Stereoselective Additions of Phenylmagnesium Bromide to *N*-Substituted-2-azabicyclo[2.2.2]octa-5- and 6-ones (1)

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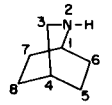
The addition of phenylmagnesium bromide to ketones derived from 2-azabicyclo[2.2.2]-octane was shown to proceed in a stereoselective manner to produce only one of two possible phenyl alcohol derivatives. Factors affecting the course of addition and the determination of relative stereochemistry of the resulting phenyl alcohols are discussed.

Derivatives of 2-azabicyclo[2.2.2]octane (**1**) have been found to possess interesting pharmacological properties.



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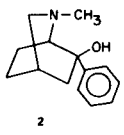
In addition to the presence of this ring system in the structures of the alkaloids ibogamine (hallucinogen) and dioscorine (analeptic), several synthetic derivatives have been investigated for biological activity (2-6). We have previously utilized this ring system as a rigid framework to investigate the importance of conformational factors in receptor interactions of local anesthetics (7). Differences in duration of action were observed among the four conformational analogs synthesized and one isomer produced approximately three times the duration of action of procaine. These results prompted us to investigate other analogs of this interesting ring system. As part of our continuing studies the following phenyl alcohols (**2-5**) were needed as intermediates.



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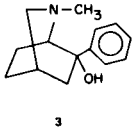

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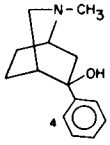

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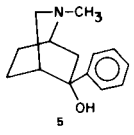

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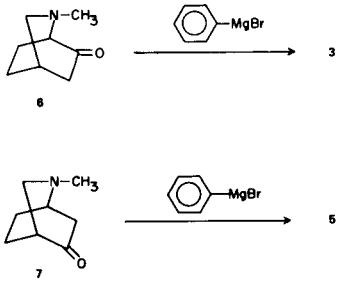
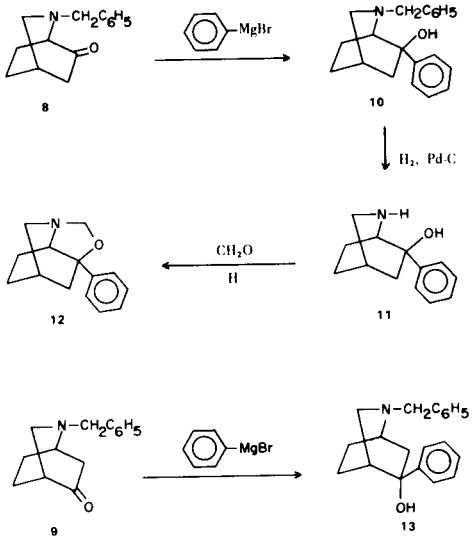
We anticipated that addition of phenylmagnesium bromide to 2-methyl-2-azabicyclo[2.2.2]oct-6-one (**6**) would yield a mixture of isomeric phenyl alcohols **2** and **3** while similar addition to the 5-ketone (**7**) would a mixture of **4** and **5**. To our surprise, only one alcohol was isolated in each case (Scheme I). Only the 6-*trans*-hydroxy-6-*cis*-phenyl alcohol (**3**) was isolated from the addition of phenylmagnesium bromide to **6**. No isomeric alcohol was detected by glc or tlc procedures or during column chromatographic purification of the reaction mixture. The stereochemistry of addition was determined primarily on the basis of dilution ir spectra of **3** which were taken as 1%, 0.01 *M* and 0.002 *M* solutions in carbon tetrachloride. A 0.005 *M* solution is regarded as sufficiently dilute to exclude all intermolecular hydrogen bonding interactions (8). The ir spectrum of **3** (0.002 *M* carbon tetrachloride) showed hydroxyl absorption at 3630 cm^{-1} indicative of an unassociated hydroxyl group. The absence of intramolecular hydrogen bonding between the hydroxyl group and the ring nitrogen atom is consistent with a *trans* orientation of the hydroxyl group with respect to the nitrogen bridge. Similar results were observed when **7** was used as the starting ketone. Again only one phenyl alcohol derivative was detected and isolated and was shown to be the 5-*trans*-hydroxy-5-*cis*-phenyl isomer (**5**). The ir spectrum of **5** (0.002 *M* carbon tetrachloride) showed absorption at 3600 cm^{-1} again indicative of an unassociated hydroxyl group. Thus, the hydroxyl is assigned a *trans* orientation with respect to the nitrogen bridge.

