A New Synthesis of Benzo- and Naphtho-fused Cycloalkenes

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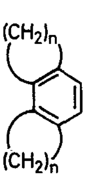
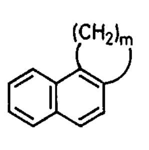
The most general synthesis of tricyclic fused hydrocarbons of the type **1** is based on the Diels-Alder reaction of bi[1-cycloalken-1-yls] with maleic anhydride[1]. The applicability of this method to the synthesis of compounds **1**, n ≥ 5, is limited, however, by the simultaneous formation of linear isomers of **1** during decomposition of the maleic anhydride adducts in the presence of phosphorus pentoxide. A variety of methods for the synthesis of hydrocarbons of the type **2** has been described. Thus, the ring system of 2,3-dihydro-1*H*-benzo[*e*]indene (**2a**) has been obtained by cyclocondensation[2-7] and cycloaddition[8] reactions. 8,9,10,11-Tetrahydro-7*H*-cyclohepta[*a*]naphthalene (**2b**) was first prepared by a rather elaborate route[9]: it has later been synthesized by a cyclocondensation reaction[10] and by rearrangement of spiro derivatives of naphthalene[11,12].

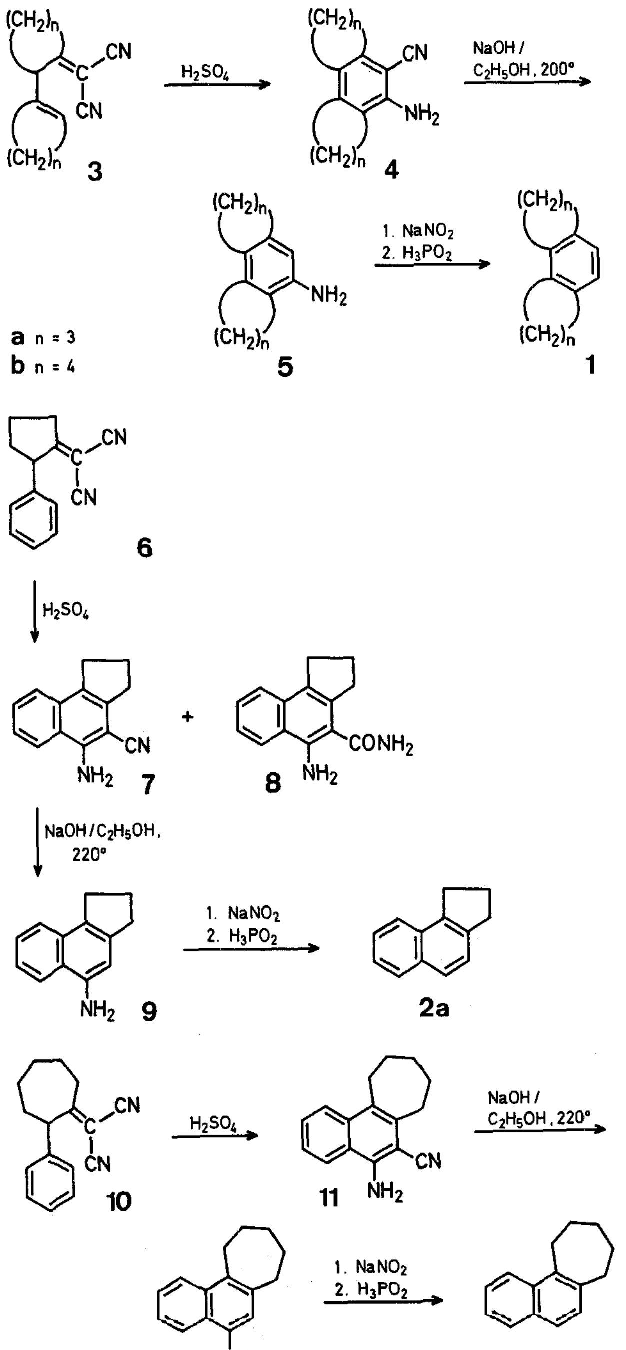


1a n = 3
b n = 4



2a m = 3
b m = 5

We report here a new four-step synthesis of hydrocarbons **1** and **2** from 2-cycloalkenylcycloalkanones and 2-phenylcycloalkanones, respectively. These ketones are condensed with malonodinitrile to afford ylidenemalonodinitriles **3**, **6**, and **10** which are then cyclized to the *o*-aminonitriles **4**, **7**, and **11** in concentrated sulfuric acid. Although this type of ring closure to carbocyclic *o*-aminonitriles is well known[13, 14, 15], the reaction has found virtually no synthetic utility mainly because of the high resistance of the nitrile group to hydrolysis[14]. Recently, we reported[16] that the nitrile function of sterically hindered *o*-aminonitriles can be eliminated with good yield by heating these compounds in an ethanolic solution of sodium hydroxide at 200° (autoclave). Employing this method, the amines **5**, **9**, and **12** can be obtained in satisfactory yields. The amines are diazotized and the diazonium groups are eliminated by known methods[17]; the method employing hypophosphorous acid as reducing agent was found to be the most satisfactory one.



