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Studies on Seven-membered Ring Compounds. XXXVII.[1] The Reaction of Benzotropones with Malononitrile[2]

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4,5-Benzotropone reacted with malononitrile in acetic anhydride or in ethanol-piperidine to afford 8,8-dicyano-3,4-benzoheptafulvene (**6a**). On the other hand, 2,3-benzotropone reacted with malononitrile in acetic anhydride to afford 8,8-dicyano-1,2-benzoheptafulvene (**8a**) and 6-cyano-7-amino-3,4-benzobicyclo[3,2,2]nona-3,5,8-trien-2-one (**9a**). The reaction mechanism revealed that **8a** was afforded not only by Knoevenagel reaction but also by Michael addition at 4-position of 2,3-benzotropone.

Tropone is very reactive compound to nucleophile because of its unique conjugated cyclic trienone system which has been thought probably to exert a contribution of aromatic 6π cationic system, and it reacts with nucleophile at 1 or 2-position. For example, tropone reacts with malononitrile in refluxing acetic anhydride or in ethanol-piperidine to afford 8,8-dicyanoheptafulvene (**1**)[4] or cycloheptofuran derivative (**2**),[5] respectively. For the benzoanalogue of tropone, it is considered that the contribution of 6π-cationic hybridization would be little, but only a few studies have been reported about the reaction of benzotropone with nucleophiles. An example is the study of Föhlisch, *et al.*[6] They reported that 1,7-dialkoxycarbonyl-4,5-benzotropone (**3**) reacted with malonic ester and malononitrile at 3- and/or 6-position to give compound **4** or **5**, but in this case 4,5-benzotropone (**3**) is exceptional compound because its 3 and 6 positions are highly activated with 2-(or 7-) substituent. We independently have studied the reaction of 4,5-benzotropone (**3a**, **3b**) and 2,3-benzotropone with malononitrile and found interesting and different (to Föhlisch's) results.

The Reaction of 4,5-Benzotropones (3) with Malononitrile

Refluxing a mixture of 4,5-benzotropone (**3a**) and equimolar amount of malononitrile in acetic anhydride gave, after usual work up, yellow crystals in 55% yield. This substance (**6a**) melted at 267° and had a formula of $C_{14}H_{18}N_2$. Other spectroscopic data were IR ν_{Nujol} 2200, 1630 cm^{-1}; UV $\lambda_{max}^{ethanol}$ 237.5 (ε=23600), 247 (27100), 304 (25100), 402.2 (27400) nm.

1) Part XXXVI: T. Watanabe and N. Soma, *Chem. Pharm. Bull.* (Tokyo), **19**, 2215 (1971).
2) This work was presented at the 91st Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April, 1971, Abst. p. 691.
3) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
4) Y. Kitahara, K. Doi, and T. Kato, *Bull. Chem. Soc. Japan*, **37**, 1747 (1964).
5) T. Nozoe, T. Mukai, and T. Suzuki, *Bull. Chem. Soc. Japan*, **36**, 38 (1963).
6) B. Foehlisch, E. Widmann, and E. Schupp, *Tetrahedron Letters*, **1969**, 2355.

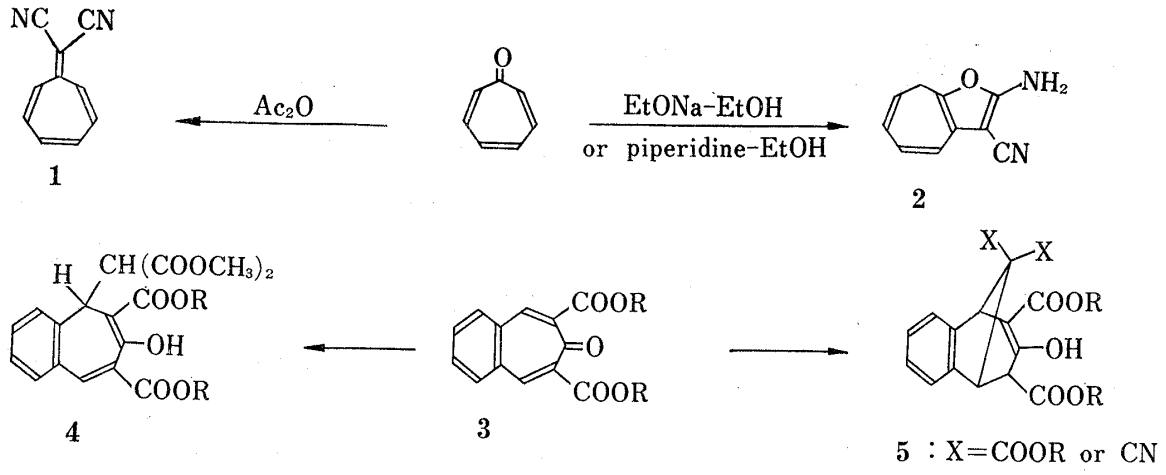
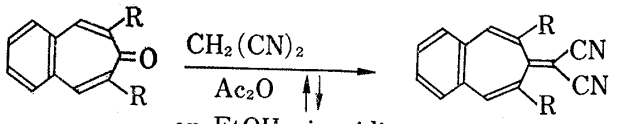