Scheme I



The stereoselectivity of these additions is presumably due to the steric hindrance of approach to the carbonyl group by the Grignard reagent by the *endo*-protons of the bicyclic ring at the 7-, 8-, and 5- (or 6-) positions. It was anticipated that the direction of attack could perhaps be altered by increasing the bulk of the substituent on the ring nitrogen atom. By increasing the bulk of the substituent at this position it was felt that attack from the *exo*-side of the ring would be less favored and could lead to attack of the Grignard from the *endo*-side of the molecule. Such a change would be expected to have a greater influence on the direction of addition of the 6-ketone than to the 5-ketone because of the closer proximity of the substituent to the carbonyl function. For this purpose the *N*-benzyl derivatives **8** and **9** were selected (Scheme II). Addition of phenylmagnesium bromide to **8**

Scheme II

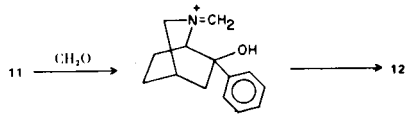


gave only one phenyl alcohol (**10**). However, as predicted the orientation of attack was influenced by the benzyl group. Assignment of relative stereochemistry of **10** was again based primarily on dilution ir spectral data. The presence of hydroxyl absorption at 3400 cm^{-1} (0.002 *M* carbon tetrachloride) was indicative of intramolecular hydrogen bonding. Intramolecular hydrogen bonding is possible only if the hydroxyl group is disposed *cis* to the ring nitrogen atom. Attempts to convert **10** to **2** failed but did yield an unexpected product which supports the assignment of stereochemistry. Debenzylation of **10** by hydrogenolysis yielded the expected secondary amine (**11**). Reductive methylation of **11** did not, however, yield the expected *N*-methyl derivative but rather a product whose ir spectrum showed no hydroxyl absorption and whose nmr spectrum showed no *N*-methyl signal. However, an AB quartet was observed centered at 4.53 δ (J_{AB} = 6.5 Hz, δ_B-δ_A = 16 Hz) indicative of a geminally coupled methylene group. The nmr spectrum, ir spectrum and mass spectral data support the structure of the tricyclic derivative **12**. It is likely that **12** arises by attack of the benzylic hydroxyl group on an intermediate immonium ion formed by the addition of formaldehyde to the secondary amine (Scheme III). The tricyclic intermediate could be formed only if the hydroxyl group is favorably disposed to attack the immonium ion, *i.e.*, the hydroxyl group must be *cis* to the ring nitrogen. The isolation of **12**, although unexpected, does serve to support the assignment of stereochemistry of **10** and supports the use of hydroxyl absorptions in the ir spectra of dilute solutions as a tool for elucidation of stereochemistry of alcohols of this series.

Addition of phenylmagnesium bromide to the *N*-benzyl ketone **9** proceeded in a manner similar to that observed for addition to the *N*-methyl ketone **7**. Again only one phenyl alcohol (**13**) was detected and its ir spectrum (0.002 *M* carbon tetrachloride) showed hydroxyl absorption at 3620 cm^{-1} indicative of a *trans* oriented hydroxyl group.

