Ring Closure of 2-Benzylamino-1-phenylethanols to 4-Phenyltetrahydroisoquinolines (1)

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Received May 1, 1974

The facile preparation of 4-phenyltetrahydroisoquinolines by the acid-catalyzed cyclization of 2-benzylamino-1-phenylethanols and related compounds is described along with a discussion of the scope, limitations, and possible mechanism of the reaction.

The preparation of 4-phenyltetrahydroisoquinolines **1** by the acid-catalyzed ring closure of derivatives of 2-benzylamino-1-phenylethanol and related structures has recently received much attention in several laboratories (2a-e). The cyclizations were carried out in sulfuric acid or polyphosphoric acid and, in one instance, ammonia was employed as the dehydrating agent. This paper describes the facile preparation of the cyclized compounds from 2-benzylamino-1-phenylethanols and analogs **2** in 48% hydrobromic acid or polyphosphoric acid along with a discussion of scope, limitations, and mechanism of the reaction.

The precursor compounds **2** (Table I) were prepared by reductive condensation of the appropriate aldehyde **3** with an aminocarbinol **4** using sodium borohydride (Method A) or acid-catalyzed reaction of an aryl ketone **3** and the free base of **4** with continuous removal of water followed by reduction of the intermediate Schiff base to **2** (Method B).

The cyclizations were initially carried out on the free bases of **2** in refluxing 48% hydrobromic acid and the products **1** separated from the cooled reaction mixture (Method C). Although cleavage to the arylmethylamine hydrobromide **5** and ketone **6** occurred in some instances, their separation from **1** posed no particular problem. This method suffered from the limitation that alkoxyl groups were cleaved during cyclization, a limitation avoided by the use of polyphosphoric acid (PPA) in the ring closure (Method D).

The aliphatic C-H signals in the nmr spectra of the products were not sufficiently resolved to permit a decision concerning the stereochemistry of **1**.

Scope and Limitations of the Reaction.

Ring closure to unsubstituted phenyl functions or those containing either electron-donating group(s) or one weakly electron-attracting function was easily effected in refluxing hydrobromic acid. For example, the benzaldehyde derivatives **2a** and **2b** afforded the corresponding isoquinolines **1a** and **1b** respectively in good yields, although a small quantity of cleavage product **5** (R = R″ = H) was isolated in the latter case (Method E). The methoxy compounds **2 (c-e)**, when treated with hydrobromic acid, gave the corresponding hydroxy derivatives **1 (c-e)** while cyclization of **2d** and **2e** in PPA afforded the dimethoxyisoquinolines **1f** and **1g**, respectively. Ring closure of the 2- and 4-chloro compounds **2f** and **2g** in hydrobromic acid gave the expected products **1h** and **1i**, the former in but 13% yield. However, attempted cyclization of the 2,4-dichloro substrate **2h** in hydrobromic acid or PPA resulted only in cleavage to the amine **5** (R = H, R″ = 2,4-diCl) (Method E). The pyridyl and the 4-dimethylamino compounds **2j** and **2k** also afforded only cleavage products in both hydrobromic acid and PPA (Method E).

The nitro compound **2i**, although giving exclusively cleavage product 5 (R = H, R″ = 4-NO_2) in hydrobromic acid, afforded the nitroisoquinoline **1j** in 9% yield when PPA was employed as a cyclizing agent.

The synthesis of 1-substituted-4-phenyltetrahydroisoquinolines was readily effected in hydrobromic acid. For example the methyl, ethyl, and phenyl compounds **2 (l-n)** gave good yields of the corresponding cyclized materials **1 (k-m)**, respectively.

The feasibility of ring closure of a *N*-substituted derivative of **2** was illustrated by the facile conversion of **7** to **8** in hydrobromic acid.

