The Reaction of Sodium 1,3-Diphenyl-2-azapropenide with 1,2-Epoxycyclohexane [1]

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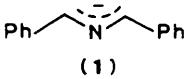
Ring opening of 1,2-epoxycyclohexane by the title aza-allylic anion afforded a mixture of anions, the quenching and subsequent hydrolysis of which gave rise to *trans*-2-(α-aminobenzyl)cyclohexanol (**10**) and benzylamine as the basic fraction, and to either 1-benzoylcyclohexene (**11**) or *trans*-2-benzoylcyclohexanol (**12**), *cis*-2-benzoylcyclohexanol (**14**), and benzaldehyde as the neutral fraction: the type of ketone obtained depended upon the hydrolytic conditions. The perhydrobenzoxazine (**7**) was shown to be the precursor of compound (**10**). Sodium 1,3-diphenyl-2-azapropenide thus behaved both as an α-benzylamine carbanion equivalent and as a benzoyl anion equivalent.

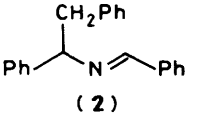
2-Aza-allylic anions have found useful synthetic applications as α-amino carbanion equivalents in alkylation reactions,[2-4] in Michael additions,[5] and as 4π components in cycloaddition reactions.[6] 2-Aza-allylic anions, as α-amino carbanion equivalents, are expected on reaction with epoxides to give rise to β-amino alcohols, an important class of organic compound; a reaction could excite particular interest with chiral epoxides. On this premise we have investigated the reaction of the 1,3-diphenyl-2-aza-allylic anion (**1**) with 1,2-epoxycyclohexane and we report herein that the anion (**1**) behaves only marginally as an α-benzylamine anion equivalent, but reacts predominantly as a benzoyl anion equivalent. Although this result discouraged the extension of the reaction of (**1**) with other epoxides, we have investigated in some detail the origin of the different intermediates.

Results and Discussion

The deep red-purple sodium 1,3-diphenyl-2-azapropenide (**1**) was prepared in THF starting from benzylidenebenzylamine, using $NaNH_2$ as the base. The addition of 1,2-epoxycyclohexane did not cause any appreciable change in colour of the solution, despite the fact that exploratory t.l.c. analysis had shown that the epoxide had disappeared. It is worth noting that this behaviour was in striking contrast to that observed under the same reaction conditions, in the benzylation of (**1**) with benzyl chloride. In this case the colour was discharged almost immediately and, after work up, the benzylation product (**2**) was



(**1**)

