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Novel Condensation of N,N'-Dibenzylidenephenylmethanediamine and 1,3-Dichloro-2-propanone

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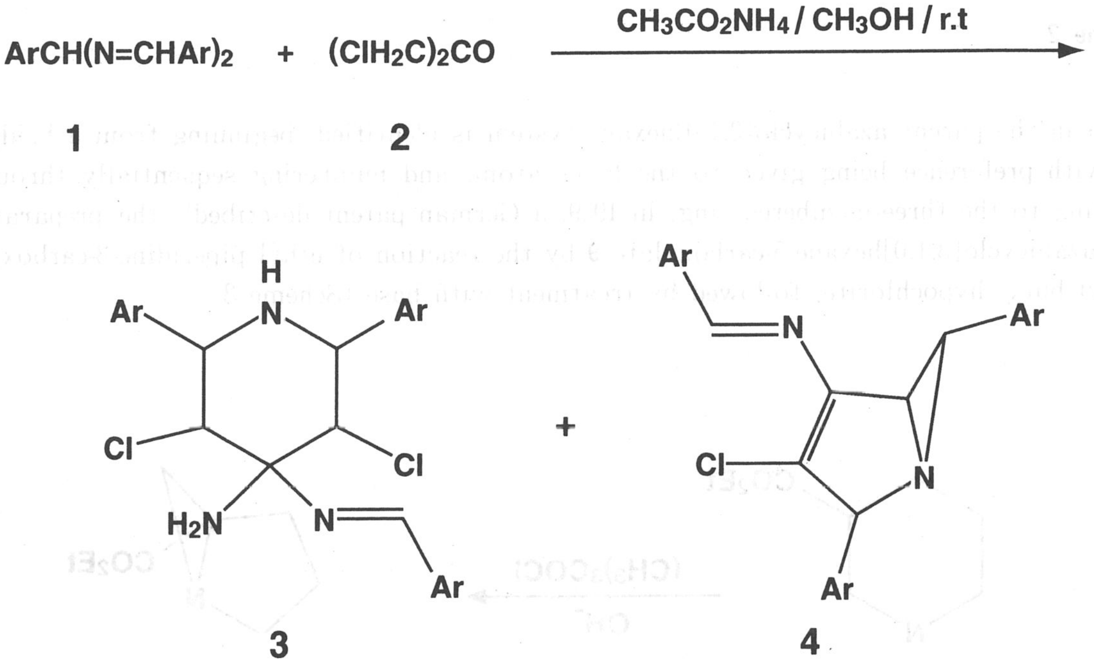
Abstract : N,N'-Dibenzylidenephenylmethanediamine and 1,3-dichloro-2-propanone afford the condensation products from which three crystal compounds are isolated. The two crystal compounds are determined to be 4-amino-4-(N-benzylideneamino)-3,5-dichloro-2,6-diphenylpiperidine and 4-(N-benzylideneamino)-3-chloro-2,6-diphenyl-1-azabicyclo[3.1.0]hex-3-ene.

Heterocyclic compounds are widespread in nature and essential for life in all living organisms. For exampe, adenine, guanine, cytosine or thymine obtained by the hydrolysis of DNA is purine base or pyrimidine base. A number of heterocyclic compounds synthesized only artifically suffer precious properties such as dyes, chemotherapeutic agents, copolymeers or agents for fine chemistry.

We were interested in the synthesis[1)] of novel nitrogen-containing heterocyclic compounds based on the double Schiff base of N,N'-diarylmethylenearylmethanediamines **1** , and wish to report here promptly on the synthesis of 4-amino-4-(N-benzylideneamino)-3,5-dichloro-2,6-diphenylpiperidine **3** and 4-(N-benzylideneamino)-3-chloro-2,6-diphenyl-1-azabicyclo[3.1.0]hex-3-ene **4** from N,N'-dibenzylidenephenylmethanediamine **1a** and 1,3-dichloro-2-propanone **2** (Scheme 1).