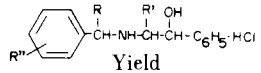
Although the cyclization was largely confined to the preparation of 3-methyl-4-phenyltetrahydroisoquinolines, the methyl group was not required for the annelation as is evidenced by the conversion of **2b** to **1b** (Method E).

The method was restricted to the preparation of 4-phenyltetrahydroisoquinolines. Attempted cyclization of the dephenyl compound **9** to **10** resulted only in the isolation of the starting material.

The use of PPA proved advantageous in the synthesis of methoxy isoquinolines as well as ring closure to deact-

Table I

2-Benzylamino-1-phenylethanols (**2**) (a)

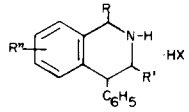


No.	R″	R	R′	Method	M.p. °C (c)	Yield %	Formula	Analysis C Calcd	C Fd	H Calcd	H Fd	N Calcd	N Fd
2a	H	H	CH_3	A	198-199 (EtOH)	89	$C_{16}H_{19}NO\cdot HCl$	69.18	69.29	7.26	7.26	5.04	5.06
2b	H	H	H	A	229-232 (MeOH)	74	$C_{15}H_{17}NO\cdot HCl$	68.30	68.36	6.88	6.65	5.31	5.33
2c	4-CH_3O	H	CH_3	A	183-185 (*i*-PrOH)	65	$C_{17}H_{21}NO_2\cdot HCl$	66.33	66.39	7.21	7.05	4.55	4.51
2d	3,4-diCH_3O	H	CH_3	A	219-221 (MeOH)	74	$C_{18}H_{23}NO_3\cdot HCl$	63.99	63.90	7.16	7.30	4.15	4.02
2e	2,3-diCH_3O	H	CH_3	A	130-133 (MeCN)	64	$C_{18}H_{23}NO_3\cdot HCl$	63.99	64.03	7.16	7.24	4.15	4.15
2f	2-Cl	H	CH_3	A	189-190 (EtOH)	74	$C_{16}H_{18}ClNO\cdot HCl$	61.55	61.80	6.13	6.02	4.49	4.55
2g	4-Cl	H	CH_3	A	218-220 (MeOH)	76	$C_{18}H_{18}ClNO\cdot HCl$	61.55	61.65	6.13	6.16	4.49	4.52
2h	2,4-diCl	H	CH_3	A	246-247 (MeOH)	76	$C_{16}H_{17}Cl_2NO\cdot HCl$	55.43	55.67	5.23	5.29	4.04	4.00
2i	4-NO_2	H	CH_3	A	242-243 (MeOH)	92	$C_{16}H_{18}N_2O_3\cdot HCl$	59.53	59.68	5.93	6.02	8.68	8.67
2j	(4-pyridyl)	H	CH_3	A	229-232 (EtOH)	74	$C_{15}H_{18}N_2O\cdot 2HCl$	57.15	56.90	6.40	6.22	8.88	8.87
2k	4-$(CH_3)_2N$	H	CH_3	A	198-200 (MeOH)	69	$C_{18}H_{24}N_2O\cdot 2HCl$ (b)	59.00	58.71	7.43	7.64	7.65	7.31
2l	H	CH_3	CH_3	B	196-197 (MeCN)	59	$C_{17}H_{21}NO\cdot HCl$	69.96	70.09	7.60	7.75	4.80	4.92
2m	H	C_2H_5	CH_3	B	228-232 (EtOH)	39	$C_{18}H_{23}NO\cdot HCl$	70.69	70.91	7.91	8.04	4.58	4.54
2n	H	C_6H_5	CH_3	B	215-217 (MeCN)	43	$C_{22}H_{23}NO\cdot HCl$	74.66	74.31	6.84	6.81	3.96	4.16

(a) The ir and nmr spectra were consistent with the assigned structures in all cases. (b) Isolated as hemihydrate. (c) Recrystallization solvent in parentheses.