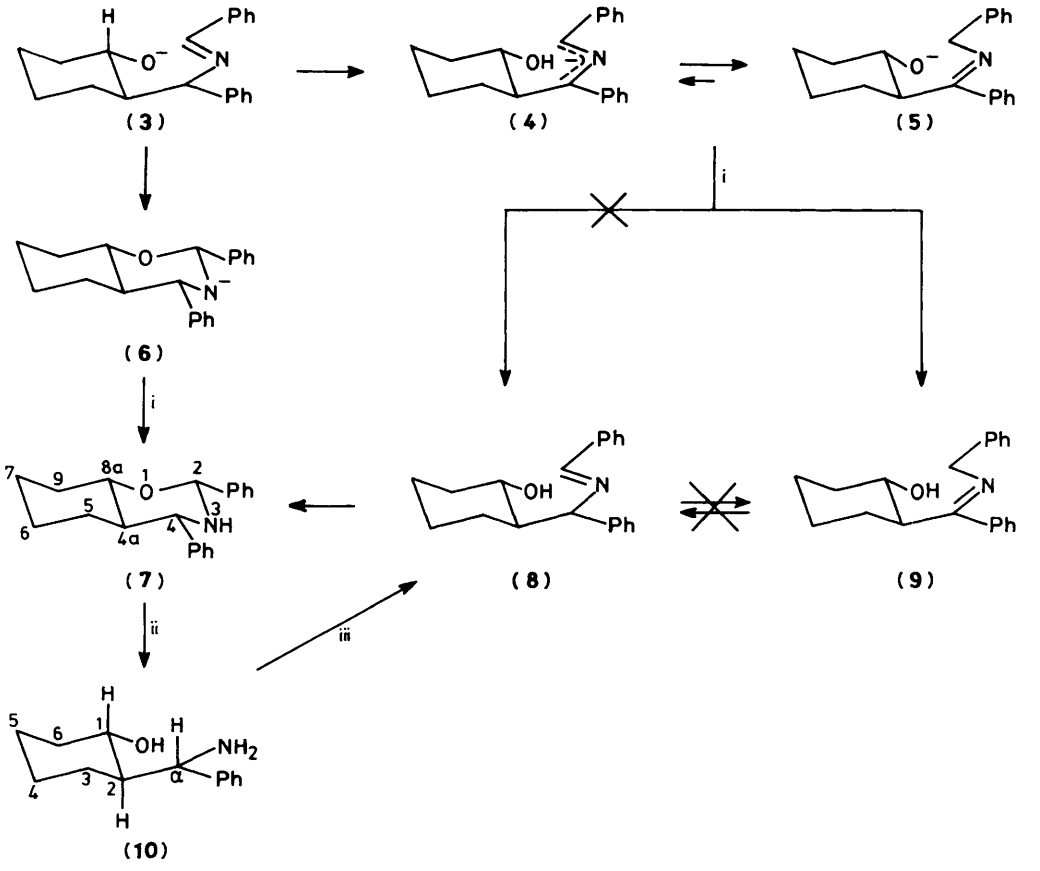


(**2**)

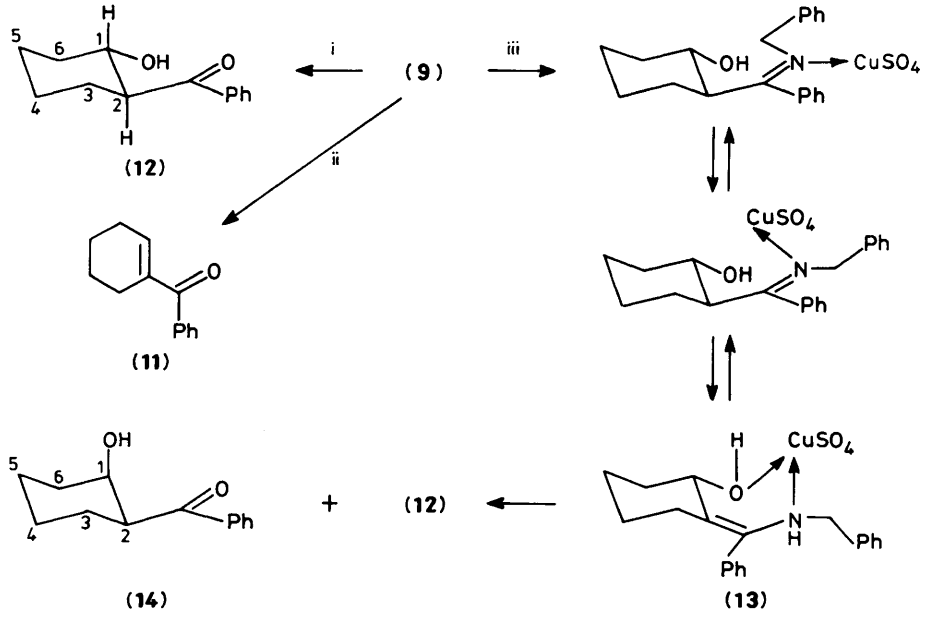
isolated in good yield. Although the discharge of the colour could have occurred by a radical anion sequence instead of a nucleophilic displacement of the chloride ion from benzyl chloride, the persistence of the purple colour in the reacion of the anion (**1**) with 1,2-epoxycyclohexane was not an indication that (**1**) did not react: instead, as it will become evident from results reported hereafter, another 2-aza-allylic anion, different from (**1**) was formed. It will be shown that the species responsible for the purple colour of the solution was the allylic carbanion (**4**). Addition of water to the reaction mixture caused immediate discharge of the colour: the product obtained after work-up was shown to be a mixture of components, the separation of which was difficult by chromatography. Some indications concerning the composition of the mixture obtained after aqueous quenching was provided by ^1H n.m.r. analysis. In particular, it was firmly established (*i*) the presence of the oxazine (**7**), (whose structure was subsequently confirmed by independent synthesis) from the singlet observed at 5.40 p.p.m. in the ^1H n.m.r. spectrum, and (*ii*) the absence of compound (**8**), from the absence of any azomethine proton, expected to appear at *ca.* 8 p.p.m.† Identification of the compounds formed in the reaction was carried out by submitting the mixture obtained after quenching to (A) acidic hydrolysis in boiling dilute hydrochloric acid, (B) acidic hydrolysis with hydrochloric acid at room temperature, or (C) hydrolytic cleavage in the cold in the presence of cupric sulphate.