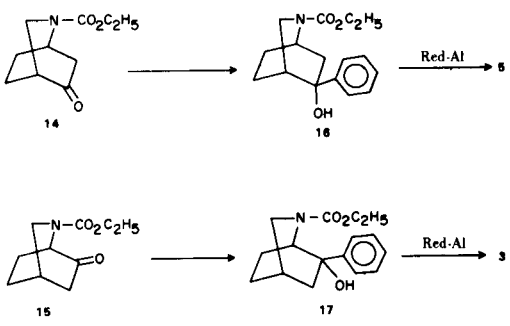
Because of the ability of Grignard reagents to complex with unshared electron pairs (9) and the suggestion that complexation of Grignard reagents with nitrogen lone pair electrons influences the stereochemistry of addition to cyclic aminoketones (10) we examined the addition of phenylmagnesium bromide to ketones **14** and **15**. It was anticipated that coordination of the nitrogen electron pair with the reagent would occur to a lesser degree than possible with the ketones previously described because

Scheme III



of the involvement of the electron pair in resonance with the carbethoxy group. Complexation with the carbonyl oxygen atom is admittedly possible in **14** and **15**, however, no significant differences were observed in the stereoselectivity of similar additions to *N*-methyl-*trans*-deca-

Scheme IV



hydro-4-quinolone (11) and to *N*-benzoyl-*trans*-decahydro-4-quinolone (12). As illustrated in Scheme IV, in each case only one phenyl alcohol was isolated. The direction of addition was shown to be identical with the direction of addition to the *N*-methyl ketones since Red-Al reduction of **16** gave **5** and reduction of **17** gave **3**. It would appear that the nitrogen electron pair plays an unimportant role in the stereoselectivity of addition of phenylmagnesium bromide to the ketones studied. Other studies on similar bicyclic aminoketones concluded that steric factors are the dominant influence on the stereochemical course of such reactions (13).

Our results indicate that the addition of phenylmagnesium bromide to ketones of the 2-azabicyclo[2.2.2]-octane ring system proceeds in a stereoselective manner and that, in the absence of bulky substituents on nitrogen, the direction of addition is controlled primarily by steric hindrance of approach of the Grignard reagent by the *endo*-protons of the bicyclic ring. The use of phenyllithium rather than phenylmagnesium bromide had no effect on the direction of addition to these ketones. If complexation were contributing to the stereoselectivity of these additions differences would be expected in the direction of addition of phenyllithium than observed from addition of phenylmagnesium bromide because of the decreased tendency of organolithium reagents to complex (14). In every addition examined only one phenyl alcohol was obtained; no other phenyl alcohol was detected by glc, tlc, or column chromatographic procedures. Unfortunately, we were unable to achieve a major goal of these studies, *viz.*, the synthesis of **2** or **4**. It should, however, be pointed out that, to our knowledge, this is the first report of Grignard addition to ketone derivatives of this ring system. Page and Pinder (15) reported Reformatsky addition of ethyl 4-bromo-3-methylcrotonate to **7** but did not determine the stereochemistry of the resulting alcohol.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover Unimelt or Mel-Temp apparatus and are corrected. Ir spectra were obtained with a Perkin-Elmer Model 257 or a Beckman IR-33 spectrophotometer. Solution ir spectra were taken in sodium chloride cells of 1.058 mm (reference) and 1.09 mm (sample) widths. Dilution studies were performed using matched sodium chloride cells of 10 mm widths for 0.01 *M* solutions and 25 mm widths for 0.002 *M* solutions. All nmr spectra were obtained on a Jeolco Model C-60-HL spectrometer and all values are reported in ppm (δ) from TMS. Mass spectral data were determined on a Dupont Model 21-492 spectrometer. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona. Thin-layer chromatography was performed on Eastman Chromagram silica gel sheets with fluorescent indicator and were developed with various mixtures of ether-petroleum ether. Gas chromatography was performed on a Varian Aerograph Model 600D Chromatograph equipped with a flame ionization detector and a 5′ x 1/8″ column containing 3% SE-30 on Varaport No. 30 (100-120 mesh). Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride] was purchased from Aldrich Chemical Company.