Scheme 1

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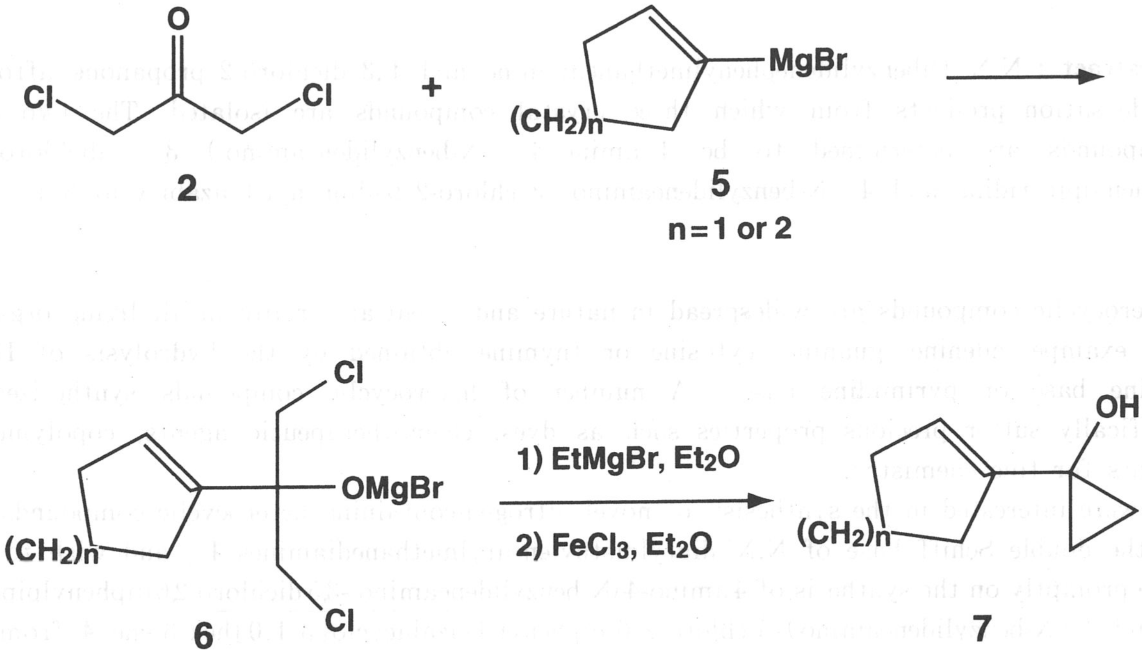
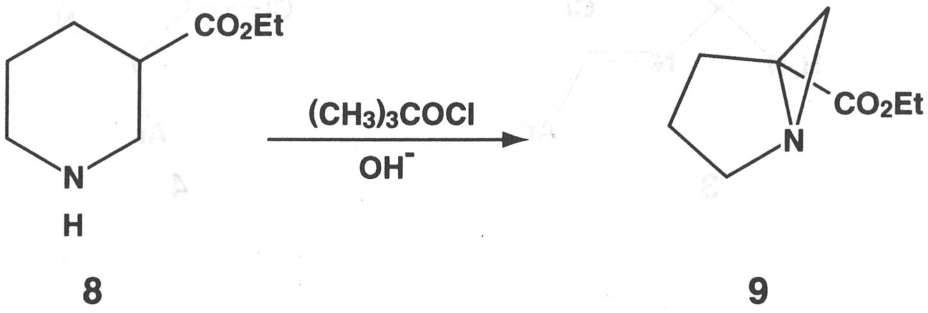
1,3-Dichloro-2-propanone **2** is used for synthesis of cyclopropanes, highly strained systems. Following a known synthesis of 1-alkylcyclopropanols[2)], addition of vinylic Grignard reagents **5** to **2** led to the magnesium salt **6** of a 1,3-dichloro alcohols which ring closed to 1-vinylcyclopropanols **7** induced by the highly reactive low valent ion formed *in situ,* by the simultaneous addition of etheral solutions of ethylmagnesium bromide and anhydrous ferric chloride[3)] (Scheme 2).



