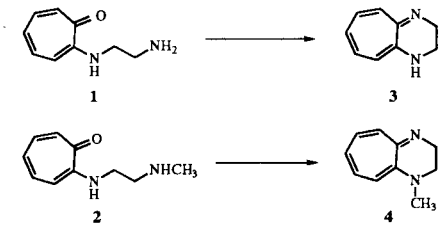
On the other hand, it was reported that *N,N'*-dimethyl-2-aminotroponimine reacted with acetyl chloride in the presence of aluminum chloride [6], although 2-aminotroponimines are nitrogen analogues of tropolones and form metal complexes. We traced this reaction but, unfortunately, we could not isolate the 5-acetyl derivative. We then tried to extend this reaction to 2,3-dihydro-1*H*-cyclohepta[*b*]pyrazines, which are cyclic analogues of 2-aminotroponimines.This paper describes these results.

Results and Discussion.

2,3-Dihydro-1*H*-cyclohepta[*b*]pyrazine (**3**) was prepared by the thermal cyclization of 2-[(2-aminoethyl)-amino]tropone (**1**) which was obtained by the reaction of 2-methoxytropone and ethylenediamine [7]. The nitration of compound **3** has been carried out as typical of electrophilic substitution reactions. 1-Methyl-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**4**) was also obtained from 2-methoxytropone and *N*-methylethylenediamine *via* 2-[[2-(methylamino)ethyl]amino]tropone (**2**) [7].

A solution of 2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**1**) and acetyl chloride in dichloromethane was stirred for 12 hours at room temperature to give a yellowish crystalline product after purification on a silica gel column. Its ir spectrum shows two carbonyl absorptions at 1660 and 1600 cm^{-1}. The latter is characteristic for tropone carbonyl absorption. The NH absorption is also observed at 3246 cm^{-1}. These results mean that the pyrazine ring

Scheme 1



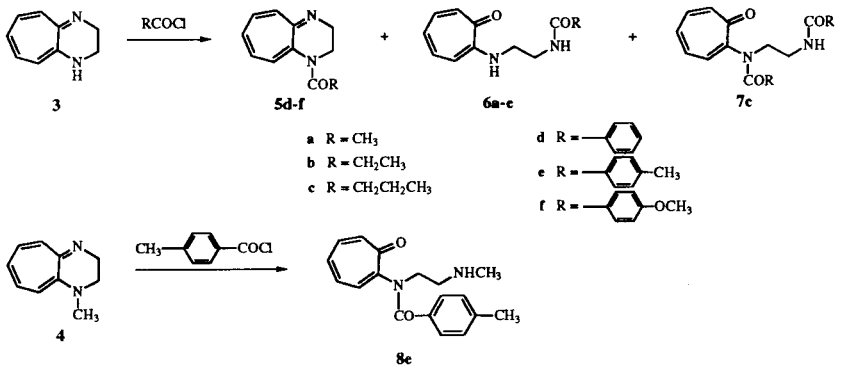
opened so that 2-[*N'*-acetyl-(2-aminoethyl)amino]tropone (**6a**) was formed. Its structure is also supported by elemental analysis $C_{11}H_{14}N_2O_2$.

The reactions with propionyl chloride and butyryl chloride gave respectively ring-opened products **6b** (29%) and **6c** (16%). Diacetyl-substituted product, 2-[*N,N'*-dibutyryl(2-aminoethyl)amino]tropone (**7c**) was isolated in a yield of 25% from the reaction with butyryl chloride. Its structure was confirmed by ir, ^1H nmr, and elemental analysis.

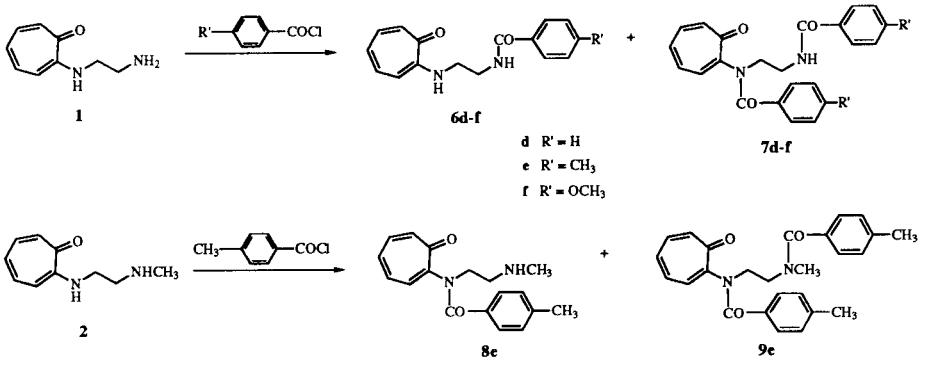
In the reactions of compound **3** with benzoyl chloride and 4-methylbenzoyl chloride, 1-benzoyl-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazines **5d,e** were obtained in addition to the ring-opened products **6d,e**. The reaction with 4-methoxybenzoyl chloride afforded 1-(4-methoxybenzoyl)-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**6f**) as the sole product in a yield of 20%. In these reactions, distinguishable behavior of 4-methoxybenzoyl chloride might depend on a strong mesomeric electron-donating effect of the methoxyl group. The yields of all the reactions were unsatisfactory. This depends on formation of considerable amount of intractable materials.