2-Methyl-6-*trans*-hydroxy-6-*cis*-phenyl-2-azabicyclo[2.2.2]octane (**3**).

Method A.

Into a 1 liter flask equipped with a mechanical stirrer, a nitrogen inlet, an addition funnel and a reflux condenser with a drying tube was added magnesium turnings (0.7 g., 0.03 g.-atom) and 50 ml. of anhydrous ether. A solution of bromobenzene (4.4 g., 0.028 mole) in 50 ml. of ether was added dropwise and the resulting mixture refluxed for 2 hours. A solution of **6** (2.0 g., 0.014 mole) in 60 ml. of ether was slowly added and the resulting mixture refluxed for 24 hours. The mixture was cooled and 10% sodium hydroxide was added dropwise until the solution cleared. The ether was extracted with 10% hydrochloric acid (3 x 70 ml.) and the extracts combined, made basic with potassium carbonate and extracted with chloroform (3 x 100 ml.). The chloroform extracts were combined, dried (magnesium sulfate), and evaporated to yield an oil which solidified on standing; glc and tlc showed only one product. The solid was recrystallized (petroleum ether) to give white crystals (1.9 g., 63%); m.p. 63-65°; ir (carbon tetrachloride): 3630 cm^{-1} (OH, unassociated); nmr (deuteriochloroform): δ 1.4-3.5 [broad signals, 14, bicyclic envelope, OH, and N-CH_3 (s, 2.37)], 7.4-8.0 (m, 5, aromatic).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.32; H, 8.69; N, 6.31.

Method B.

To a solution of phenylmagnesium bromide (13.6 g., 0.075 mole) in 60 ml. of dry tetrahydrofuran was added a solution of **15** (9.9 g., 0.05 mole) in 50 ml. of dry tetrahydrofuran. The resulting mixture refluxed for 24 hours, then cooled to room temperature and 30% ammonium chloride added until the mixture cleared. The tetrahydrofuran was decanted, the aqueous layer washed with tetrahydrofuran (2 x 50 ml.), and the combined organic solutions evaporated; the residue was taken up in chloroform (250 ml.), dried over magnesium sulfate and evaporated to yield a yellow viscous oil (11.2 g., 84%). The crude bicyclic alcohol (1.5 g., 0.0054 mole) was dissolved in 50 ml. of dry benzene and added dropwise to a stirred solution of Red-Al (5.7 ml., 0.02 mole) at room temperature. After addition was complete, the mixture was refluxed for 3 hours and then cooled to room temperature. Ethanol and then water were added dropwise to destroy the excess hydride and the mixture filtered. The filtrate was then washed with water (2 x 50 ml.) and the organic layer dried over magnesium sulfate and evaporated to yield a yellow viscous oil (0.5 g., 36%) which solidified on standing; m.p. 64-65°; glc and tlc indicated only one product; ir and nmr spectral data were identical with the product obtained by Method A.

2-Methyl-5-*trans*-hydroxy-5-*cis*-phenyl-2-azabicyclo[2.2.2]octane (**5**).

Method A.

A solution of **7** (2.0 g., 0.014 mole) in 50 ml. of ether was added dropwise to a stirring solution of phenylmagnesium bromide (7.65 g., 0.042 mole) in 60 ml. of ether. The reaction mixture was refluxed for 24 hours then cooled and 10% sodium hydroxide added dropwise until the solution cleared. The ether was extracted with 10% hydrochloric acid (3 x 60 ml.) and the extracts com-

bined, made basic with potassium carbonate and extracted with chloroform (3 x 80 ml.). The chloroform extracts were combined, dried, and evaporated. The residue was triturated with petroleum ether and filtered to give a white solid (0.9 g., 42%); m.p. 136-138°; ir (carbon tetrachloride): 3600 cm^{-1} (OH, unassociated); nmr (deuteriochloroform): δ 1.1-3.1 [broad signals, 13, bicyclic envelope and NCH_3 (s, 2.33)], 4.2 (broad signal, 1, OH), 7.36-8.1 (m, 5, aromatic).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.19; H, 8.62; N, 6.43.