All amines investigated form salts which are poorly soluble in water. Thus, their hydrochlorides can be prepared by precipitation from solutions in petroleum ether. Unexpectedly, cyclization of **6** in cold, concentrated sulfuric acid gave the *o*-aminonitrile **7** and a small amount of the *o*-aminoamide **8**. It seems that the cyclopentane ring of **7** imposes less steric hindrance on the nitrile function which may be hydrated to a carboxamide group even at low temperatures (5°). In contrast to these observations, Campaigne et al.[15] reported that an analog of **7**, 9-amino-10-cyano-1,2,3,4-tetrahydrophenanthrene was hydrolyzed to the *o*-aminocarboxamide only when heated in polyphosphoric acid at 90° for 4 hours. The crude ylidenemalonodinitrile **3a** was cyclized to **4a** in concentrated sulfuric acid without prior isolation and purification. On the basis of the ^{1}H-N.M.R. spectrum, **3b** was assigned the structure of 2-(1-cyclohexen-1-yl)-cyclohexylidenemalonodinitrile. Previously, Jaeger[14] assigned to **3b** the structure of 2-cyclohexylidenecyclohexylidenemalonodinitrile without any spectroscopic investigations. It also seems reasonable that the ring closure **3b**→**4b** proceeds via electrophilic attack of the protonated nitrile group on the olefinic C-atom C-2 of the cycloalkene ring rather than on a saturated C-atom as was assumed by Jaeger.

Since the 2-(1-alkenyl)-cycloalkanones and 2-phenylcycloalkanones used as starting materials are relatively easily available the synthesis of compounds **1** and **2** reported here may be of practical interest.

5-Amino-4-cyano-1,2,3,6,7,8-hexahydro-*as*-indacene (4a):

2-Cyclopentylidenecyclopentanone[18] (21.1 g, 0.14 mol), malonodinitrile (9.4 g, 0.14 mol), ammonium acetate (6.8 g, 0.09 mol), acetic acid (2.1 g, 0.03 mol), and benzene (80 ml) are heated under a reflux condenser equipped with a Dean-Stark water separator until separation of water ceases. The solution is washed with water and saturated sodium hydrogen carbonate solution and is dried with anhydrous magnesium sulfate. Benzene and unreacted ketone are thoroughly removed under reduced pressure. The resultant dark, viscous oil is slowly dissolved with stirring in ice-cold conc. sulfuric acid (100 ml). The solution is kept at room temperature overnight and is then poured onto crushed ice. The dark, semisolid substance is isolated by filtration, washed with water, dried in the air for three days, and purified by sublimation in vacuo (0.05 torr). Recrystallization from ethanol affords **4a** as colorless crystals: yield: 8.7 g (31%); m.p. 124° (Ref.[19], m.p. 123°).

I.R. (KBr): $\nu_{max}=3468, 3380, 3267$ (NH$_2$); 2204 cm^{-1} (CN).