Chart 1

The nuclear magnetic resonance (NMR) could not be taken due to its insufficient solubility to almost all solvents. These data, especially its characteristic ultraviolet (UV) spectrum, indicated that **6a** was 8,8-dicyano-3,4-benzoheptafulvene. When the same mixture dissolved in ethanol containing a catalytic amount of piperidine also gave **6a**, but in lower yield. Analogous reaction of 2,7-dimethyl-4,5-benzotropone (**3b**) in acetic anhydride gave 1,6-dimethyl-8,8-dicyano-3,4-benzoheptafulvene (**6b**), mp 185—187°, in low yield (13%). The low yield would be a reflection of the steric hindrance due to the neighboring methyl groups. Physicochemical data of **6b** were as follows: $C_{16}H_{12}N_2$: IR ν_{Nujol} 2200, 1635 cm^{-1}; UV $\lambda_{max}^{ethanol}$ 231 (ε=38000), 299 (8000), 375 (9500) nm; NMR (δ ppm, in $CDCl_3$) 2.52 (6H, d, J=1.0 Hz), 7.00 (2H, q, J=1.0), 7.4—7.55 (4H, aromatic). The infrared (IR) spectrum of **5b** highly resembled to that of **6a**, but the UV differed widely. This fact suggests that in **6b** a full conjugation of π-electrons is broken because of the steric interference between 1-(and 6-)methyl and 8-cyano group and thereby causing a twisting C_7-C_8 bond.[7]



3a : R=H or EtOH-piperidine **6a** : R=H
3b : R=CH_3 or EtOH-EtONa **6b** : R=CH_3

Chart 2

The Reaction of 2,3-Benzotropones (7) with Malononitrile

The reaction of 2,3-benzotropone (**7a**) with malononitrile in refluxing acetic anhydride for 5 hours afforded reddish yellow crystals (**8a**, 30.5%) and white crystals (**9a**, 8.9%). The isolation and purification were performed by alumina column chromatography followed by recrystallization. The physicochemical data for **8a** were as follows: **8a**: mp 155° (recrystallized from cyclohexane-benzene); IR ν_{Nujol} 2200, 1635 cm^{-1}; UV $\lambda_{max}^{ethanol}$ 243 (ε=21,400), 292.5 (10000), 392.7 (14000) nm; NMR (δ ppm, in $CDCl_3$) is shown in Fig. 1.

These data indicated that **8a** was 8,8-dicyano-1,2-benzoheptafulvene. The data for **9a**: mp 250—251°, $C_{14}H_{10}ON_2$; IR ν_{Nujol} 3400, 3250, 1680, 1660, 1595 cm^{-1}; UV $\lambda_{max}^{ethanol}$ 255 (ε=1200) nm; NMR and NMDR (δ ppm, in pyridine-d_5) is shown in Fig. 3, 4.25 (H-5, d of d, J=6.8 and 1.2 Hz), 4.63 (H-1, d of d, J=6.8 and 1.2), 6.30 (H-9, d of d, J=7.8, 6.8, and 1.2), 7.15—7.4 (3H, aromatic), 7.95 (NH_2, s), 8.1—8.25 (H-10, m). Twenty five percent NOE was observed between aromatic protons (irradiation at 7.20) and H-5 (4.25) as shown in Fig. 4.

These data and the reaction mechanism indicated that **9a** was 6-cyano-7-amino-3,4-benzobicyclo[3.2.2]nona-3,6,8-trien-2-one. The same 2,3-benzotropone (**7a**) reacted also with

7) H. Shimanouchi, Y. Sasada, C. Kabuto, and Y. Kitahara, *Tetrahedron Letters*, **1968**, 2537.