In a similar manner, the reaction of the *N*-methyl-substituted compound, 1-methyl-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**4**), with 4-methylbenzoyl chloride was carried out to give a ring-opened 2-[*N*-(4-methylbenzoyl)-[2-(methylamino)ethyl]amino]tropone (**8e**) in very low yield (8%).

Scheme 2



Scheme 3



In order to confirm the formation of ring-opened products, the reactions of 2-[(2-aminoethyl)amino]tropone (**1**) with benzoyl chlorides were carried out to give *N'*-benzoyl- **6d-f** and *N,N'*-dibenzoyl-substituted 2-[(2-aminoethyl)amino]tropones **7d-f**. Furthermore, 2-[[2-(methylamino)ethyl]amino]tropone (**2**) was treated with 4-methylbenzoyl chloride to give ring-opened *N*-(4-methyl)- **8e** and *N,N'*-bis(4-methylbenzoyl)-substituted 2-[2-(methylamino)ethyl]amino]tropone **9e** in 52 and 25% yield, respectively.

In the reactions of 2,3-dihydro-1*H*-cyclohepta-[*b*]pyrazines **3** and **4**, the formation of the ring-opened products is considered as follows. Two nitrogen atoms are more reactive towards electrophiles than the carbon atoms in the seven-membered ring and are not hindered sterically. Thus, acylium ions attacked the nitrogen atom and the pyrazine ring collapsed to afford more stable aminotropone derivatives.

EXPERIMENTAL

Measurements.

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer. The ^{1}H nmr spectra were recorded with a JEOL JNM-PMX60SI spectrometer (60 MHz). The mass spectra were measured on a JEOL JMS-01-SG2 spectrometer.

Reaction of 2,3-Dihydro-1*H*-cyclohepta[*b*]pyrazine (**3**) with Acetyl Chloride.

To dichloromethane (100 ml) containing acetyl chloride (390 mg, 5.0 mmoles) and anhydrous aluminum chloride (730 mg, 5.5 mmoles) was added a solution of **3** (730 mg, 5.0 mmoles) in dichloromethane (20 ml). After stirring for 12 hours at room temperature, the mixture was treated with 3*M* hydrochloric acid, neutralized with 2*M* sodium hydroxide solution, and extracted with dichloromethane. The extract was dried over potassium carbonate and chromatographed on a silica gel column with ethyl acetate to give 2-[*N'*-acetyl(2-aminoethyl)amino]tropone (**6a**) in a yield of 294 mg (29%) as yellow crystals (from benzene-petroleum ether), mp 133-134°; ir (potassium bromide): ν max 3289 (NH), 3246 (NH), 1660 (C=O), 1600 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 2.30 (3H, s, CH_3), 3.3-4.1 (4H, m, CH_2 x 2), 6.5-7.5 (6H, m), 7.8 (1H, br, NH).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.04; H, 6.72; N, 13.47.

Reaction of **3** with Propionyl Chloride.

The reaction of **3** (730 mg, 5.0 mmoles) with propionyl chloride (463 mg, 5.0 mmoles) was carried out in the presence of anhydrous aluminum chloride (730 mg, 5.5 mmoles). The mixture was worked up, as described above, to give 2-[*N'*-propionyl-(2-aminoethyl)amino]tropone (**6b**) in a yield of 324 mg (29%) as yellow crystals (from benzene-petroleum ether), mp

100-101°; ir (potassium bromide): ν max 3245 (NH), 3204 (NH), 1667 (C=O), 1601 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.14 (3H, t, J = 7 Hz, CH_3), 2.21 (2H, q, J = 7 Hz, $COCH_2$), 3.4-4.2 (4H, m, N-CH_2 x 2), 6.4 (1H, br, NH), 6.6-7.3 (5H, m), 7.5 (1H, br, NH).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.24; H, 7.06; N, 12.63.