^{1}H-N.M.R. (CDCl$_3$): $\delta=4.06$ (s, 2H, —N$\underline{H}_2$); 2.77 (m, 8H$_{benzylic}$); 2.07 ppm (m, 4H).

4-Amino-1,2,3,6,7,8-hexahydro-*as*-indacene (5a):

A solution of the o-aminonitrile **4a** (5.0 g, 0.02 mol) and sodium hydroxide (5.0 g) in ethanol (80 ml) is heated in an autoclave at 200° for 7 h. The mixture is then diluted with water (60 ml) and the ethanol is distilled off. The precipitated oil solidifies on cooling and is purified by sublimation in vacuo: yield: 2.0 g (46%): m.p. 45–46°.

$C_{12}H_{15}N$	calc.	C 83.19	H 8.73	N 8.08
(173.3)	found	82.91	9.09	7.99

I.R. (CCl$_4$): $\nu_{max}=3480$; 3400 cm^{-1} (NH$_2$).

^{1}H-N.M.R. (CCl$_4$): $\delta=6.10$ (s, 1H$_{arom}$); 3.10 (s, 2H, —NH$_2$); 2.58 (m, 8H$_{benzylic}$); 1.99 ppm (m, 4H).

1,2,3,6,7,8-Hexahydro-*as*-indacene (1a):

The amine **5a** (150 mg, 0.86 mmol) is dissolved in petroleum ether (5 ml), hydrochloric acid (1 ml) is added dropwise with stirring, and then the solvent is evaporated on a steam bath. A second portion of hydrochloric acid (1 ml) and water (0.4 ml) are then added, the mixture is cooled to 0°, and is diazotized with sodium nitrite (90 mg) dissolved in a small amount of water. Precooled 50% hypophosphorous acid (4.0 g) is slowly added and the mixture is kept in a refrigerator overnight. The crude hydrocarbon is isolated by suction, washed with water, and sublimed in vacuo. Recrystallization from methanol gives **1a** as colorless needles; yield: 103 mg (75 %); m.p. 40–41° (Ref.[20], m.p. 39–40°).

^{1}H-N.M.R. (CDCl$_3$): $\delta=6.93$ (s, 2H$_{arom}$); 2.82 (t, 4H); 2.74 (t, 4H); 2.00 ppm (quintet, 4H).

9-Amino-1,2,3,4,5,6,7,8-octahydrophenanthrene (5b):

The *o*-aminonitrile **4b**[21] (5.0 g, 0.02 mol) and sodium hydroxide (5.0 g) are dissolved in ethanol (80 ml) and the solution is heated in an autoclave at 200° for 8 h. After work-up as described for **5a**, the amine **5b** is purified by sublimation in vacuo and recrystallization from petroleum ether: yield: 3.3 g (74%); m.p. 65–66°.

$C_{14}H_{19}N$	calc.	C 83.53	H 9.51	N 6.96
(201.3)	found	83.29	9.32	6.88

I.R. (CCl$_4$): $\nu_{max}=3400$; 3482 cm^{-1} (NH$_2$).

^{1}H-N.M.R. (CCl$_4$): $\delta=6.08$ (s, 1H$_{arom}$); 3.24 (s, 2H, —NH$_2$); 2.48 (m, 8H$_{benzylic}$); 1.74 ppm (m, 8H).

1,2,3,4,5,6,7,8-Octahydrophenanthrene (1b):

The amine **5b** (2.0 g, 0.01 mol) is converted into the hydrochloride with conc. hydrochloric acid (2.5 ml). Then, conc. hydrochloric acid (2.5 ml) and water (1 ml) are added and the suspension is cooled to 0°. The mixture is diazotized with a solution of sodium nitrite (403 mg) and is then treated slowly with cold 50% hypophosphorous acid (8.0 g) and kept in a refrigerator overnight. The oily substance is extracted with petroleum ether, the combined extracts are dried with magnesium sulfate, and filtered through aluminum oxide. The solvent is evaporated and the product is purified using a micro distillation apparatus; yield: 700 mg (38%) of yellowish oil: $n_D^{20}=1.5668$ (Ref.[22], $n_D^{17}=1.5669$).