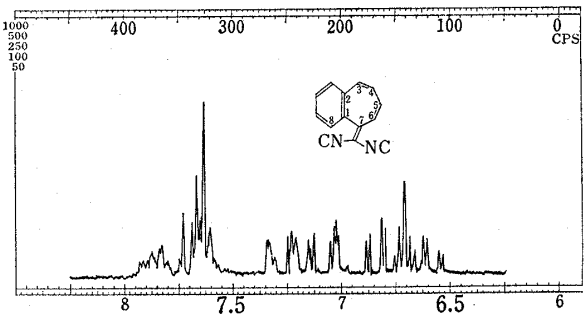


Fig. 1. The NMR Spectrum of 8,8-Dicyano-1,2-benzoheptafulvene (**7a**)

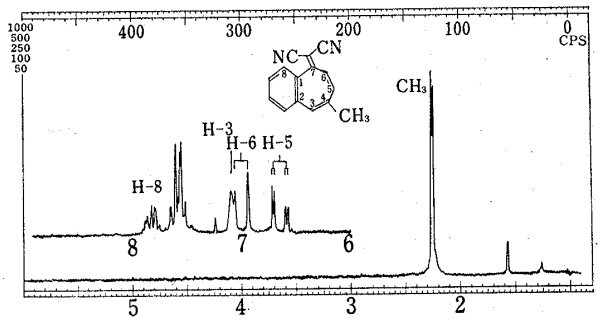
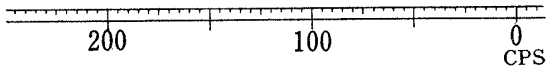


Fig. 2. The NMR Spectrum of 4-Methyl-8,8-dicyano-1,2-benzoheptafulvene (**7b**)



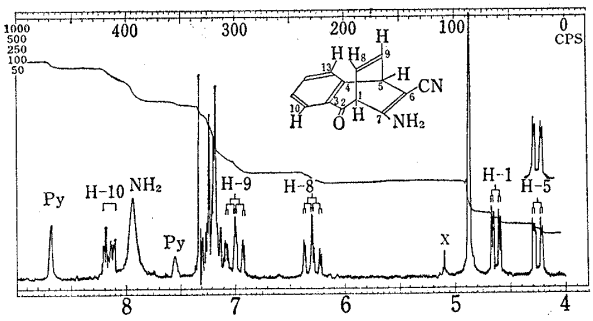


Fig. 3. The NMR Spectrum of 6-Cyano-7-amino-3,4-benzobicyclo[3,2,2]nona-3,6,8-trien-2-one (**8a**)

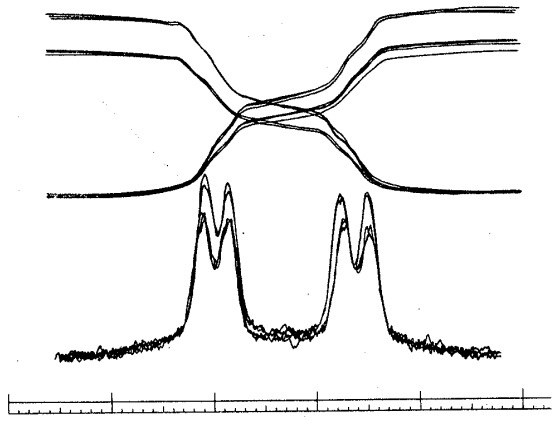
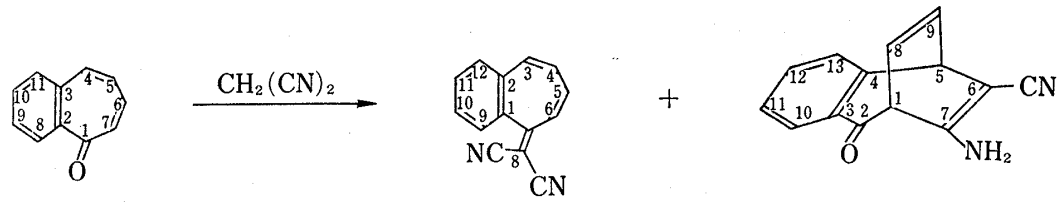


Fig. 4. Twenty five Percent NOE was observed between Aromatic Proton (H-13, irradiation at 7.20) and H-5 (4.25) of **8a**

malononitrile under basic conditions (ethanol-piperidine) to afford **8a** (7.2%) and **9a** (15%), however, in ethanol-sodium ethoxide only **9a** was obtained (28.6%). Then we first presumed that in acetic anhydride the reaction occured mainly to Knoevenagel type at 1-posision giving **8b** and partially to Michael type at 4-position giving the bicyclic ocmpound of **9a**. But following experiment denied that this presumption was correct.

