

**Synthesis of 3,4,5,6,7,8-Hexahydro-2*H*-4a,8-alkanopyrido[4,3-*d*]pyrimidines from *N,N'*-Dibenzylidenephénylmethanediamines and Some 2-Substituted Cyclanones**

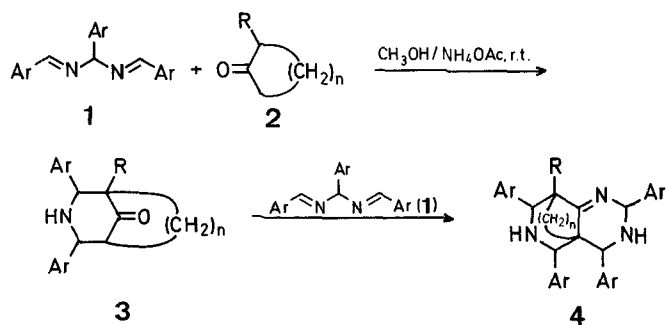
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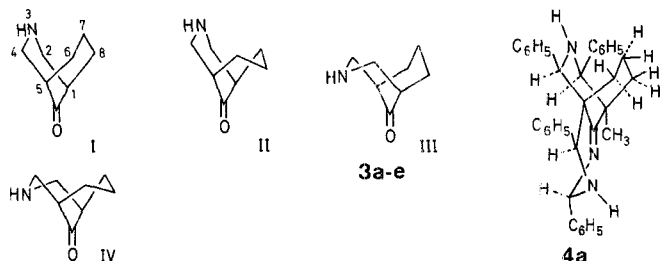
In the course of our studies on *N,N'*-dibenzylidenephénylmethanediamine (**1a**; Ar = C<sub>6</sub>H<sub>5</sub>) for the synthesis of heterocycles, we have found that the double Schiff base **1**, via the Michael reaction, sometimes affords novel nitrogen-containing heterocyclic compounds on treatment with active methylene compounds in the presence of ammonium acetate<sup>1-4</sup>. We report here on the synthesis of 8-substituted 2,4,5,7-tetraaryl-3,4,5,6,7,8-hexahydro-2*H*-4a,8-alkanopyrido[4,3-*d*]pyrimidine **4** from the reaction of **1** with 2-substituted cyclanones **2**. The reaction of **1** with 2-methylcyclohexanone (**2**; R = CH<sub>3</sub>, n = 3) sometimes gave 1-methyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones<sup>5</sup> (**3**) as the reaction intermediate.



3	Ar	R	n	4	Ar	R	n
3a	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	3	4a	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	3
3b	4-H <sub>3</sub> C-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	3	4b	C <sub>6</sub> H <sub>5</sub>	COOCH <sub>3</sub>	2
3c	4-H <sub>3</sub> CO-C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	3	4c	4-H <sub>3</sub> C-C <sub>6</sub> H <sub>4</sub>	COOCH <sub>3</sub>	2
				4d	4-H <sub>3</sub> C-C <sub>6</sub> H <sub>4</sub>	COOC <sub>2</sub> H <sub>5</sub>	2
				4e	4-H <sub>3</sub> CO-C <sub>6</sub> H <sub>4</sub>	COOC <sub>2</sub> H <sub>5</sub>	2

In general, the reaction was carried out by magnetically stirring a mixture of **1**, **2**, and ammonium acetate in methanol at ambient temperature (25–35 °C) until no further precipitate was produced. From the reaction with **1a** (Ar = C<sub>6</sub>H<sub>5</sub>), 2-methylcyclohexanone (**2a**) afforded, via the intermediate 1-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**3a**), crystals whose structure was assigned as 8-methyl-2,4,5,7-tetraphenyl-3,4,5,6,7,8-hexahydro-2*H*-4a,8-propanopyrido[4,3-*d*]pyrimidine (**4a**; yield 9% by method A, 29% by method B). 2-Methoxycarbonylcyclopentanone (**2b**) also gave 8-methoxycarbonyl-2,4,5,7-tetraphenyl-3,4,5,6,7,8-hexahydro-2*H*-4a,8-ethanopyrido[4,3-*d*]pyrimidine (**4b**), but in this case, intermediate **3** was not isolated. In contrast, cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, or cyclopentanone react with **2b** to afford a polymeric mass that does not crystallize. *N,N'*-Bis[4-methylbenzylidene]-4-methylphenylmethanediamine (**1b**) or *N,N'*-bis[4-methoxybenzylidene]-4-methoxyphenylmethanediamine (**1c**) gave **3b** or **3c** on similar treatment with **2a**, but products of the type **4** were not formed.