^{1}H-N.M.R. (CCl$_4$): $\delta=6.72$ (s, 2H$_{arom}$); 2.57 (m, 8H$_{benzylic}$); 1.80 ppm (m, 8H).

2-Phenylcyclopentylidenemalonodinitrile (6):

2-Phenylcyclopentanone[23] (8.0 g, 0.05 mol), malonodinitrile (3.3 g, 0.05 mol), ammonium acetate (0.75 g, 0.01 mol), acetic acid (2.4 g, 0.04 mol), and benzene (45 ml) are refluxed for 4 h with continuous water separation. The mixture is then washed with water and with sodium hydrogen carbonate solution and is dried with magnesium sulfate. Benzene is removed by distillation under reduced pressure. The oily residue solidifies on cooling and is recrystallized twice from petroleum ether; yield: 6.2 g (60%); m.p. 71–72°.

$C_{14}H_{12}N_2$	calc.	C 80.74	H 5.80	N 13.45
(208.3)	found	80.92	5.90	13.24

I.R. (KBr): $\nu_{max}=2238$ cm^{-1} (CN).

^{1}H-N.M.R. (CDCl$_3$): $\delta=7.12$ (m, 5H$_{arom}$); 3.97 (t, 1H, CH$_{tert}$, $J=7.0$ Hz); 2.92 [m, 2H, $(NC)_2C{=}C{-}CH_2{-}$]; 247–1.65 ppm (m, 4H).

5-Amino-4-cyano-2,3-dihydro-1*H*-benzo[*e*]indene (7) and 5-Amino-4-aminocarbonyl-2,3-dihydro-1*H*-benzo[*e*]indene (8):

The ylidenemalonodinitrile **6** (2.5 g, 0.01 mol) is dissolved in conc. sulfuric acid (12.5 ml) at 5–10°. The mixture is kept at room temperature overnight and is then poured onto ice. The precipitated solid is isolated by suction (the filtrate is saved), washed with water, dried, sublimed in vacuo, and recrystallized from dilute methanol: yield of *5-amino-4-cyano-2,3-dihydro-1*H*-benzo*[e]*indene* (**7**): 1.2 g (48%): m.p. 136.5–138°.

$C_{14}H_{12}N_2$	calc.	C 80.74	H 5.80	N 13.45
(208.3)	found	80.36	5.88	13.40

I.R. (KBr): $\nu_{max}=3475$: 3382, 3255 (NH$_2$): 2211 cm^{-1} (CN).

^{1}H-N.M.R. (CDCl$_3$): $\delta=7.55$–7.25 (m, 4H$_{arom}$); 4.87 (s, 2H, —NH$_2$); 3.00 (t, 4H); 2.10 ppm (quintet, 2H).

The filtrate obtained upon isolation of **7** is neutralized with aqueous sodium hydroxide. The resultant precipitate is isolated by suction, washed with water, dried, and recrystallized from methanol to give *5-amino-4-aminocarbonyl-2,3-dihydro-1*H*-benzo*[e]*indene* (**8**) as fluffy colorless needles; yield: 0.5 g (18%): m.p. 260–262° (dec.).

$C_{14}H_{14}N_2O$	calc.	C 74.31	H 6.23	N 12.38
(226.3)	found	74.12	6.28	12.34

I.R. (KBr): $\nu_{max}=3428$, 3397, 3350, 3200 (NH$_2$); 1594 cm^{-1} (C=O).

^{1}H-N.M.R. (DMSO-d_6): $\delta=8.42$–7.65 (m, 4H$_{arom}$); 3.72 (s, 2H, —NH$_2$); 3.32 (m, 4H$_{benzylic}$); 2.30 ppm (m, 2H); no signals for —CONH$_2$ could be detected.