Analogous reaction of 7-methyl-2,3-benzotropone (**7b**)[8] with malononitrile in acetic anhydride should, expectedly, give 6-methyl-8,8-dicyano-1,2-benzoheptafulvene (**8c**) and



7a **8a** **9a**

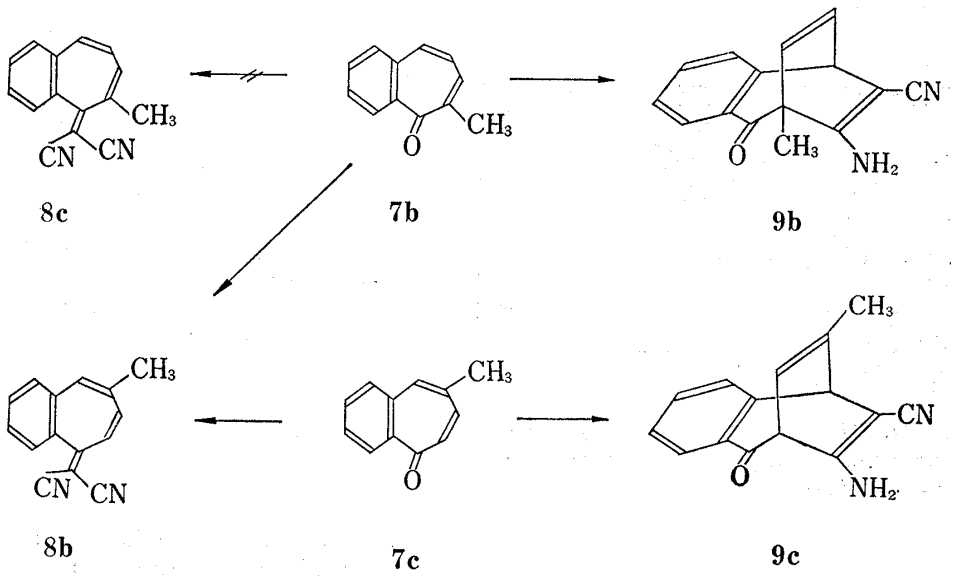
Chart 3

8) This new benzotropone was synthesized from the corresponding benzosuberone according to the methods of Buchanan[9] and Collington.[10]

9) G.L. Buchanan and D.R. Lockhart, *J. Chem. Soc.*, **1959**, 3586.

10) G.L. Collington and G. Jones, *J. Chem. Soc.*, **1969**, 2656.

1-methyl-6-cyano-7-amino-3,4-benzobicyclo[3,2,2]nona-3,6,7-trien-2-one (**9b**), but in fact, gave 4-methyl-8,8-dicyano-1,2-benzoheptafulvene (**8b**), mp 160—162° and the **9b**, mp 192—194°. That is, malononitrile did not react as Knoevenagel type, but did as Michael type at 4-position. The structure of **8b** was determined from the physicochemical data, especially NMR and NMDR, as follows: **8b**: $C_{15}H_{10}N_2$: IR ν_{Nujol} 2200, 1630 cm^{-1}, UV $\lambda_{max}^{ethanol}$ 244.5 (ε=22900), 293 (19200), 406.5 (20900) mm; NMR (δ ppm, in $CDCl_3$) shown in Fig. 2, 2.25 (CH_3-4, d, J=1.3 Hz), 6.65 (H-5, d of d, J=12.2 and 1.7), 7.01 (H-6, d of d, J=12.2 and 0.6), 7.10 (H-3, d of d, J=1.7 and 0.6), 7.5—7.7 (3H, aromatic), 7.75—7.95 (H-8). Irradiation at the CH_3 (2.25) effected an increment of 6% and 13% NOE at H-5 (6.65) and H-3 (7.10), respectively. On the other hand, the reaction of 5-methyl-2,3-benzotropone (**7c**) with malononitrile under similar conditions afforded **8b** and **9c** instead of **8c**. These facts suggested that the steric factors largely affected the attacking sites.