The following four conformations (I-IV) for the 3-azabicyclo[3.3.1] ring moiety of **3a-e** or **4a** are possible, and the  $^1\text{H-N.M.R.}$  spectra, which exhibit a multiplet signal for one proton at  $\delta = \sim 3\text{--}3.5$  ppm, suggest that these compounds adopt the double-chair conformation (I); the signal is assigned to the axial proton at C-7 in I which is deshielded by a van der Waals effect of the nitrogen (1.9 Å away from the proton, by inspection of Dreiding models) lone pair, and by the effect of the magnetic anisotropy of carbonyl or azomethine bond. The most probable conformation of **4a** is also illustrated.



**1-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (3a); Typical Procedure:**

A mixture of **1a** (1.5 g, 5 mmol), **2a** (1.12 g, 10 mmol), and ammonium acetate (0.4 g, 5 mmol) in methanol (5 ml) is magnetically stirred at ambient temperature for two days. The resultant white precipitate is collected by vacuum filtration, washed with methanol ( $2 \times 5$  ml), and air-dried at room temperature to give **3a**; yield: 1.0 g (65%).

**5-Methyl-2,4,5,7-tetraphenyl-3,4,5,6,7,8-hexahydro-2H-4a,8-propano-pyrido[4,3-d]pyrimidine (4a):**

Method A: A mixture of **1a** (3.58 g, 12 mmol), **2a** (1.01 g, 9 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (5 ml) is intermittently stirred at ambient temperature for one month and similarly treated to give white crystalline **4a**; yield: 0.4 g (9%).

Method B: A mixture of **1a** (1.5 g, 5 mmol), **3a** (1.52 g, 5 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (10 ml) is magnetically stirred at ambient temperature for 10 days and worked up as described above to give **4a**; yield 0.73 g (29%).