5-Amino-2,3-dihydro-1*H*-benzo[*e*]indene (9):

The *o*-aminonitrile **7** (1.0 g, 4.8 mmol), sodium hydroxide (2.0 g), and ethanol (70 ml) are heated in an autoclave at 200° for 8 h. The mixture is then diluted with water (40 ml), the ethanol is distilled off, the precipitated solid is isolated by suction, and purified by sublimation in vacuo to give **9** as colorless needles; yield: 0.7 g (79%); m.p. 68–68.5°.

$C_{13}H_{13}N$	calc.	C 85.20	H 7.15	N 7.64
(183.3)	found	85.31	7.24	7.49

I.R. (CCl$_4$): $\nu_{max}=3485$; 3402 cm^{-1} (NH$_2$).

^{1}H-N.M.R. (CDCl$_3$): $\delta=7.75$–7.23 (m, 4H$_{arom}$); 6.55 [s, 1H$_{arom}$ (C-4)]; 3.75 (s, 2H, —NH$_2$); 3.04 (t, 2H$_{benzylic}$); 2.90 (t, 2H$_{benzylic}$); 2.05 ppm (quintet, 2H).

2,3-Dihydro-1*H*-benzo[*e*]indene (2a):

The hydrochloride prepared from amine **9** (123 mg, 0.67 mmol) is diazotized in suspension with a solution of sodium nitrite (81 mg). The resultant diazonium salt is reduced in solution with hypophosphorous acid (4.5 g). After work-up as described for **1b** and distillation under reduced pressure, **2a** is obtained as faintly yellow liquid: yield: 70 mg (62%): $n_D^{21.5}$: 1.6313 (Ref.[5], n_D^{25}: 1.6299–1.6306).

^{1}H-N.M.R. (CDCl$_3$)[24]: $\delta=7.82$–7.12 (m, 6H$_{arom}$); 3.19 (t, 2H$_{benzylic}$); 3.04 (t, 2H$_{benzylic}$); 2.15 ppm (quintet, 2H).

2-Phenylcycloheptylidenemalonodinitrile (10):

2-Phenylcycloheptanone[25] (18.8 g, 0.10 mol), malonodinitrile (6.6 g, 0.10 mol), ammonium acetate (1.5 g, 0.02 mol), acetic acid (4.8 g, 0.08 mol), and benzene (60 ml) are refluxed for 4 h with continuous water separation. The mixture is then washed with water and aqueous sodium hydrogen carbonate, and dried with magnesium sulfate. The solvent is removed under reduced pressure and the residue is recrystallized twice from petroleum ether to give **10** as colorless crystals; yield: 13.5 g (57%): m.p. 70.5–71.5°.

$C_{16}H_{16}N_2$	calc.	C 81.32	H 6.82	N 11.85
(236.3)	found	81.42	6.87	11.86

I.R. (KBr): $\nu_{max}=2236$ cm^{-1} (CN).

^{1}H-N.M.R. (CCl$_4$): $\delta=7.55$ (s, 5H$_{arom}$); 4.27 (m, 1H, CH$_{tert}$);3.20–1.05 ppm (m, 10H).

5-Amino-6-cyano-8,9,10,11-tetrahydro-7*H*-cyclohepta[*a*]naphthalene (11):

The ylidenemalonodinitrile **10** (2.0 g, 8.4 mmol) is dissolved in ice-cold sulfuric acid (10 ml) and the mixture is kept at this temperature overnight and then poured onto crushed ice. The precipitated solid is isolated by suction, washed with water, dried, sublimed in vacuo, and recrystallized from petroleum ether (65–85°) to give **11** as colorless crystals; yield: 1.9 g (95%); m.p. 150–151.5°.

$C_{16}H_{16}N_2$	calc.	C 81.32	H 6.82	N 11.85
(236.3)	found	81.38	6.82	11.75

I.R. (KBr): $\nu_{max}=3472$; 3380; 3250 (NH$_2$); 2207 cm^{-1} (CN).