The hydrolysis under conditions (A) allowed the isolation of 1-benzoylcyclohexene (**11**)[8] and of racemic *trans*-2-(α-aminobenzyl)cyclohexanol (**10**), together with benzaldehyde and benzylamine. The *trans* diequatorial arrangement of the two substituents on the cyclohexane ring of (**10**) was confirmed by the high *trans*-diaxial coupling constant between 1-H and 2-H (Scheme 1). Also, an antiperiplanar arrangement between 2-H and 7-H is confirmed by the size of their coupling constant (10 Hz). The origin of the α,β-unsaturated ketone (**11**) can be ascribed to an acid-catalysed dehydration of the hydroxy ketone (**12**), formed as a primary product by hydrolysis of the Schiff base (**9**). The aminoalcohol (**10**) cannot involve the isomeric Schiff base (**8**) as a precursor since this compound was ascertained to be absent in the original crude mixture obtained after aqueous quenching. The hypothesis that the imine (**9**) could equilibrate with the isomeric imine (**8**) through an immonium ion formed under the acidic conditions used for the hydrolytic cleavage, should also be discarded on the basis of results reported hereafter. Since we failed to isolate either compound (**8**) or (**9**), to check experimentally the above hypothesis we had to revert to model compounds. We chose the isomeric methyl homologues (**15**) and (**18**) of benzylidenebenzylamine; analytically pure samples of both of them were submitted to the same hydrolytic cleavage conditions used for the original mixture obtained after quenching of the reaction of (**1**) with 1,2-epoxycyclohexane. If the immonium ions (**16**) and (**17**), derived respectively from (**15**) and (**18**), would equilibrate, both (**15**) and (**18**) should give rise to the same hydrolysis products: instead, (**15**) gave benzaldehyde and α-phenylethylamine only, and (**18**) gave acetophenone and benzylamine only. Hence, analogously, (**9**) cannot equilibrate with (**8**) under the

† This was indeed the range we always found for the many benzylideneamines we had in hand from other investigations.[7]

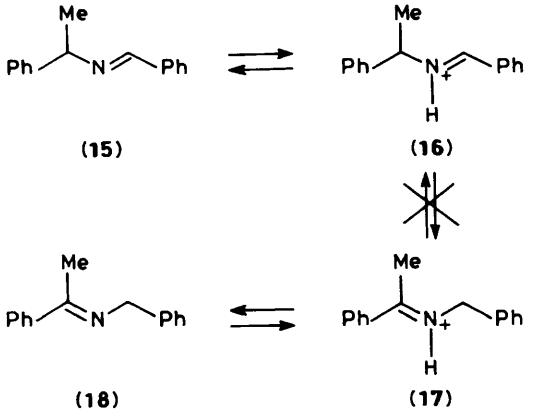


Scheme 1. *Reagents:* i, water; ii, aqueous HCl; iii, PhCHO–Et_2O



Scheme 2. *Reagents:* i, aqueous HCl room temp.; ii, boiling aqueous HCl; iii, aqueous $CuSO_4$.

acidic conditions we used and therefore (**8**) cannot be a precursor of (**10**). We must conclude then that only the perhydrobenzoxazine (**7**) can be the precursor of the amino alcohol (**10**). Treatment of the amino alcohol (**10**) with benzaldehyde in ether and in the presence of a dessicant furnished in high yield the perhydrobenzoxazine (**7**), most probably through the intermediacy of the Schiff base (**8**) which would undergo immediate cyclisation. The obtained product appeared to be a single diastereoisomer: the *trans* diaxial coupling between 4-H and 4a-H indicates an equatorial



disposition of the phenyl group at position 4. Although no evidence is available for the relative stereochemical arrangement of the phenyl ring at position 2, we consider that it would also adopt an equatorial disposition giving rise to a 2,4-*cis* relationship.