Table II

4-Phenyltetrahydroisoquinolines (**1**) (a)



No.	From	R″	R	R′	Method	M.p. °C (b)	Yield %	Formula	Analysis C Calcd	C Fd	H Calcd	H Fd	N Calcd	N Fd
1a	2a	H	H	CH_3	C	260-262 (EtOH)	84	$C_{16}H_{17}N\cdot HBr$	63.17	62.91	5.96	5.95	4.60	4.59
1a	2a	H	H	CH_3	D	260-262 (EtOH)	53	$C_{16}H_{17}N\cdot HBr$	63.17	62.91	5.96	5.95	4.60	4.59
1b	2b	H	H	H	E	223-225 (EtOH)	58	$C_{15}H_{15}N\cdot HBr$	62.06	61.73	5.56	5.52	4.93	4.79
1c	2c	6-OH	H	CH_3	C	294-297 (EtOH)	76	$C_{16}H_{17}NO\cdot HBr$	60.01	60.11	5.66	5.63	4.37	4.44
1d	2d	6,7-diOH	H	CH_3	C	300-302 (EtOH)	55	$C_{16}H_{17}NO_2\cdot HBr$	57.15	57.44	5.40	5.45	4.17	4.07
1e	2e	7,8-diOH	H	CH_3	C	271-273 (EtOH)	57	$C_{16}H_{17}NO_2\cdot HBr$	57.15	56.99	5.40	5.72	4.17	3.99
1f	2d	6,7-diCH_3O	H	CH_3	D	263-265 (EtOH)	67	$C_{18}H_{21}NO_2\cdot HCl$	67.59	67.54	6.93	6.87	4.38	4.39
1g	2e	7,8-diCH_3O	H	CH_3	D	207-208 (MeCN)	53	$C_{18}H_{21}NO_2\cdot HCl$	67.59	67.63	6.93	6.96	4.38	4.44
1h	2f	8-Cl	H	CH_3	C	218-220 (EtOH)	13	$C_{16}H_{16}ClN\cdot HBr$	56.74	56.77	5.06	5.05	4.14	4.12
1i	2g	6-Cl	H	CH_3	C	298-300 (EtOH)	66	$C_{16}H_{16}ClN\cdot HBr$	56.74	56.74	5.06	5.26	4.14	4.10
1j	2i	6-NO_2	H	CH_3	D	261-262 (MeOH)	9	$C_{15}H_{16}N_2O_2\cdot HCl$	63.05	63.24	5.62	5.61	9.19	9.29
1k	2l	H	CH_3	CH_3	C	279-284 (MeCN)	63	$C_{17}H_{19}N\cdot HBr$	64.15	64.36	6.33	6.25	4.40	4.24
1l	2m	H	C_2H_5	CH_3	C	247-249 (EtOAc)	35	$C_{18}H_{21}N\cdot HBr$	65.06	64.93	6.67	6.68	4.22	4.13
1m	2n	H	C_6H_5	CH_3	C	> 300 (subl.) (MeCN)	44	$C_{22}H_{21}N\cdot HBr$	69.47	69.22	5.83	5.89	3.68	3.67

(a) The ir and nmr spectra were consistent with the assigned structures in all cases. (b) Recrystallization solvent in parentheses.