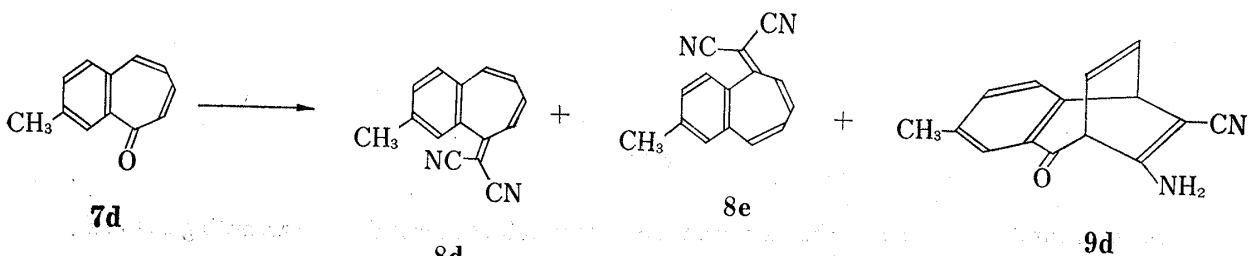


8c **7b** **9b**

8b **7c** **9c**

Chart 4

For the purpose of revealing the mechanism of the formation of **8a**, the similar reaction of 9-methyl-2,3-benzotropone, which has no steric hindrance at 1- and 4-positions, with malononitrile was further investigated. A mixture of 8,8-dicyano-9-methyl- and 8,8-dicyano-10-methyl-1,2-benzoheptafulvene (**8d**: **8e**=2: 1, 21%), mp 130—134°, and 6-cyano-7-amino-11-methyl-3,4-benzobicyclo[3,2,2]nona-3,6,8-trien-2-one (**8d**, 3%), mp 195—197°, were obtained. The ratio of **8d**/**8e** was determined from the integration of the methyl proton signal in the NMR (**8d**: 2.02, **8e**: 2.00) and that of H-8 (**8d**: 7.72, s, **8e**: 7.78, d). From these data, plausible mechanism of the above reaction is shown in Fig. 5. In the reaction of 2,3-benzotropone (**7d**) with malononitrile in acetic anhydride, malononitril attacks carbonyl carbon of 2,3-benzotropone following elimination of acetic acid to afford **8d** (path A), and



7d **8d** 2 : 1 **8e** **9d**

Chart 5

also attacks at 4-position of 2,3-benzotropone following thermal 1,5-hydrogen shift[11] and elimination of acetic acid to afford **8e** (path B). That is **8a** would be formed through both path A and B. On the other hand, cycloaddition product (**9**) is the result of Michael addition of malononitril at 4-position (path C).