^{1}H-N.M.R. (CDCl$_3$): $\delta=8.15$–7.30 (m, 4H$_{arom}$); 5.02 (s, 2H, —NH$_2$); 3.15 (m, 4H$_{benzylic}$); 1.75 ppm (m, 6H).

5-Amino-8,9,10,11-tetrahydro-7*H*-cyclohepta[*a*]naphthalene (12):

The *o*-aminonitrile **11** (2.0 g, 8.4 mmol), sodium hydroxide (2.0 g), and ethanol (80 ml) are heated in an autoclave at 220° for 8 h.

The mixture is then diluted with water (50 ml) and ethanol is distilled off. The precipitated product is sublimed in vacuo to give **12** as fluffy colorless needles; yield: 1.6 g (89 %); m.p. 84–86°.

$C_{15}H_{17}N$	calc.	C 85.26	H 8.11	N 6.63
(211.3)	found	85.42	8.00	6.38

I.R. (CCl_4): ν_{max} = 3485; 3400 cm^{-1} (NH_2).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.17–7.22 (m, 4 H_{arom}); 6.45 [s, 1 H_{arom} (C-6)]; 3.87 (s, 2H, —NH_2); 3.17 (m, 2 $H_{benzylic}$); 2.88 (m, 2 $H_{benzylic}$); 1.70 ppm (m, 6H).

8,9,10,11-Tetrahydro-7*H*-cyclohepta[*a*]naphthalene (2b):

The amine **12** (150 mg, 0.71 mmol) is converted into the hydrochloride. Acetic acid (1 ml) and water (0.5 ml) are added and **12** is then diazotized in suspension with sodium nitrite (90 mg). Cold hypophosphorous acid (4.0 g) is added and the mixture is kept in a refrigerator overnight. The dark, viscous oil is purified by sublimation under reduced pressure. Recrystallization from methanol gives **2b** as colorless needles; yield: 60 mg (43 %); m.p. 38–39° (Ref.[9], m.p. 40–41°).

M.S. (70 *eV*): *m/e* = 197 (17 %), 196 (M^+, 100), 181 (19), 167 (33), 165 (22), 155 (22), 154 (18), 153 (20), 152 (18), 142 (16), 141 (25).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.12–7.15 (m, 6 H_{arom}); 3.20 (m, 2 $H_{benzylic}$); 2.94 (m, 2 $H_{benzylic}$); 1.70 ppm (m, 6H).

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[21] 2-(1-Cyclohexen-1-yl)-cyclohexylidenemalonodinitrile (**3b**) and 10-amino-9-cyano-1,2,3,4,5,6,7,8-octahydrophenanthrene (**4b**) were prepared following Jaeger's procedure (see Ref. 14).

Compound **3b**; yield: 75 %; m.p. 70–71° (from petroleum ether).

$C_{15}H_{18}N_2$	calc.	C 79.61	H 8.02	N 12.38
(226.3)	found	79.38	7.89	12.43

I.R. (KBr): ν_{max} = 2227 (CN); 1595 cm^{-1} (C=C).

^{1}H-N.M.R. (CCl_4): δ = 5.52 (m, 1H, =CH—); 3.55 (m, 1H, CH_{tert}); 3.0–1.65 ppm (m, 14H).

Compound **4b**; yield: 96 %; m.p. 157° (from ethanol).

$C_{15}H_{18}N_2$	calc.	C 79.61	H 8.02	N 12.38
(226.3)	found	79.47	7.94	12.45

I.R. (Nujol): ν_{max} = 3478; 3389; 3260 (NH_2); 2204 cm^{-1} (CN).

^{1}H-N.M.R. ($CDCl_3$): δ = 4.05 (s, 2H, —NH_2); 2.80 [m, 2H(C-8)]; 2.45 (m, 6 $H_{benzylic}$); 1.77 ppm (m, 8H).

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[24] For compounds **1a**, **2a**, **7**, and **9**, the ^{1}H-N.M.R. signals of the benzylic cyclopentene protons appear as two overlapped triplets. The coupling between the methylene protons of these compounds is in the range J = 7.1–7.5 Hz.

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