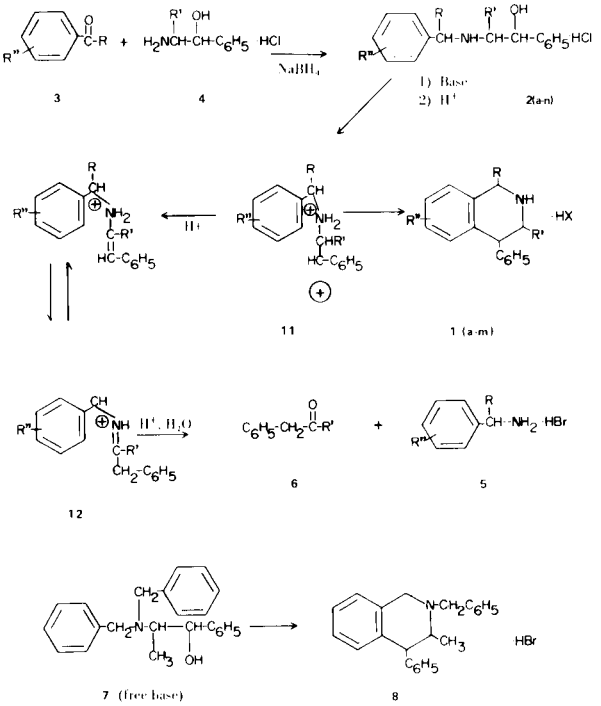
ivated aryl functions (*e.g.* conversion of **2i** → **1j**). However, in cyclizations to a phenyl group containing no deactivating substituent, the use of hydrobromic acid rather than PPA appeared more beneficial. For example, cyclization of **2a** to **1a** proceeded in 84% yield when hydrobromic acid was employed while a 53% yield of the isoquinoline was isolated when PPA was used.

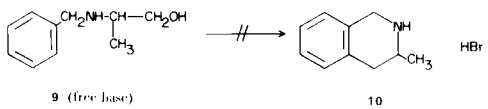
The more facile work-up of the reaction mixture suggests that hydrobromic acid be used for the cyclization whenever possible.

Proposed Mechanism of the Reaction.

The carbonium ion **11**, resulting from the acid treatment of the carbinol **2**, can be invoked in pathways leading to both cyclized and cleavage products. In instances where R″ is hydrogen, electron-donating (*e.g.*, methoxyl), or weakly electron-attracting (*e.g.*, monochloro), the electron density of the phenyl function is sufficiently great that cyclization to the isoquinoline **1** can occur.

Conversely, when the phenyl function contains substituents that are more strongly electron-attracting (*e.g.* dichloro and ammonium), cyclization is prohibited. Instead the carbonium ion **11** gives rise to the Schiff base 12 which is hydrolyzed to **5** and **6** either under the reaction conditions in the case of hydrobromic acid or during work-up when PPA is used. Both **5** and **6** (R′ = CH_3) were isolated in several instances where cyclization failed to occur.





EXPERIMENTAL

The nmr spectra were taken on a Varian A-60A instrument and were compared with TMS as an internal standard. Ir spectra were determined on a Perkin-Elmer 137B spectrophotometer. Melting points were taken on a Mel-Temp block and are uncorrected.

General Method for the Preparation of 2-Benzylamino-1-phenylethanols (**2 a-n**). Table I. Method A. Example: 2-Benzylamino-1-phenyl-1-propanol Hydrochloride (**2a**).

A mixture of 53.0 g. (0.50 mole) of benzaldehyde, 93.5 g. (0.50 mole) of 2-amino-1-phenyl-1-propanol hydrochloride, 50.5 g. (0.50 mole) of triethylamine, and 500 ml. methanol was stirred at room temperature for 30 minutes, and then cooled to 20°. Sodium borohydride (14 g., 0.38 mole) was added at 20-25° over 1 hour. The mixture was stirred at room temperature for 1 hour, concentrated to dryness *in vacuo*, and the residue was slurried with 500 ml. of water. The mixture was extracted with chloroform (2 x 300 ml.); the combined extracts were dried (magnesium sulfate) and concentrated to dryness to give the free base which was used directly in cyclization. Treatment of the free base in methanol with methanolic hydrogen chloride gave the desired compound, m.p. 198-199°; nmr (DMSO-d_6) δ: 1.05 (d, J = 7 Hz, 3, CH_3-CH); 3.35 (m, 1, $CH^{<NH}_{<CH_3}$) 4.35 (s, 2, benzylic CH_2); 5.40 (m, 1, $CH^{<OH}_{<CH}$), 6.15 (broad m, 1, CH-O*H*), 7.30-7.80 (m, 10, aromatic C-H); 9.60 (broad m, 2, NH_2^+); ir (Nujol) μ: 3.00 (O-H); 6.29 (C=C); 9.40 (C-OH).