The acidic hydrolysis under conditions (B) of the crude mixture obtained after aqueous quenching gave a neutral and a basic fraction. The neutral fraction was essentially composed of benzaldehyde and of the *trans*-2-benzoylcyclohexanol (**12**), identified by spectral comparison with authentic (**12**) isolated from treatment (C). The basic fraction contained benzylamine and the amino alcohol (**10**), identified by spectral comparison with the analytically pure sample previously isolated under treatment (A).

The treatment of the crude mixture obtained after quenching of the reaction of (**1**) and 1,2-epoxycyclohexane, with aqueous cupric sulphate gave a neutral fraction from which column chromatography allowed the isolation and characterisation of *trans*-2-benzoylcyclohexanol (**12**) and *cis*-2-benzoylcyclohexanol (**14**), which were formed in approximately equal amounts, and benzaldehyde. Since nucleophiles open annellated epoxide rings with a high degree of stereospecificity to give *trans*-substitution products,[9] the formation of (**14**) with a *cis* arrangement of the 1,2-substituents on the cyclohexane ring should arise from the intervention of the cupric salt. The simplest explanation for the randomisation of the stereochemistry of C-2 of the cyclohexane ring involves an $sp^3 \longrightarrow sp^2$ rehybridisation at this centre. We propose that the cupric ion promotes, through chelation, the isomerisation of the imine (**9**) into the enamine (**13**), the hydrolytic cleavage of which is expected to give the two isomeric hydroxy ketones (**12**) and (**14**).

A final point which merits consideration is the origin of the perhydrobenzoxazine (**7**). Two hypotheses are possible: either the ring was formed prior to quenching with water or, alternatively it was formed simultaneously with the quenching of the anionic solution. In the first case it would originate from the protonation of the anion (**6**), in turn formed from the anion (**3**) by the attack of the alkoxide oxygen on the azomethine double bond. The net result would be the transformation of an oxy anion into a nitrogen anion. In Me_2SO, alcohols (pK_a = 29—30)[10] are more than a million fold more acidic than ammonia.[11] Relative acidities of alcohols and amines are not known in THF—it may well be that their difference in acidities is greatly reduced in THF relative to Me_2SO thanks to ion pairing or aggregation. If so, the conversion of the oxy anion (**3**) into the nitrogen anion (**6**) should not be a disfavoured 'uphill' transformation and may well take place.

If, alternatively, the benzoxazine (**7**) was formed after the aqueous quenching of the anionic solution, it must arise from the benzylideneamine (**8**), in turn formed by protonation of the anion (**4**). Such a species should be in equilibrium only with the oxy anion (**5**), because, under thermodynamic control, the anion (**3**) should be absent. In fact, unsymmetrically 1,3-disubstituted- and 1,1,3-trisubstituted 2-aza-allylic anions protonate[7] and alkylate[2] at the most acidic site. Indeed we had the opportunity to observe that, under conditions strictly analogous to those we used for quenching the anionic mixture of the anions (**3**)—(**5**), the several other 2-aza-allylic anions we have been studying,[7] invariably afforded products arising from the protonation at the most acidic site. On the basis of these arguments the anion (**3**) should disappear, reverting under thermodynamic control (as seems to be the case) to an equilibrium of anions (**4**) and (**5**).

Protonation of the anion (**4**) at the less substituted terminus should give rise to the Schiff base (**9**), and not to the isomer (**8**), from which the benzoxazine could only be formed. In conclusion, we believe that circumstantial evidence indicates that the benzoxazine (**7**) originates from the nitrogen anion (**6**) already present in the reaction mixture before quenching.