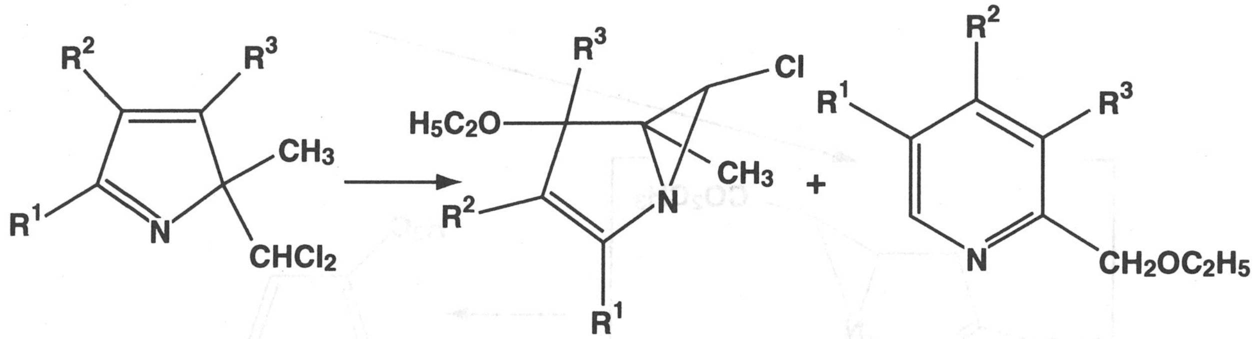
Scheme 2

Position in the parent azabicyclo[3.1.0]hexane system is identified, beginning from a bridgehead atom, with preference being given to the heteroatom, and numbering sequentially through the larger ring to the three-membered ring. In 1959, a German patent described[4)] the preparation of ethyl 1-azabicyclo[3.1.0]hexane-5-carboxylate **9** by the reaction of ethyl piperidine-3-carboxylate **8** with tert-butyl hypochlorite, followed by treatment with base (Scheme 3).



Scheme 3

Azabicyclohexenes can be prepared by substitution reactions, but the method is not general. Treatment of the 2H-pyrroles **10a** and **10b** with sodium ethoxide in ethanol gives the azabicyclohexenes **11a** and **11b**5) 6). In the case of **10b**, the pyridine compound **12b** is also formed and the 2H-pyrrole **10c** affords only the pyridine compound **12c** and no azabicyclohexene **11c**6). Compound **11a** can be recoverted to the 2H-pyrrole **10a** by treatment with hydrochloric acid5) (Scheme 4).