Method B: Example: 2-(Diphenylmethylamino)-1-phenylpropanol Hydrochloride (**2n**).

A mixture containing 45.3 g. (0.30 mole) of 2-amino-1-phenyl-1-propanol, 54.6 g. (0.30 mole) of benzophenone, 0.5 g. of *p*-toluenesulfonic acid monohydrate, and 225 ml. of xylene was stirred and refluxed using a Dean-Stark apparatus until the theoretical quantity of water was collected (6-8 hours). The solvent was removed *in vacuo* and the residue was partitioned between 500 ml. of water and 250 ml. of chloroform. The aqueous phase was extracted with 250 ml. of chloroform and the combined organic extracts were dried (magnesium sulfate) and concentrated to dryness to give an oil. Sodium borohydride reduction as described above gave the desired compound, m.p. 215-217°; nmr (DMSO-d_6) δ: 1.10 (d, J = 7 Hz, 3, CH_3-CH); 3.10-3.30 (m, 1, $CH^{<NH}_{<CH_3}$); 5.45 (m, 1, $CH^{<OH}_{<CH_3}$); 5.95 (broad m, 2, CH-O*H* and (C_6H_5) *CH*); 7.10-7.90 (m, 15, aromatic C-H); 10.0 (broad m, 2, NH_2^+); ir (Nujol) μ: 3.01 (O-H); 6.31 (C=C); 9.33 (C-OH).

2-(Dibenzylamino)-1-phenylpropanol Hydrochloride (**7**).

A suspension of **2a** free base (45 g., 0.19 mole), benzyl chloride (25.0 g., 0.20 mole), sodium iodide (10 g.), and potassium carbonate (27.6 g., 0.2 mole) in 200 ml. DMF was refluxed for 20 hours. The mixture was concentrated to dryness *in vacuo* and the residue was partitioned between 500 ml. of water and 250 ml. of ethyl acetate. The aqueous phase was extracted with 250 ml. of ethyl acetate and the combined extracts were dried (magnesium sulfate) and concentrated to dryness to give 51 g. of the free base which was suitable for subsequent cyclization. Treatment of an ethanolic solution of the free base with methanolic hydrogen

chloride gave the product in 57% overall yield.

The analytical sample, m.p. 213-214°, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{25}NO \cdot HCl$: C, 75.08; H, 7.12; N, 3.81. Found: C, 75.06; H, 7.09; N, 3.84.

2-Benzylaminopropanol Hydrochloride (**9**).

The title compound was prepared in 58% yield from benzaldehyde and 2-aminopropanol hydrochloride using Method A. The analytical sample, m.p. 109-111°, was obtained from acetonitrile.

Anal. Calcd. for $C_{10}H_{15}NO \cdot HCl$: C, 59.55; H, 8.00; N, 6.94. Found: C, 59.76; H, 8.18; N, 7.00.

General Method for the Preparation of 4-Phenyltetrahydroisoquinolines (**1 a-m**). Table II. Method C. Example: 6-Chloro-3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (**1i**).

A mixture of 55 g. (0.20 mole) of the free base of **2g** and 700 ml. of 48% hydrobromic acid was stirred and refluxed for 18 hours and then cooled in an ice bath. The solid was filtered and thoroughly washed with ethyl acetate to give 44 g. (66%) of the isoquinoline.

The analytical sample, m.p. 298-300°, was recrystallized from ethanol; nmr (DMSO-d_6) δ: 1.28 (d, J = 7 Hz, 3, CH_3-CH); 3.35-4.15 (m, 2,3-CH,4-CH); 4.50 (s, 2, benzylic CH_2); 6.60 (s, 1, aromatic C-H); 7.30 (s, 7, aromatic C-H); 9.60 (broad m, 2, NH_2^+); ir (Nujol) μ: 6.30 (C=C); no O-H at 3.0.