Reaction of **3** with Butyryl Chloride.

The reaction of **3** (730 mg, 5.0 mmoles) with butyryl chloride (533 mg, 5.0 mmoles) was carried out in the presence of aluminum chloride (730 mg, 5.5 mmoles). The mixture was worked up, as described above, and column-chromatographed. 2-[*N'*-Butyryl-(2-aminoethyl)amino]tropone (**6c**) was obtained from the second fraction in a yield of 188 mg (16%) as a yellow oil; ir (neat): ν max 3310 (NH), 3284 (NH), 1655 (C=O), 1599 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.86 (3H, t, J = 7 Hz, CH_3), 1.62 (2H, m, CH_2CH_3), 2.07 (2H, t, J = 7 Hz, $COCH_2$), 3.5-4.1 (4H, m, N-CH_2 x 2), 6.6 (1H, br, NH), 6.65-7.8 (5H, m), 7.55 (1H, br, NH).

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.78; H, 7.81; N, 11.85.

2-[*N,N'*-Dibutyryl-(2-aminoethyl)amino]tropone (**7c**) was obtained from the first fraction in a yield of 378 mg (25%) as yellowish orange needles (from benzene-petroleum ether), mp 88-89°; ir (potassium bromide): ν max 3286 (NH), 1656 (C=O), 1640 (C=O), 1584 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 0.86 (3H, t, J = 7 Hz, CH_3), 0.92 (3H, t, J = 7 Hz, CH_3), 1.61 (2H, m, CH_2CH_3), 1.64 (2H, m, CH_2CH_3), 2.07 (2H, t, J = 7 Hz, $COCH_2$), 2.11 (2H, t, J = 7 Hz, $COCH_2$), 3.3-4.0 (4H, m, N-CH_2 x 2), 6.9 (1H, br, NH), 7.0-7.7 (5H, m).

Anal. Calcd. for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.21. Found: C, 66.95; H, 8.01; N, 9.06.

Reaction of **3** with Benzoyl Chloride.

A mixture of 3 (292 mg, 2.0 mmoles) and benzoyl chloride (232 mg, 2.0 mmoles) in dichloromethane (20 ml) containing anhydrous aluminum chloride (292 mg, 2.2 mg) was allowed to stir for 13 hours at room temperature. The mixture was worked up, as described above, and chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform-methanol (10:1).

1-Benzoyl-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**5d**) was obtained from the upper fraction in a yield of 24 mg (4.9%) as a deep yellow oil; ir (chloroform): ν max 1641 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.90 (4H, m, CH_2 x 2), 5.8-7.0 (5H, m), 7.42 (5H, br.s, Ph); ms: m/z (%) 250 (M^+, 100), 145 (M^+-COPh, 28), 105 (COPh, 96). Calcd. for $C_{16}H_{14}N_2O$: M, 250.1107. Found: m/z 250.1112 (M^+).

2-[*N'*-Benzoyl-(2-aminoethyl)amino]tropone (**6d**) was obtained from the lower fraction in a yield of 162 mg (13%) as yellow crystals (from benzene-methanol), mp 146-148°; ir (chloroform): ν max 3460 (NH), 3280 (NH), 1655 (C=O), 1605 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.45 (4H, m, CH_2 x 2), 6.5-7.0 (2H, m), 7.0-7.4 (8H, m), 7.75-8.5 (2H, m).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.40; N, 6.03; N, 10.42.

Reaction of **3** with 4-Methylbenzoyl Chloride.

A mixture of 3 (292 mg, 2.0 mmoles) and 4-methylbenzoyl chloride (309 mg, 2.0 mmoles) in dichloromethane (20 ml) containing anhydrous aluminum chloride (292 mg, 2.2 mmoles) was allowed to stir for 14 hours. The mixture was worked up, as described above, and chromatographed on a silica gel plate.

1-(4-Methylbenzoyl)-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**5e**) was obtained from the upper fraction in a yield of 47 mg (8.8%) as a deep yellow oil; ir (chloroform): ν max 1636 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.33 (3H, s, CH_3), 3.89 (4H, s, CH_2 x 2), 5.8-6.9 (5H, m), 7.05-7.2 (2H, m, 3'-,5'-H), 7.3-7.6 (2H, m, 2'-,6'-H); ms: m/z (%) 264 (M^+, 100), 145 (M^+-COAr, 32), 119 (COAr, 85). Calcd. for $C_{17}H_{16}N_2O$: M, 264.1263. Found: m/z 264.1249 (M^+).