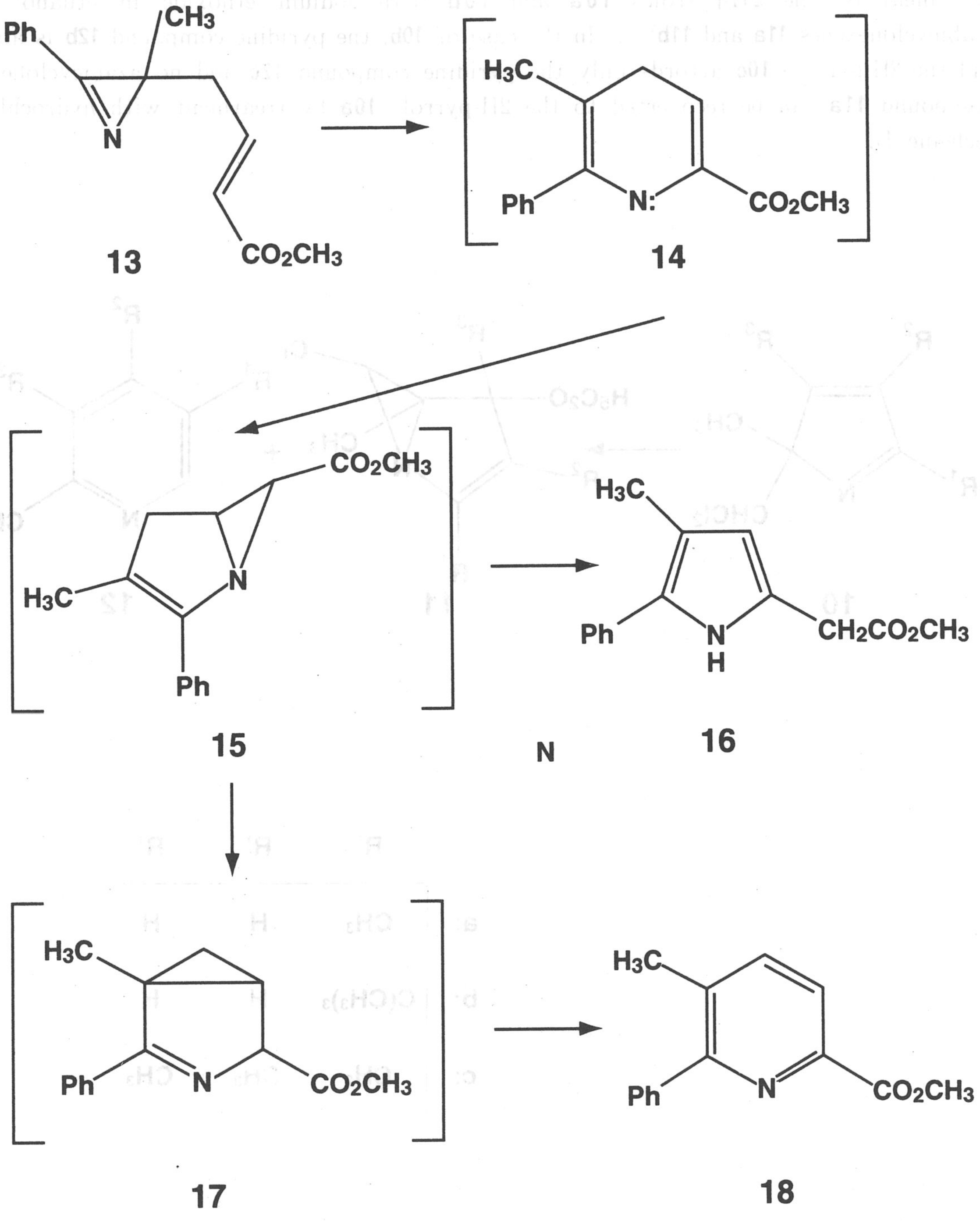


10 **11** **12**

	R^1	R^1	R^1
a:	CH_3	H	H
b:	$C(CH_3)_3$	H	H
c:	CH_3	CH_3	CH_3

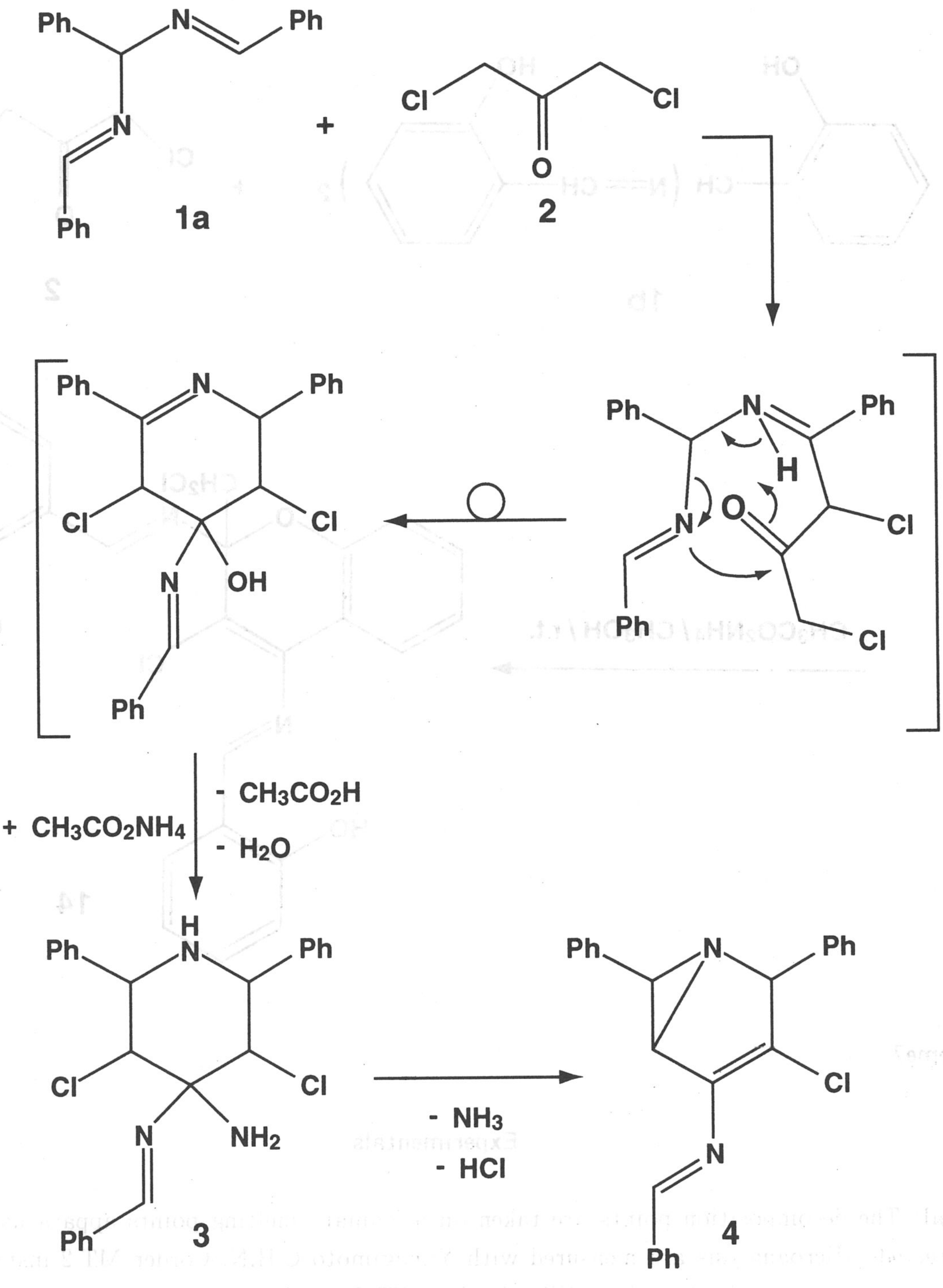
Scheme 4

The 1-azabicyclo[3.1.0]hex-2-ene **15** has been postulated as an intermediate in the thermal rearrangement of the 2H-azirine **13** at 180℃ to the pyrrole **16** and the pyridine **18**7), the latter formed via the intermediate **17**. The formation of **15** is thought to arise via intramolecular addition of the vinyl nitrene **14** (Scheme 5).