Experimental

Formation of Sodium 1,3-*Diphenyl-2-azapropenide and its Reaction with* 1,2-*Epoxycyclohexane.*—Sodium amide as a 50% w/w suspension in toluene (Fluka) (4—5 ml) was introduced into a tared round bottomed flask equipped with serum caps and a stirring bar. The flask was connected through a stainless steel needle to the vacuum line and the solvent was eliminated to leave powdered sodium amide (2.26 g, 50 mmol). Nitrogen was then introduced: three cycles of vacuum and nitrogen filling were performed. Anhydrous THF (30 ml) was then introduced and thereafter, with stirring, a solution of *N*-benzylidenebenzylamine[2] (5.65 g, 29 mmol) in THF (30 ml). The colour changed gradually to purple-violet and after 4 h, 1,2-epoxycyclohexane (2.85 g, 29 mmol) in THF (15 ml) was then introduced. No change in colour was observed and after 5 h distilled water (1—2 ml) was added; the colour was immediately discharged. The solution was then poured onto brine (80 ml) and extracted with ether (2 × 100 ml). The organic phase was dried (Na_2SO_4) and evaporated to leave a thick brown oil (7.85 g) which was directly treated as indicated in the following procedures (A)—(C), δ_H (90 MHz; $CDCl_3$) peaks at 0.30—2.68 (m), 3.3—4.2 (m), 4.42 (s), 5.38 (s), and 7.0—7.9 (m, ArH) in the ratios 44:11:5:1:40. No peaks were present in the region around 8 p.p.m. characteristic of the N=CH protons: *e.g.* 8.4 p.p.m. for *N*-benzylidenebenzylamine or 7.98 p.p.m. for compound (**15**). The peak at 5.38 p.p.m. can be ascribed to 2-H of compound (**7**) and the singlet at 4.42 p.p.m. to the benzylic protons of compound (**9**).

Hydrolysis of the Crude Hydroxyalkylation Mixture.—Procedure (*A*)*: Isolation of* 1-*benzoylcyclohexene* (**11**) *and* trans-2-(α-*aminobenzyl*)*cyclohexanol* (**10**). The crude reaction mixture obtained as described above (7 g) was treated with 10% hydrochloric acid (80 ml) and heated under reflux for 2.5 h with stirring. The cold mixture was then extracted with ether (40 ml): the organic phase was dried (Na_2SO_4) and evaporated to dryness to leave a residue (3.1 g), the ^1H n.m.r. molar analysis of which revealed it to be composed of 1-benzoylcyclohexene (**11**) (65%) and benzaldehyde (35%). Chromatography on silica gel (120 g) with ethyl acetate–hexane (1:1) as the eluant yielded 1-benzoylcyclohexene,[8] (1.5 g), $\nu_{max.}$(neat) 1 640 cm^{-1} (α,β-unsaturated ketone); δ_H (90 MHz; $CDCl_3$) 1.75 (4 H, m, CH_2CH_2), 2.41 (4 H, m, CH_2–HC=), 6.55 (1 H, m, –CH=), 7.40 (3 H, m, ArH), and 7.60 (2 H, m, *o*-ArH); *m/z* 186 (M^+), and 105 (100%, $M^+ - 81$). The original acidic aqueous fraction was treated with 10% sodium hydroxide to pH 12—13, saturated with NaCl, and extracted with ether (2 × 50 ml). The organic phase was dried (Na_2SO_4), and evaporated to leave a residue (3.06 g), the ^1H n.m.r. molar analysis of which revealed it to be composed of benzylamine (75%) and *trans*-2-(α-aminobenzyl)-

cyclohexanol (**10**) (25%). The residue, when taken up in hexane produced crystals which were recrystallised first from water and then from benzene–hexane to give compound (**10**) (0.83 g), m.p. 118—120 °C (Found: C, 76.3; H, 9.2; N, 6.9. $C_{13}H_{19}NO$ requires C, 76.05; H, 9.3; N, 6.8%); δ_H (220 MHz; $CDCl_3$) 0.5—1.8 (8 H, m, 2-$H_{ax.}$, 3-H, 4-H, 5-H, 6-$H_{ax.}$), 2.0 (1 H, m, 6-$H_{eq.}$, J_{gem} −11.2 Hz), 3.5 (2 H, s, NH_2), 3.61 (1 H, d, $J_{7,2\text{-}ax}$ 10 Hz), 3.63 (1 H, m, $J_{1,2\text{-}ax.}$ 10, $J_{1,6\text{-}ax.}$ 10, and $J_{1,6\text{-}eq.}$ 4.5 Hz, 1-$H_{ax.}$), and 7.2—7.5 (5 H, m, ArH) (assignments were based on decoupling experiments); *m/z* 205 (M^+) and 188 ($M^+ - 17$).