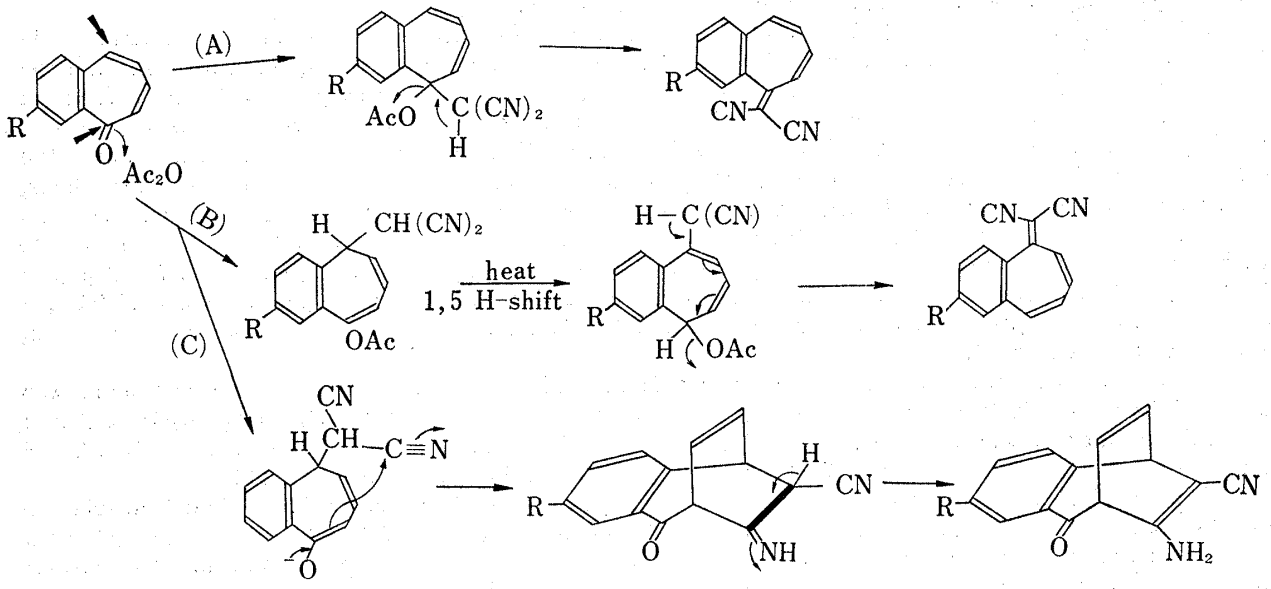


Fig. 5

Experimental

All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were tken using Varian HA-100 spectrometer and the chemical shifts were expressed in ppm unit (δ) from internal standard of tetramethylsilane. Ultra violet (UV) spectra were taken using Cary 14 spectrophotometer.

8,8-Dicyano-3,4-benzoheptafulvene (**6a**)——(A) In Acetic Anhydride: The mixture of 4,5-benzotropone (**3a**, 780 mg) and malononitrile (400 mg) in acetic anhydride (10 ml) was refluxed for 5 hours. The reaction mixture was poured onto ice-water and the precipitated yellow crystals (**6a**) were collected by filtration and the filtrate was extracted with chloroform. The extract was washed with 10% aqueous sodium hydroxide and dried over magnesium sulfate. The solvent was distilled off to give the same yellow crystals (**6a**). These were combined and recrystallized from benzene–chloroform to give 587 mg of the pure sample of mp 267°. *Anal.* Calcd. for $C_{14}H_{18}N_2$: C, 82.33; H, 3.95; N, 13.72%. Found: C, 82.37; H, 4.04; N, 13.87%. (B) In Ethanol-piperidine: To a solution of 4,5-benzotropone (156 mg) and malononitrile (80 mg) in absolute ethanol (10 ml) added 3 drops of piperidine and the reaction mixture was left to stand at room temperature for three days. The precipitated crystals (**5a**) were collected by filtration and recrystallized from chloroform–benzene to give 14 mg of **6a**. The filtrate was extracted with chloroform, and then passed through alumina column to recover 4,5-benzotropone (**3a**, 72 mg).

1,6-Dimethyl-8,8-dicyano-3,4-benzoheptafulvene (**6b**)——By analogous procedure described above (method A), the title compound, **6b** (200 mg) was obtained from 2,7-dimethyl-4,5-benzotropone (**3b** 1.22 g) and malononitrile (600 mg), and 400 mg of the starting benzotropone was recovered. **6b**: mp 185—187° (recrystallized from benzene–cyclohexane). *Anal.* Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06%. Found: C, 82.68; H, 5.40; N, 12.52%. IR ν_{Nujol}: 2200, 1620 cm^{-1}.

7-Methyl-2,3-benzotropone (**7b**)——To a solution of 2,3-benzosuberone (50 g) in dry ether (500 ml) was added dropwise a solution of bromine (17.5 ml) in carbontetrachloride (50 ml) at room temperature. After one hour the reaction mixture was poured onto ice-water and extracted with ether. The extract was washed with water, dried and distilled. The distillate, bp 121—122°/0.5 mmHg, was 7-bromo-7-methyl-2,3-benzosuberone, 62 g. This bromoketone was refluxed with N-bromosuccinimide (49.5 g) in carbontetrachloride (450 ml) for 3 hours, and the reaction mixture was cooled and filtered. The filtrate was washed with water, dried over magnesium sulfate and evaporated to dryness to give 91 g of crude, 4,7-dibromo-2,3-benzosuberone, as a brown syrup which could be used to the next reaction without purification. A

11) W. Tochtermann, G. Schnabel, and A. Manschreck, *Ann. Chemie*, **711**, 88 (1968).