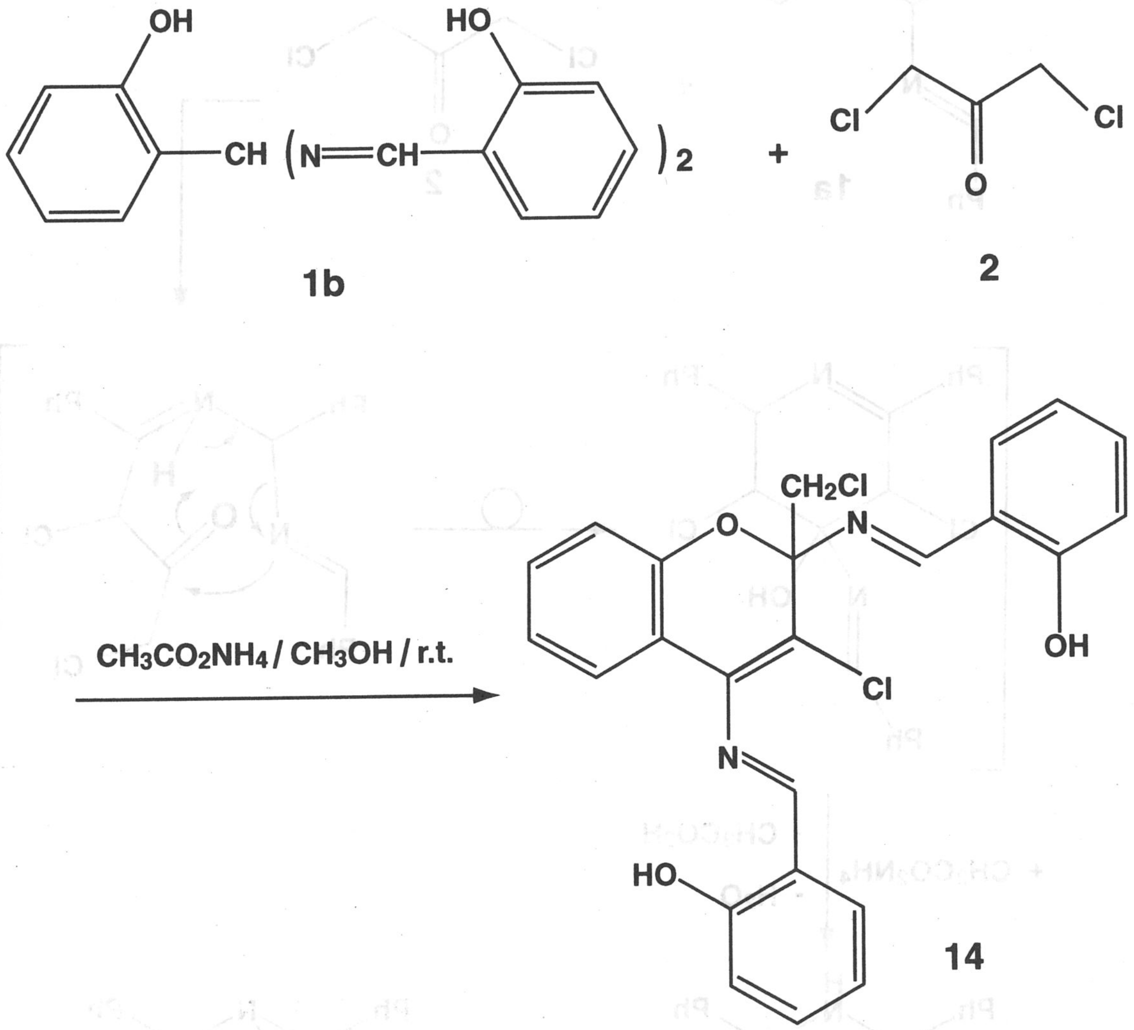
Scheme 5

The condensation reaction of N,N'-dibenzylidenephenylmethanediamine **1a** and 1,3-dichloro-2-propanone **2** is believed to be initiated by the Michael type reaction of the active methylene compound to one azomethine group of the double Schiff base, followed by the rearrangements of another azomethine group and the protone of imino group, and then the intramolecular cyclocondensation and the conversion of hydroxy group into amino group to produce 4-amino-4-(N-benzylideneamino)-3,5-dichloro-2,6-diphenylpiperidine **3** of which dehydrochlorination and deamination result in the formation of 4-(N-benzylideneamino)-3-chloro-2,6-diphenyl-1-azabicyclo [3.1.0]hex-3-ene **4** (Scheme 6).



Scheme 6

On the other hand, similar treatment of N,N'-bis[2-hydroxybenzylidene]-2-hydroxyphenylmethanediamine **1b** and **2** fails to yield 4-amino-4-(N-2-hydoxybenzylideneamino)-3,5-dichloro-2,6-bis[2-hydroxyphenyl]piperidine and 4-(N-2-hydroxybenzylideneamino)-3-chloro-2,6-bis[2-hydroxyphenyl]-1-azabicyclo[3.1.0]hex-3-ene, but expected product[8] of 2N,4N-bis[2-hydroxyphenylmethylene]-2-chloromethyl-3-chloro-2,3-dihydro-4H-1-benzopyran-2,4-diamine **14** (Scheme 7).



Scheme7

Experimentals

General: The decomposition points are taken on a Yamato melting points apparatus MP-21 and uncorrected. Microanalysis are measured with Yanagimoto C.H.N. Corder MT-2 instrument. The FT-IR specra are obtained with a Nihonbunkou FT-7300 type spectrometer. High resolution ^{1}H -NMR spectra are recorded on a Hitachi R-900 NMR spectrometer at 90 MHz. Spin decoupling are used for the assignments. The ^{13}C -NMR spectra are recorded on a Hitachi R-900 NMR spectrometer at 22.6 MHz. Proton wide band decoupling, off resonance decoupling and gate (NOE) decoupling methods are used. The NMR spectra are determined in deuteriochloroform using tetramethylsilane as the internal standard; the chemical shifts are expressed in terms of values (ppm), the coupling constants are simply first order values obtained from the spacing in the spectra, and given on Hz; s = singlet, d = doublet, m = multiplet.