Method D. Example: 7,8-Dimethoxy-3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**1g**).

A mixture of 75.0 g. (0.25 mole) of the free base of **2e** and 525 g. of polyphosphoric acid was stirred for 96 hours and the initial reaction temperature was held at 75-85° by external cooling. The reaction mixture was poured into 2000 ml. of ice water and the mixture was made alkaline with 2000 ml. of 20% sodium hydroxide. The free base was isolated, 47 g. The solid was dissolved in ethanol and the addition of methanolic hydrogen chloride gave 43 g. (53% based on **2e**) of the product. Recrystallization from acetonitrile gave the analytical sample, m.p. 207-208°; nmr (DMSO-d_6) δ: 1.25 (d, J = 7 Hz, 3, CH_3-CH); 3.35-4.20 (m, 2,3-CH,4-CH); 3.70, 3.75 (2s, 6, CH_3O); 4.35 (s, 2, benzylic CH_2); 6.25 (d, J = 9 Hz, 1, aromatic C-H); 6.82 (d, J = 9 Hz, 1, aromatic C-H); 7.20 (s, 5, aromatic C-H); 9.80-10.50 (broad m, 2, NH_2^+); ir (Nujol) μ: 6.21, 6.29 (C=C). No O-H at 3.0.

Method E. Example: Isolation of benzylamine hydrobromide from **2b** and 48% Hydrobromic Acid.

Reaction of **2b** and 48% hydrobromic acid gave a 58% yield of 4-phenyl-1,2,3,4-tetrahydroisoquinoline **1b**, m.p. 223-225° (cf Method C). Concentration of the hydrobromic acid filtrate to dryness gave a semisolid to which was added 200 ml. ethanol and 100 ml. toluene. The mixture was concentrated to dryness and the residue was dissolved in 75 ml. of ethanol. Upon cooling 6.0 g. (11%) of benzylamine hydrobromide was obtained, the ir spectrum of which was identical with an authentic sample of the compound.

Treatment of the phenylethanols **2 (h-k)** with refluxing 48% hydrobromic acid as described above failed to give an acid-insoluble isoquinoline salt. Extraction of the acidic filtrate with chloroform gave the cleavage product phenylacetone **6** ($R' = CH_3$) and concentration of the resulting acidic phase gave the arylmethylamine hydrobromide **5**. Similarly, reaction of **2 (h, j, k)** with PPA yielded only cleavage products.

No attempt was made to isolate possible cleavage products in the synthesis of the other tetrahydroisoquinolines described in Table II.

2-Benzyl-3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (**8**).

Treatment of 10.65 g. (0.032 mole) of the free base of **7** with 160 ml. 48% hydrobromic acid according to Method C gave 9.13 g. (72%) of **8**. Recrystallization from ethanol gave the analytical sample, m.p. 254-258°.

Anal. Calcd. for $C_{23}H_{23}N \cdot HBr$: C, 70.05; H, 6.13; N, 3.55. Found: C, 70.12; H, 6.29; N, 3.54.

Attempted Cyclization of **9** to **10**.

Treatment of **9** free base with refluxing 48% hydrobromic acid failed to give an acid-insoluble isoquinoline salt. Concentration of the acidic reaction mixture and subsequent work-up resulted in the recovery of unreacted carbinol **9**. No attempt was made to cyclize **9** in PPA.

Acknowledgements.

The assistance of Dr. Jerrold T. Meinwald of Cornell University in many fruitful discussions during the course of this work is gratefully acknowledged. Thanks are expressed to Mr. Grant Gustin and Mr. Marvin Tefft for the microanalyses and Mrs. Patricia Curtis for the nmr spectra.

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