2-[*N'*-(4-Methylbenzoyl)-(2-aminoethyl)amino]tropone (**6e**) was obtained from the lower fraction in a yield of 101 mg (17%) as yellow crystals (from benzene-methanol), mp 148-149°; ir (chloroform): ν max 3475 (NH), 3300 (NH), 1658 (C=O), 1602 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.32 (3H, s, CH_3), 3.25-4.25 (4H, m, CH_2 x 2), 6.4-6.95 (2H, m), 6.95-7.55 (5H, m), 7.55-7.85 (2H, m, 2'-,6'-H), 7.90 (2H, br, NH x 2).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.05; H, 6.40; N, 9.94.

Reaction of **3** with 4-Methoxybenzoyl Chloride.

A mixture of **3** (292 mg, 2.0 mmoles) and 4-methoxybenzoyl chloride (341 mg, 2.0 mmoles) in dichloromethane (20 ml) containing anhydrous aluminum chloride (292 mg, 2.2 mmoles) was allowed to stir for 14 hours. The mixture was worked up, as described above, and chromatographed to give 1-(4-methoxybenzoyl)-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**5f**) in a yield of 116 mg (20%) as deep yellow crystals (from ethyl acetate-hexane), mp 130-132°; ir (chloroform): ν max 1645 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.83 (3H, s, OCH_3), 3.92 (4H, s, CH_2 x 2), 5.7-6.7 (5H, m), 6.75-6.9 (2H, m, 3'-,5'-H), 7.3-7.5 (2H, m, 2'-,6'-H).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 10.00. Found: C, 72.68; H, 5.78; N, 10.02.

Reaction of 2-[(2-Aminoethyl)amino]tropone (**1**) with Benzoyl Chloride.

To a solution of (303 mg, 1.8 mmoles) and triethylamine (280 mg, 2.8 mmoles) in dichloromethane (4 ml) was added benzoyl chloride (390 mg, 2.8 mmoles) in dichloromethane (1 ml). After stirring for 2 hours at room temperature, the mixture was triturated with water (100 ml) and extracted with chloroform. The extract was washed twice with water, dried over sodium sulfate, and evaporated. The oily residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform-methanol (10:1).

From the lower fraction, 2-[*N'*-benzoyl-(2-aminoethyl)-amino]tropone (**6d**) was obtained in a yield of 135 mg (27%).

From the upper fraction, 2-[*N,N'*-dibenzoyl-(2-aminoethyl)amino]tropone (**7d**) was obtained in a yield of 28 mg (4%) as pale yellow crystals (from methanol), mp 192-194°; ir (chloroform): ν max 3375 (NH), 1647 (C=O), 1595 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.55-3.9 (2H, m, NH-CH_2), 3.9-4.4 (2H, m, >N-CH_2), 6.5-7.65 (13H, m), 7.65-8.1 (2H, m).

Anal. Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.17; H, 5.41; N, 7.52. Found: C, 74.43; H, 5.31; N, 7.72.

Reaction of **1** with 4-Methylbenzoyl Chloride.

A solution of **1** (312 mg, 1.9 mmoles), 4-methylbenzoyl chloride (441 mg, 2.8 mmoles), and triethylamine (280 mg, 2.8 mmoles) in dichloromethane (1 ml) was stirred for 1 hour at

room temperature. The mixture was worked up, as described above, and chromatographed.

From the lower fraction, 2-[*N'*-(4-methylbenzoyl)-(2-aminoethyl)amino]tropone (**6e**) was obtained in a yield of 116 mg (22%).

From the upper fraction, 2-[*N,N'*-bis(4-methylbenzoyl)(2-aminoethyl)amino]tropone (**7e**) was obtained in a yield of 65 mg (8.5%) as yellow crystals (from benzene), mp 175-177°; ir (chloroform): ν max 3375 (NH), 1650 (C=O), 1595 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.24 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.5-3.95 (2H, m, NH-CH_2), 3.95-4.25 (2H, m, >N-CH_2), 6.5-7.5 (11H, m), 7.5-7.95 (3H, m).

Anal. Calcd. for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.87; H, 6.14; N, 7.10.

Reaction of **1** with 4-Methoxybenzoyl Chloride.

A solution of 1 (633 mg, 3.8 mmoles), 4-methoxybenzoyl chloride (986 mg, 5.8 mmoles), and triethylamine (585 mg, 5.8 mmoles) in dichloromethane (5 ml) was stirred for 1 hour at room temperature. The reaction mixture was worked up, as described above, and chromatographed.

From the lower fraction, 2-[*N'*-(4-methoxybenzoyl)(2-aminoethyl)amino]tropone (**6f**) was obtained in a yield of 126 mg (11%).