mixture of the dibromoketone and 2,4,6-colidine (550 ml) was stirred at 100° for 3 hours followed by heating to 170° for 1 hour, and then poured onto water. The chloroform extract was washed with 6N hydrochloric acid, water, dried over magnesium sulfate, and concentrated *in vacuo*. The residual syrup was distilled under reduced pressure and the distillate of 125—130°/0.6 mmHg was collected to give 7-methyl-2,3-benzotropone (**7b**). *Anal.* Calcd. for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.34; H, 5.85. NMR (in $CDCl_3$) 2.37 (CH_3-7, d, J=1.0 Hz), 6.67 (H-5, d of d, J=11.0, and 8.5) 7.23 (H-6, d of d, J=8.5 and 1.0) 7.32 (H-4, d, J=11.0), 7.65—7.85 (3H, aromatic), 8.5—8.8 (H-8, m).

5-Methyl-2,3-benzotropone (7c)——To a solution of 5-methylbenzosuberone in carbontetrachloride (30 ml) was added dropwise a solution of bromine (5.34 g) in carbontetrachloride (10 ml) at −10° and the reaction mixture was stirred for 4 hours at the temperature. The mixture was washed with aqueous sodium bicarbonate and water, dried, and concentrated *in vacuo* to give crude 5-methyl-7,7-dibromobenzosuberone (5.04 g) as a brown syrup which could be used to the next reaction without purification. A mixture of the dibromoketone (5.04 g) and lithium chloride (1 g) in dimethylformamide (30 ml) was refluxed for 1 hour, after water was added, extracted with ether. The extract was dried over magnesium sulfate and concentrated to give a brown syrup (2.3 g) which was purified by alumina column chromatography. The eluate with benzene–cyclohexane gave pure 5-methyl-2,3-benzotropone (**7c**), 220 mg. *Anal.* Calcd. for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.34; H, 5.85. NMR (in $CDCl_3$) 2.25 (CH_3-5, d, J=1.2 Hz), 6.34 (H-6, d of d, J=12.3 and 1.0), 6.78 (H-7, d of d, J=12.5 and 1.5) 6.97 (H-4, d, J=1.2) *ca.* 8.32 (center, H-8, m), 7.35—7.60 (3H, aromatic).

9-Methyl-2,3-benzotropone (7d)——By analogous method for preparing **7c**, the title compound was obtained from 9-methylbenzosuberone in 50.5% yield. mp 36—40°. *Anal.* Calcd. for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.35; H, 5.83. NMR (in $CDCl_3$) 2.50 (CH_3-9, s), 6.60 (H-5, d of d of d, J=10.5, 6 and 3), 6.87 (H-7), 7.02 (H-6, d of d, J=3.0 and 1.0), 7.28 (H-4, d of d, J=10.5 and 1.0).

The Reaction of 2,3-Benzotropone (7a) with Malononitrile——(A) In Acetic Anhydride: The mixture of 2,3-benzotropone (7a, 1.58 g) and malononitrile (0.7 g) in acetic anhydride (20 ml) was refluxed for 5 hours. The reaction mixture was poured onto ice-water and extracted with chloroform. The extract was washed with 10% aqueous sodium hydroxide, water, and dried over magnesium sulfate. After evaporation of the solvent, the residual syrup (1.55 g) was chromatographed on alumina (100 g). The eluate with cyclohexane–benzene (1:1) gave 8,8-dicyano-1,2-benzoheptafulvene (**8a**), 350 mg, as reddish yellow crystals which were recrystallized from benzene-cyclohexane (1: 3), mp 154—155°. *Anal.* Calcd. for $C_{14}H_8N_2$: C, 82.33; H, 3.95; N, 13.72. Found: C, 82.16; H, 4.11; N, 14.06. Eluation with benzene recovered the starting 2,3-benzotropone (700 mg) and then eluate with benzene–chloroform gave 6-cyano-7-amino-3,4-benzobicyclo[3,2,2]nona-3,6,8-trien-2-one (**9a**), 100 mg, as white crystals, mp 250—251°. *Anal.* Calcd. for $C_{14}H_{10}ON_2$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.69; H, 4.48; N, 12.94. (B) In Ethanol-piperidine: To a solution of 2,3-benzotropone (**7a**, 468 mg) and malononitrile (260 mg) in absolute ethanol (10 ml) was added 3 drops of piperidine and the reaction mixture was refluxed for 1.5 hours. After evaporation of the solvent, the residual syrup was chromatographed on alumina (60 g) and eluated successively cyclohexane–benzene (1:1), benzene, and benzene–chloroform (1:1) to give **8a** (25 mg), **7a** (200 mg) and **9a** (57 mg), respectively. (C) In Ethanol Sodium Ethoxide: To a solution of 2,3-benzotropone (3.2 g) and malononitrile (2.5 g) in absolute ethanol (60 ml) was added sodium ethoxide (2.5 g) and the reaction mixture was refluxed for 4 hours. Water was added and then the whole was extracted with chloroform. The extract was washed with water, dried over magnesium sulfate, and concentrated to give crystals of **9a**, 85 mg. The mother liquor was chromatographed on alumina to give **9a**, 15 mg and the starting **7a**, 191 mg.