Procedure (*B*): *Identification of* trans-2-*benzoylcyclohexanol* (**12**) *and* trans-2-(α-*aminobenzyl*)*cyclohexanol* (**10**). The crude mixture from the hydroxyalkylation reaction obtained as described before (2.0 g) was taken up with methanol (25 ml), added of 20% hydrochloric acid (17 ml), and stirred at room temperature for 3 h. The solution was then concentrated to one third of the original volume to eliminate the methanol and then extracted with diethyl ether (2 × 30 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness to leave a residue (0.67 g), the ^1H n.m.r. analysis of which showed it to be a mixture of compound (**12**) (as subsequently characterised) and benzaldehyde in the molar ratio of 70:30. The aqueous layer basified with 10% sodium hydroxide to pH 12—13, saturated with sodium chloride, and extracted with ethyl ether (2 × 35 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness to leave a residue (0.64 g), the ^1H n.m.r. analysis of which showed to be a mixture of benzylamine, *trans*-2-(α-aminobenzyl)cyclohexanol (**10**), and *cis*-2,4-diphenyl-*trans*-4a,8a-perhydrobenz[*e*]-1,3-oxazine (**7**) in the molar ratio 60:30:10.

Procedure (*C*): *Isolation of* trans- *and* cis-2-*benzoylcyclohexanol* (**12**) *and* (**14**). The crude hydroxyalkylation mixture obtained as described above (1.45 g) was dissolved in methanol (5 ml) and treated, with stirring, with a solution of cupric sulphate (0.79 g, 4.9 mmol) in water (7 ml). After 1.5 h the mixture was filtered, the solution was evaporated to dryness, and the residue was taken up in water (2 ml) and extracted with diethyl ether (10 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness to give a residue (0.3 g) which upon chromatography on silica gel (20 g) eluting with hexane–ethyl acetate 9.5:0.5 afforded as the first eluate the *cis*-2-benzoylcyclohexanol (**14**) (0.11 g) as an oil, δ_H (220 MHz; $CDCl_3$) 0.9—2.0 (8 H, m, 3—6-H), 3.35 (1 H, m, $J_{2,3\text{-}ax.}$ 12.5, $J_{2,1\text{-}eq.}$ 4.5, $J_{2,3\text{-}eq.}$ 1.6 Hz, 2-$H_{ax.}$) 4.25 (1 H, m, $J_{1,2\text{-}ax.}$ 4.5, $J_{1,6\text{-}ax.}$ 4, and $J_{1,6\text{-}eq.}$ 1.6 Hz, 1-$H_{eq.}$), 7.4—7.6 (3 H, m, ArH), and 7.88—7.92 (2 H, m, *o*-ArH); *m/z* 204 (M^+) and 186 ($M^+ - 18$). The *trans*-isomer was obtained as the second eluate (0.1 g), m.p. 74—75 °C (Found: C, 76.1; H, 8.0. $C_{13}H_{16}O_2$ requires C, 76.3; H, 7.8%); $\nu_{max.}$(Nujol) 3 350 (OH) and 1 660 cm^{-1} (CO); δ_H (220 MHz; $CDCl_3$) 0.81—1.90 (6 H, m, 3-$H_{ax.}$, 4-H, 5-H, 6-$H_{ax.}$), 1.93 (1 H, m, 3-$H_{eq.}$), 2.03 (1 H, m, 6-$H_{eq.}$), 3.23 (1 H, m, $J_{1\text{-}ax,2\text{-}ax.}$ 10.5, $J_{2,3\text{-}ax.}$ 12, and $J_{2,3\text{-}eq.}$ 3.5 Hz, 2-$H_{ax.}$), 4.03 (1 H, m, $J_{1,2\text{-}ax.}$ 10.5, $J_{1,6\text{-}ax.}$ 10.5, and $J_{1,6\text{-}eq.}$ 4.5 Hz, 1-$H_{ax.}$), 7.4—7.6 (3 H, m, ArH), and 7.9—7.94 (2 H, m, *o*-ArH); *m/z* 186 ($M^+ - 18$).