From the upper fraction, 2-[*N,N'*-bis(4-methoxybenzoyl)(2-aminoethyl)amino]tropone (**7f**) was obtained in a yield of 1.06 g (64%) as yellow prisms (from benzene-methanol), mp 177-179°; ir (chloroform): ν max 3375 (NH), 1645 (C=O), 1610 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.75 (2H, m, NH-CH_2), 3.78 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.0-4.35 (2H, m, >N-CH_2), 6.5-7.2 (8H, m), 7.2-7.55 (3H, m), 7.55-8.0 (3H, m).

Anal. Calcd. for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.23; H, 5.61; N, 6.59.

Reaction of 1-Methyl-2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine (**4**) with 4-Methylbenzoyl Chloride.

To a suspension of anhydrous aluminum chloride (292 mg, 2.2 mmoles) in dichloromethane (20 ml) was added 4-methylbenzoyl chloride (309 mg, 2.0 mmoles) and **4** (320 mg, 2.0 mmoles). After stirring for 12 hours at room temperature, the mixture was triturated with water (6 ml), acidified with 3*M* hydrochloric acid, neutralized with 2*M* sodium hydroxide solution, and extracted with chloroform. The extract was washed twice with water and dried over sodium sulfate. The evaporation residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform-methanol (10:1) to give 2-[*N*-(4-methylbenzoyl)-[2-(methylamino)ethyl]amino]tropone (**8e**) in a yield of 55 mg (8%) as yellow needles (from benzene), mp 112-114°; ir (chloroform): ν max 3008 (NH), 1624 (C=O), 1594 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.32 (3H, s, 4"-CH_3), 3.02 (3H, s, N-CH_3), 3.3-4.0 (4H, m, CH_2 x 2), 6.35-6.95 (2H, m), 6.95-7.35 (5H, m), 7.35-7.6 (2H, m, 2"-,6"-H), 7.64 (1H, br, NH).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.01; H, 6.64; N, 9.43.

Reaction of 2-[[2-(Methylamino)ethyl]amino]tropone (**2**) with 4-Methylbenzoyl Chloride.

To a solution of **2** (329 mg, 1.8 mmoles) and triethylamine (288 mg, 2.8 mmoles) in dichloromethane (4 ml) was added a solution of 4-methylbenzoyl chloride (441 mg, 2.8 mmoles) in dichloromethane (1 ml). After stirring for 2 hours at room temperature, the mixture was triturated with water (100 ml) and extracted with chlorofrom. The extract was washed twice with water and dried over sodium sulfate. The evaporation residue was chromatographed on a Wakogel B-10 plate (30 x 30 cm) with chloroform.

From the lower fraction, 2-[*N*-(4-methylbenzoyl)-[2-(methylamino)ethyl]amino]tropone (**8e**) was obtained in a yield of 300 mg (52%).

From the upper fraction, 2-[*N,N'*-bis(4-methylbenzoyl)[2-(methylamino)ethyl]amino]tropone (**9e**) was obtained in a yield of 209 mg (25%) as yellow needles (from methanol), mp 156-159°; ir (chloroform): ν max 1640 (C=O), 1603 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 2.23 (3H, s, C-CH_3), 2.35 (3H, s, C-CH_3), 3.14 (3H, s, N-CH_3), 3.55-4.35 (4H, m, CH_2 x 2), 6.6-7.2 (6H, m), 7.2-7.55 (7H, m).

Anal. Calcd. for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.07; H, 6.39; N, 7.02.

REFERENCES AND NOTES

[1] T. Nozoe, Non-benzenoid Aromatic Compounds, D. Ginsburg, ed, Interscience Publishers, Inc., New York, 1959, pp 339-463.

[2] T. Nozoe, K. Takase and H. Matsumura, Dai Yuki Kagaku, M. Kotake, ed, Asakura Shoten, Tokyo, 1960, Vol **13**, pp 1-437.

[3] F. Pietra, *Chem. Rev.*, **73**, 293 (1973).

[4] D. Lloyd, Non-benzenoid Conjugated Carbocyclic Compounds, Elsevier, Amsterdam, 1984, pp 107-125.

[5] T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, *Sci. Rep. Tohoku Univ.*, **I**, **36**, 126 (1952).

[6] W. F. Richter, K. Hartke, W. Massa and G. Munninghoff, *Chem. Ber.*, **122**, 1133 (1989).

[7] T. Nozoe, S. Ishikawa and K. Shindo, *Heterocycles*, **28**, 733 (1989).