Method B.

A solution of **14** (5.0 g., 0.025 mole) in 50 ml. of ether was added dropwise to a stirring solution of phenylmagnesium bromide (6.8 g., 0.037 mole) in 70 ml. of ether. The reaction mixture was refluxed for 24 hours then cooled and a saturated solution of ammonium chloride was added dropwise until the mixture cleared. The ether was washed with water (2 x 50 ml.), dried and evaporated to yield a yellow oil. The oil was taken up in 50 ml. of dry benzene and added dropwise to stirring Red-Al (50 ml., 0.36 mole). The resulting solution was refluxed for 2 hours then cooled and the excess hydride destroyed with ethanol-water and filtered. The filtrate was washed with water (2 x 100 ml.), dried, and evaporated. The residue was triturated with petroleum ether and filtered to yield a white solid. Recrystallization from benzene gave white needles (1.4 g., 26%), m.p. 136-138°; ir and nmr data were identical with those of the product in Method A.

2-Benzyl-6-*cis*-hydroxy-6-*trans*-phenyl-2-azabicyclo[2.2.2]octane (**10**).

Method A. Use of Phenylmagnesium Bromide.

To a solution of phenylmagnesium bromide (7.2 g., 0.04 mole) in 50 ml. of dry ether was added a solution of **8** (4.0 g., 0.018 mole) in 50 ml. of dry ether. The resulting mixture was refluxed for 24 hours then cooled to room temperature and 10% sodium hydroxide added until the mixture cleared. The ether was extracted with 10% hydrochloric acid (6 x 100 ml.) and the extracts combined, made basic with potassium carbonate and extracted with chloroform (4 x 100 ml.). The chloroform extracts were combined, dried and evaporated to yield a yellow oil (4.1 g.). The oil was chromatographed on 65 g. of silica gel using ether-petroleum ether (1:4) as eluent to yield the title compound as a clear oil: (2.1 g., 40%); ir (carbon tetrachloride): 3400 cm^{-1} (OH, associated); nmr (deuteriochloroform): δ 1.2-2.80 (broad signal, 9, bicyclic envelope), 3.1-3.4 (broad signal, 1, H at C_1), 3.8 (s, 2, -N-CH_2-Ar), 5.4-5.9 (broad signal, 1, OH), 7.25-7.9 (m, 10, aromatic).

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 82.01; H, 8.03; N, 4.66.

Elution of the column with ether then with acetone failed to yield any other characterizable product.

Method B. Use of Phenyllithium.

To a 1 l. 3-necked flask fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel, and a reflux condenser equipped with a drying tube was added 75 ml. of dry ether and finely cut lithium wire (0.6 g., 0.084 g.-atom). A solution of bromobenzene (8.0 g., 0.05 mole) in 50 ml. of dry ether was added dropwise at a rate to maintain gentle reflux and the resulting mixture was refluxed for 2 hours. The reaction mixture was cooled in an ice bath and a solution of **8** (4.5 g., 0.02 mole) in 60 ml. of dry ether was added dropwise. The solution was refluxed for 24 hours then cooled and 10% sodium hydroxide added dropwise until the solution cleared. The ether was extracted with 10% hydrochloric acid (4 x 100 ml.) and the extracts combined, made basic with potassium carbonate and extracted with chloroform (4 x 100 ml.). The chloroform solution was dried and evaporated to yield a yellow oil (5.7 g.); glc and tlc indicated only one product. Chromatography on 70 g. of silica gel using ether petroleum ether (1:4) as eluent yielded a clear oil (2.8 g., 46%). The ir and nmr spectra of this oil were identical in all respects with the product obtained by Method A.