**Table.** Compounds **3** and **4** prepared

Product	Reaction time	Yield [%]	m.p. <sup>a</sup> [°C]	Molecular formula <sup>b</sup>	I.R. (Nujol) $\nu$ [cm <sup>-1</sup> ]	$^1\text{H-N.M.R.}$ (CDCl <sub>3</sub> ) $\delta$ [ppm]
<b>3a</b>	2 days	65	124–125°	C <sub>21</sub> H <sub>23</sub> NO (305.4)	3310 (NH); 1710 (C=O); 1130, 765, 702 (CH)	7.6–7.1 (m, 10H <sub>arom</sub> ); 4.31 (d, 1H, N—CH—CH, $J=2.5$ Hz); 3.88 (s, 1H, N—CH); 3.1 (m, 1H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 2.53 (m, 1H, N—CH—CH); 2.3–1.0 (m, 5H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 1.74 (s, 1H, NH); 0.80 (s, 3H, CH <sub>3</sub> )
<b>3b</b>	7 days	67	107–109°	C <sub>23</sub> H <sub>27</sub> NO (333.5)	3310 (NH); 1720 (C=O); 1570, 820, 710 (CH)	7.42, 7.38 (2d, 2H <sub>arom</sub> each, $J=8.6$ Hz); 7.14 (d, 4H <sub>arom</sub> , $J=8.6$ Hz); 4.33 (d, 1H, N—CH—CH, $J=3.5$ Hz); 3.88 (s, 1H, N—CH); 3.1 (m, 1H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 2.53 (m, 1H, CH—CH—CH <sub>2</sub> ); 2.36 (s, 6H, 2CH <sub>3</sub> ); 2.3–1.1 (m, 5H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 1.81 (s, 1H, NH); 0.81 (s, 3H, CH <sub>3</sub> )
<b>3c</b>	6 days	59	139–140°	C <sub>23</sub> H <sub>27</sub> NO <sub>3</sub> (365.5)	3320 (NH); 1702 (C=O); 1611, 1510; 1250 (C—O); 1037; 828, 716, 681	7.46, 7.40 (2d, 2H <sub>arom</sub> each, $J=9.0$ Hz); 6.88 (d, 4H <sub>arom</sub> , $J=9.0$ Hz); 4.28 (d, 1H, N—CH—CH, $J=3$ Hz); 3.85 (s, 1H, N—CH); 3.80, 3.77 (2s, 3H each, OCH <sub>3</sub> ); 3.1 (m, 1H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 2.47 (m, 1H, N—CH—CH); 2.3–1.0 (m, 5H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 1.92 (s, 1H, NH); 0.79 (s, 3H, CH <sub>3</sub> )
<b>4a</b>	10 days	29	194–195°	C <sub>35</sub> H <sub>35</sub> N <sub>3</sub> (497.7)	3330, 3320 (NH); 1652 (C=N); 1280; 760, 742, 700 (CH)	7.6–6.5 (m, 20H <sub>arom</sub> ); 5.48 (s, 1H, N—CH—N); 4.18, 4.10, 4.06 (3s, 1H each, N—CH—C); 3.4 (m, 1H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 2.4–1.0 (m, 5H, CH <sub>2</sub> —HCH—CH <sub>2</sub> ); 1.73 (s, 2H, 2NH); 0.97 (s, 3H, CH <sub>3</sub> )
<b>4b</b>	72 days	65	216–217°	C <sub>35</sub> H <sub>33</sub> N <sub>3</sub> O <sub>2</sub> (527.6)	3320 (NH); 1668, 1609 (C=O, C=N); 1255 (C—O); 765, 699 (CH)	7.9–6.7 (m, 20H <sub>arom</sub> ); 5.42, 4.35 (2s, 1H each, N—CH—C); 5.23, 4.83 (2d, 1H each, NH—CH—C, $J=8.0$ Hz) <sup>c</sup> ; 3.70 (s, 3H, CH <sub>3</sub> ); 2.5 (br, 2H, 2NH); 2.7–1.4 (m, 4H, CH <sub>2</sub> —CH <sub>2</sub> )
<b>4c</b>	14 days	26	175–176°	C <sub>39</sub> H <sub>41</sub> N <sub>3</sub> O <sub>2</sub> (583.7)	3310 (NH); 1665, 1610 (C=O, C=N); 1255 (C—O); 810, 720 (CH)	8.0–7.0 (m, 16H <sub>arom</sub> ); 5.83, 5.22, 4.77, 4.31 (4s, 1H each, N—CH—C); 3.71 (s, 3H, OCH <sub>3</sub> ); 2.36 (s, 9H, 3CH <sub>3</sub> ); 2.31 (s, 3H, CH <sub>3</sub> ); 2.1–1.6 (m, 4H, CH <sub>2</sub> —CH <sub>2</sub> ); 1.9 (br, 2H, 2NH)
<b>4d</b>	30 days	88	172–174°	C <sub>40</sub> H <sub>43</sub> N <sub>3</sub> O <sub>2</sub> (597.8)	3330 (NH); 1650, 1600 (C=O, C=N); 1260 (C—O); 810, 720 (CH)	7.9–6.7 (m, 16H <sub>arom</sub> ); 5.37, 5.21, 4.77, 4.30 (4s, 1H each, N—CH—C); 4.19 (q, 2H, OCH <sub>2</sub> CH <sub>3</sub> , $J=7.0$ Hz); 2.35 (s, 9H, 3CH <sub>3</sub> ); 2.29 (s, 3H, CH <sub>3</sub> ); 2.6–1.0 (m, 4H, CH <sub>2</sub> —CH <sub>2</sub> ); 1.9 (br, 2H, 2NH); 1.24 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , $J=7.0$ Hz)
<b>4e</b>	45 days	57	194–196°	C <sub>40</sub> H <sub>43</sub> N <sub>3</sub> O <sub>6</sub> (661.8)	3340, 3310 (NH); 1645, 1611, 1597, 1580, 1509; 1251 (C—O); 1180, 1029, 826, 780, 540	7.9–6.7 (m, 16H <sub>arom</sub> ); 5.35, 5.16, 4.75, 4.28 (4s, 1H each, N—CH—C); 4.17 (q, 2H, OCH <sub>2</sub> CH <sub>3</sub> , $J=7.0$ Hz); 3.81 (s, 9H, 3OCH <sub>3</sub> ); 3.75 (s, 3H, OCH <sub>3</sub> ); 2.4–1.0 (m, 4H, CH <sub>2</sub> —CH <sub>2</sub> ); 2.4 (br, 2H, 2NH); 1.26 (t, 3H, OCH <sub>2</sub> CH <sub>3</sub> , $J=7.0$ Hz)

<sup>a</sup> Recrystallized from 1:1 v/v tetrahydrofuran/methanol; not corrected.

<sup>b</sup> Satisfactory microanalyses obtained: C  $\pm 0.24$ , H  $\pm 0.19$ , N  $\pm 0.33$ .

<sup>c</sup> A singlet was observed for ND—CH—C (D<sub>2</sub>O exchanged).

**8-Methoxycarbonyl-2,4,5,7-tetraphenyl-3,4,5,6,7,8-hexahydro-2H-4a,8-ethanopyrido[4,3-d]pyrimidine (4b); Typical Procedure:**

A mixture of **1a** (3.58 g, 12 mmol), **2b** (1.28 g, 9 mmol), and ammonium acetate (0.77 g, 10 mmol) in methanol (5 ml) is magnetically stirred for one week, then methanol (15 ml) is added, and intermittent stirring is continued for two month. The deposited precipitate is collected and washed with methanol (15 ml) to give **4b** as a white crystalline product; yield: 3.1 g (65%).

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<sup>1</sup> S. Kambe et al., *Synthesis* **1975**, 802.

<sup>2</sup> T. Takajo et al., *Synthesis* **1977**, 647.

<sup>3</sup> T. Takajo, S. Kambe, *Synthesis* **1980**, 833.

<sup>4</sup> T. Takajo, S. Kambe, *Synthesis* **1981**, 151.

<sup>5</sup> V. Baliah, R. Jeyaraman, *Indian J. Chem.* **9**, 1020 (1971).