Materials: A mixture of N,N'-dibenzylidenephenylmethanediamine **1a** (6.0 g, 20 mmol), 1,3-dichloro-2-propanone **2** (2.6 g, 20 mmol) and ammonium acetate (3.2 g, 40 mmol) in methanol (25 ml at first and 25 ml added after 3 hours and then 25 ml further added after 2 days) is stirred at ambient temperature for **4** days. A crystalline matter which precipitates is filtered, washed with methanol and dried, gives 3.85 g of the crude products.. By the fractional crystallization of them, three colorless crystallines having respectively a melting point of 157-158 ℃、195-195.5 ℃ or 228-229 ℃ are isolated. On the other hand, the compound, mp 157-158 ℃、 is main product in the cases stirred only for one days, and buttressed to be 4-amino-4 (N-benzylideneamino)-3,5-dichloro-2,6-diphenylpiperidine **3** by the following data.

$C_{24}H_{23}N_3Cl_2$ (424.4)	calc.	C 67.92	H 5.47	N 9.90
	found	67.80	5.39	9.98

I.R.(KBr): ν =3409(NH); 3331(NH); 1652(C=N); 1600; 1455; 1032; 757; 698; 663; 557 cm^{-1}.

^{1}H -N.M.R.(CDCl$_3$/TMS$_{int}$): δ = 8.40 (s, 2"-H); 7.88-7.77, 7.56-7.23(2m, 3 and 12 H$_{arom}$); 4.54(d, 2-H + 6-H, $J_{2,3}$, $J_{6,5}$ = 8.9 Hz) ; 4.48(d, 3-H + 5-H, $J_{3,2}$, $J_{5,6}$ = 8.9 Hz); 2.14 (br. s, NH$_2$); 2.10 ppm (shoulder s, NH).

^{13}C -M.N.R.(CDCl$_3$/TMS$_{int}$): δ = 157.5 (d, C-2", $^1J_{CH}$ =156 Hz); 140.6 (s, C-1'+C-2"); 135.7 (s, C-3"); 131.0 (d, C-6", $^1J_{CH}$ =160 Hz); 128.9 (d, 2C$_{arom}$, $^1J_{CH}$ =160 Hz); 128.7 (d, 2C$_{arom}$, $^1J_{CH}$ =160 Hz); 128.4 (d, 6C$_{arom}$, $^1J_{CH}$ =160 Hz); 128.3 (d, 4C$_{arom}$, $^1J_{CH}$ =160 Hz); 78.2 (s, C-4); 69.5 (d, C-2 + C-6, $^1J_{CH}$ =160 Hz); 63.5 ppm (d, C-3 + C-5, $^1J_{CH}$ =159 Hz).

The compound, mp 195-195.5 ℃、is similarly determained to be 4-(N-benzylideneamino)-3-chloro-2,6-diphenyl-1-azabicyclo[3.1.0]hex-3-ene **4**.

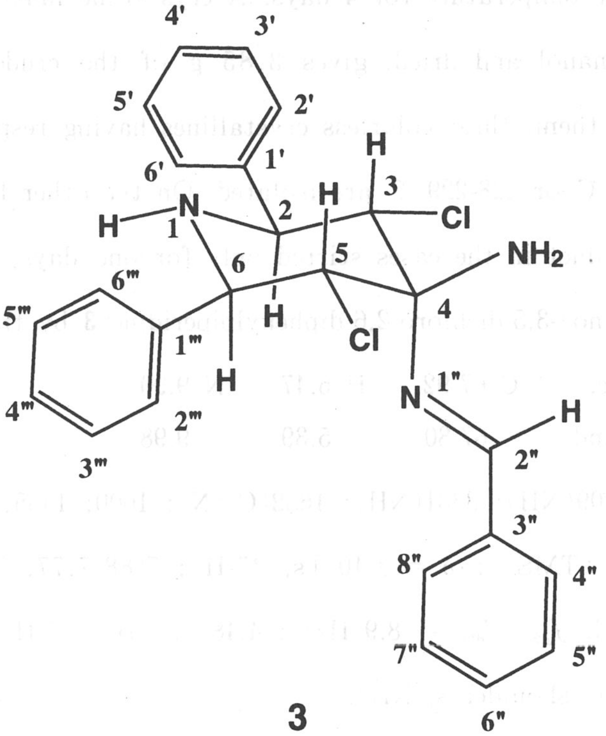
$C_{24}H_{19}N_2Cl$ (370.9)	calc.	C 77.73	H 5.16	N 7.55
	found	78.01	5.06	7.49