6-*cis*-Hydroxy-6-*trans*-phenyl-2-azabicyclo[2.2.2]octane (**11**).

A solution of **10** (3.0 g., 0.01 mole) in 100 ml. of absolute ethanol was hydrogenated (3.15 kg./cm^2) over 0.2 g. of 10% palladium on carbon for 6 hours. The catalyst was removed by filtration through Celite and the filtrate evaporated to yield a clear oil (1.8 g.); ir (liquid film): 3360 cm^{-1} (broad, NH and OH); nmr (deuteriochloroform): δ 1.0-3.4 (broad signals, 11, bicyclic envelope and NH), 3.9 (broad signal, 1, OH), 7.4-8.1 (m, 5, aromatic). The hydrochloride was prepared in the normal manner and recrystallized from ethanol-ether to give white needles (1.6 g., 66%), m.p. 238-239°.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.84. Found: C, 64.95; H, 7.66; N, 5.86.

1-Phenyl-2-oxa-4-azatricyclo[4.3.1.0^4]decane (**12**).

A solution of **10** (1.6 g., 0.005 mole) in 50 ml. of ethanol was added to a Paar flask and hydrogenated (3.15 kg/cm^2) over 0.3 g. 10% palladium on carbon for 8 hours then 3 ml. of a 37% aqueous solution of formaldehyde was added and the hydrogenation continued for 4 hours. The catalyst was removed by filtration through Celite and the ethanol evaporated. The residue was taken up in chloroform (100 ml.) and the resulting solution was washed with water (2 x 100 ml.) then dried and evaporated. The residue was chromatographed on 20 g. of silica gel with ether-petroleum ether (1:1) as eluent to yield a clear oil (0.6 g., 54%), ir (carbon tetrachloride): 3100-3000 cm^{-1} (aromatic), 1605 cm^{-1} and 1500 cm^{-1} (aromatic); nmr (deuteriochloroform): δ 1.3-2.6 (broad signals, 7, tricyclic envelope), 2.7-3.1 (broad signals, 2, H at C_5), 3.3-3.6 (broad signal, 1, H at C_9), 4.53 (q, 2, H at C_3), 7.3-7.8 (m, 5, aromatic). The picrate was prepared in the normal manner, m.p. 182-184°.

Anal. Calcd. for $C_{20}H_{20}N_4O_8$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.26; H, 4.38; N, 12.68.

2-Benzyl-5-*trans*-hydroxy-5-*cis*-phenyl-2-azabicyclo[2.2.2]octane (**13**).

A solution of **9** (1.5 g., 0.007 mole) in 30 ml. of ether was added dropwise to a stirring solution of phenylmagnesium bromide (3.8 g., 0.021 mole) in 50 ml. of ether. The resulting solution was refluxed for 24 hours then cooled and 10% sodium hydroxide added dropwise until the solution cleared. The ether was extracted with 10% hydrochloric acid (3 x 50 ml.) and the extracts combined, basified with potassium carbonate, and extracted with chloroform (4 x 30 ml.). The chloroform extracts were combined, washed with water (2 x 40 ml.), dried, and evaporated. The residue was chromatographed on 20 g. of silica gel using ether-petroleum ether (1:4) as eluent to yield an oil which solidified on standing. The solid was recrystallized (*n*-hexane) to yield white needles (0.6 g., 30%), m.p. 91-93°; ir (carbon tetrachloride): 3620 cm^{-1} (OH, unassociated); nmr (deuteriochloroform): δ 1.0-3.2 (broad signals, 10, bicyclic envelope), 3.8 (s, 2, CH_2-Ph), 5.1 (broad s, 1, OH), 7.2-8.2 (broad signals, 10, aromatic).

Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 82.10; H, 7.91; N, 4.98.

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(1) The authors gratefully acknowledge the financial support of this research by a grant (1 R01 NS09188) from the National Institute of Neurological Diseases and Stroke and, in part, by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

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