The Reaction of 7-Methyl-2,3-benzotropone with Malononitrile in Acetic Anhydride——From 7-methyl-2,3-benzotropone (**7b**, 1.0 g) and malononitrile (800 mg), 8,8-dicyano-4-methyl-1,2-benzoheptafulvene (**8b**, 154 mg) and 1-methyl-6-cyano-7-amino-3,4-benzobicyclo[3,2,2]nona-3,6,8-trien-2-one (**9b**, 15 mg) were obtained by analogous procedure. **8b**: mp 161—162° (recrystallized from cyclohexane–benzene). *Anal.* Calcd. for $C_{15}H_{10}N_2$: C, 82.54; H, 4.62; N, 12.84. Found: C, 82.48; H, 4.66; N, 13.26. IR ν_{Nujol} 2210, 1600 cm^{-1}, **9b**: mp 192—194° (recrystallized from benzene–chloroform). *Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86%. Found: C, 76.10; H, 5.08; N, 12.21%. IR ν_{Nujol} 3470, 2240, 1720 cm^{-1}. NMR (in pyridine-d_5) 1.84 (CH_3-1, s), 4.21 (H-5, d of d, J=7 and 1.5 Hz), 5.26 (NH_2, s), 5.97 (H-8, d of d, J=7 and 1.5), 6.01 (H-9, t, J=7), 7.15—7.4 (3H, aromatic), 8.15—8.3 (H-10, m).

The Reaction of 5-Methyl-2,3-benzotropone with Malononitrile in Acetic Anhydride——From 5-methyl-2,3-benzotropone (**7c**, 140 mg) and malononitrile (140 mg), **8b** (21 mg) and 6-cyano-7-amino-8-methyl-3,4-benzobicyclo[3,2,2]nona-3,6,8-trien-2-one (**9c**, 6 mg) were obtained. **9c**: mp 147—149°. *Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.40; H, 5.20; N, 11.55.

The Reaction of 9-Methyl-2,3-benzotropone (7d) with Malononitrile in Acetic Anhydride——From 9-methyl-2,3-benzotropone (**7d**, 1.5 g) and malononitrile (0.72 g), the mixture of 8,8-dicyano-9-methyl- and 8,8-dicyano-10-methyl-1,2-benzoheptafulvene (**8d**: **8e**=2:1, 414 mg) and 6-cyano-7-amino-11-methyl-3,4-benzobicyclo[3,2,2]nona-3,6,8-trien-2-one (**9d**, 70 mg) were obtained. **8d**+**8e**: mp 130—134°. *Anal.* Calcd. for $C_{15}H_{10}N_2$: C, 82.54; H, 4.62; N, 12.84. Found: C, 82.52; H, 4.38; N, 12.65%. IR ν_{Nujol} 2200, 1605 cm^{-1}; NMR (in $CDCl_3$) 2.00 (CH_3-10 of 7e, s), 2.02 (CH_3-9 of 7d, s) 6.4—7.4 (3H proton on seven membered ring, analogous signal pattern to **8a**), 7.4—7.6 (aromatic 3H), 7.72 (H-8 of 7d, s), 7.78 (H-8 of 7e, d, J=

9 Hz) **9d**: mp 195—197°. *Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.08; H, 5.25; N, 12.04. IR ν_{Nujol} 3380, 3240, 1980, 1665, 1615, 1605 cm^{-1}. NMR (in $CDCl_3$) 2.27 (CH_3-11, s), 4.10 (H-1, and H-5, d of m, J=6.5 Hz) 6.30 (H-8, t of m, J=6.5), 7.00 (H-9, t of m, J=6.5), 7.1—7.2 (2H, aromatic), 7.8 (H-10, s).

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