I.R.(KBr): ν =1620(C=N); 1563; 1496; 1455; 1260; 1077; 990; 831; 760; 739; 701; 540; 503; 487 cm^{-1}.

^{1}II -N.M.R.(CDCl$_3$/TMS$_{int}$): δ = 8.50 (s, 2"-II); 7.95-7.84, 7.52-7.22(2m, 2 and 13 Harom); 4.93(d, 2-H , $J_{2,5}$ = 3.1 Hz) ; 3.32(dd, 5-H, $J_{5,2}$, = 3.1 Hz, $J_{5,6}$ = 2.1 Hz); 2.88 ppm (d, 6-H, $J_{6,5}$ = 2.1 Hz).

^{13}C -N.M.R.(CDCl$_3$/TMS$_{int}$): δ = 158.7 (d, C-2", $^1J_{CH}$ =159 Hz); 146.0, 140.4, 138.2, 136.0, 126.2 (5s, C-3,4,1',3",1'"); 132.0, 128.3, 127.7(3d, C-4',6",4'", $^1J_{CH}$ =161 Hz); 129.1, 128.9, 128.7, 128.5, 128.0, 126.5 (6d, 2C$_{arom}$ each, $^{1}J_{CH}$ =158~161 Hz); 77.1 (d, C-2, $^{1}J_{CH}$ =143 Hz); 51.7 (d, C-5, 1JCH=166 Hz); 50.3 ppm (d, C-6, 1JCH=181 Hz).

The most reasonable conformations of **3** and **4** are shown as following.



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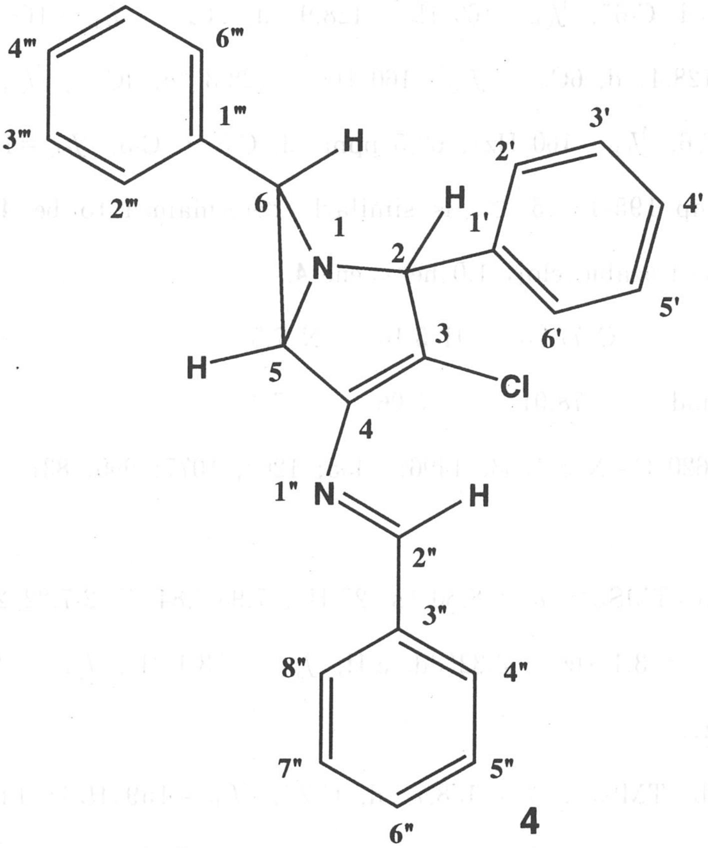

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