cis-2,4-*Diphenyl*-trans-4a,8a-*perhydrobenz*[e]-1,3-*Oxazine* (**7**).—The amino alcohol (**10**) (179 mg, 0.87 mmol) in ether (40 ml) was treated with freshly distilled benzaldehyde (92.7 mg, 0.87 mmol). To the solution was added anhydrous Na_2SO_4 and the reaction was set aside for 4 h, when it was filtered and evaporated to dryness to leave *compound* (**7**) (208 mg, 81%), m.p. 92—93 °C (Found: C, 81.4; H, 7.7; N, 4.7. $C_{26}H_{23}NO$ requires C, 81.9; H, 7.9; N, 4.8%); δ_H (220 MHz; $CDCl_3$) 0.8—2.1 (9 H, m, CH_2 and 4a-H), 2.45 (1 H, s, NH), 3.50 (1 H, ddd, *J* 11.03, 10, and 4.5 Hz, 8a-H), 3.68 (1 H, d, *J* 11.7 Hz, 4-$H_{ax.}$), 5.40 (1 H, s, 2-H), 7.30 (8 H, m, ArH), and 7.52 (2 H, m, *o*-ArH); *m/z* 293 (M^+).

Acidic Hydrolysis of N-*Benzylidene*-α-*methylbenzylamine* (**15**) *and of* N-(α-*Methylbenzylidene*)*benzylamine* (**18**): *General procedure*.—The authentic Schiff base (**15**)[12] [δ_H (90 MHz; $CDCl_3$) 1.64 (3 H, d, *J* 6 Hz, Me), 4.56 (1 H, q, *J* 6 Hz, CH), 7.4 (8 H, m, ArH), and 7.82 (2 H, m, *o*-ArH), 8.40 (1 H, s, =CH)] or (**18**)[13] [δ_H (90 MHz; $CDCl_3$) 2.35 (3 H, s, Me), 4.78 (2 H, s, CH_2), 7.35 (8 H, m, ArH), and 7.85 (2 H, m, *o*-ArH)], (1.42 g, 7 mmol) in 10% hydrochloric acid (20 ml) was heated at reflux for 2 h; each mixture was cooled, extracted with ethyl ether (20 ml), and, after evaporation to dryness, each afforded a single carbonyl component, benzaldehyde (83%), and acetophenone (85%) respectively. Each acidic aqueous fraction was basified with sodium hydroxide to pH 12—13, and extracted with ether to give each a single amine component, α-methylbenzylamine (80%) and benzylamine (83%) respectively.

α-*Benzyl*-N-*benzylidenebenzylamine* (**2**).—To a solution in THF (25 ml) of sodium 1,3-diphenyl-2-azapropenide (**1**) [obtained from powdered sodium amide (0.5 g, 13 mmol) and *N*-benzylidenebenzylamine[2] (1.3 g, 6.5 mmol) according to the procedure described above] was added dropwise benzyl chloride (1.13 g, 9 mmol) in THF (7 ml) under nitrogen, with stirring. Immediate discharge of the colour was observed and after 10 min, brine was added (60 ml): the mixture was extracted with ether (3 × 30 ml). The combined organic phases were dried (Na_2SO_4) and evaporated to dryness to give *compound* (**2**) (1.5 g, 80%) m.p. 56—58 °C [from light petroleum (b.p. 40—60 °C)] (Found: C, 88.1; H, 6.3; N, 5.1. $C_{21}H_{19}N$ requires: C, 88.4; H, 6.6; N, 4.9%); δ_H (90 MHz; $CDCl_3$) 3.28 (2 H, d, *J* 7 Hz, CH_2), 4.5 (1 H, t, *J* 7 Hz, C*H*CH_2), 7.05—7.60 (13 H, m, ArH), 7.65 (2 H, m, *o*-ArH), and 7.98 (1 H, s, =CH).

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