Cyclization of *N*-[2-(1-Cyclohexen-1-yl)ethyl]aralkylamides. Synthesis of 1,2,3,4,5,6,7,8-Octahydroisoquinolines and 1-Oxa-3-azaspiro[5.5]undec-2-enes

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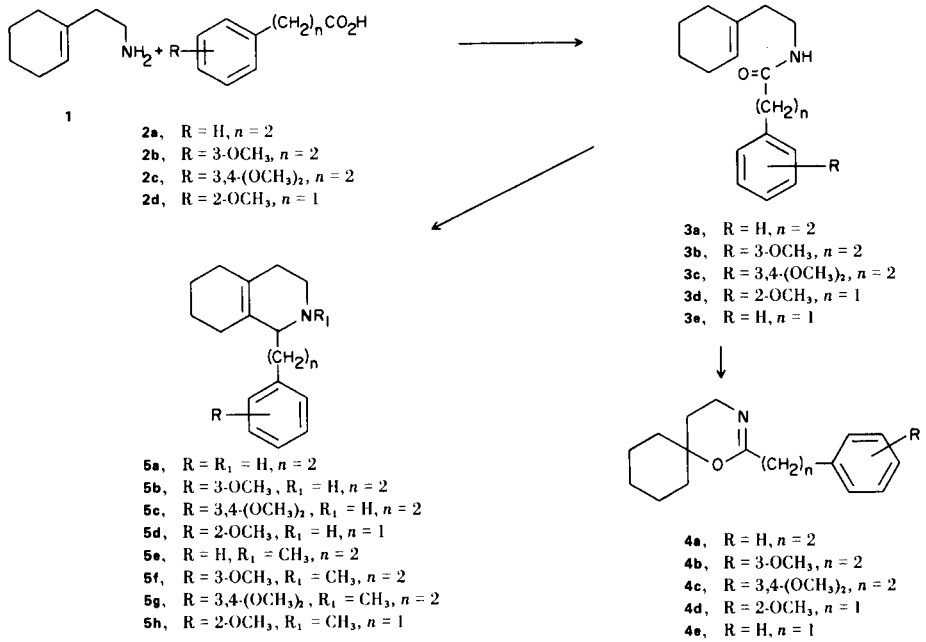
Numerous examples of the conversion of cyclohexenethylamides **3** to octahydroisoquinolines **5** by cyclization with phosphorus oxychloride followed by reduction of the intermediate hexahydro derivatives **10** have been recorded in the literature (2). On the other hand, few examples of the Brønsted acid-induced spirocyclization of amides **3** to 1-oxa-3-azaspiro[5.5]undec-2-enes **4** have been reported (3). In connection with other programs, we prepared olefinic amides **3a-3d** and, for comparative purposes, treated each with phosphorus oxychloride and with polyphosphoric acid. This Note is concerned with the results of these experiments.

The olefinic amides **3a-3d**, prepared from 2-(1-cyclohexen-1-yl)ethylamine (**1**) (4) and commercially available acids **2a-2d** by previously described methods (5), were characterized by spectroscopy; each showed a typical secondary amide absorption band in the 1665 cm^{-1} region of the infrared spectrum (6) and a one-proton multiplet, assignable to the vinyl hydrogen atom, in the δ 5.3 ppm region of the nuclear magnetic resonance spectrum (7).

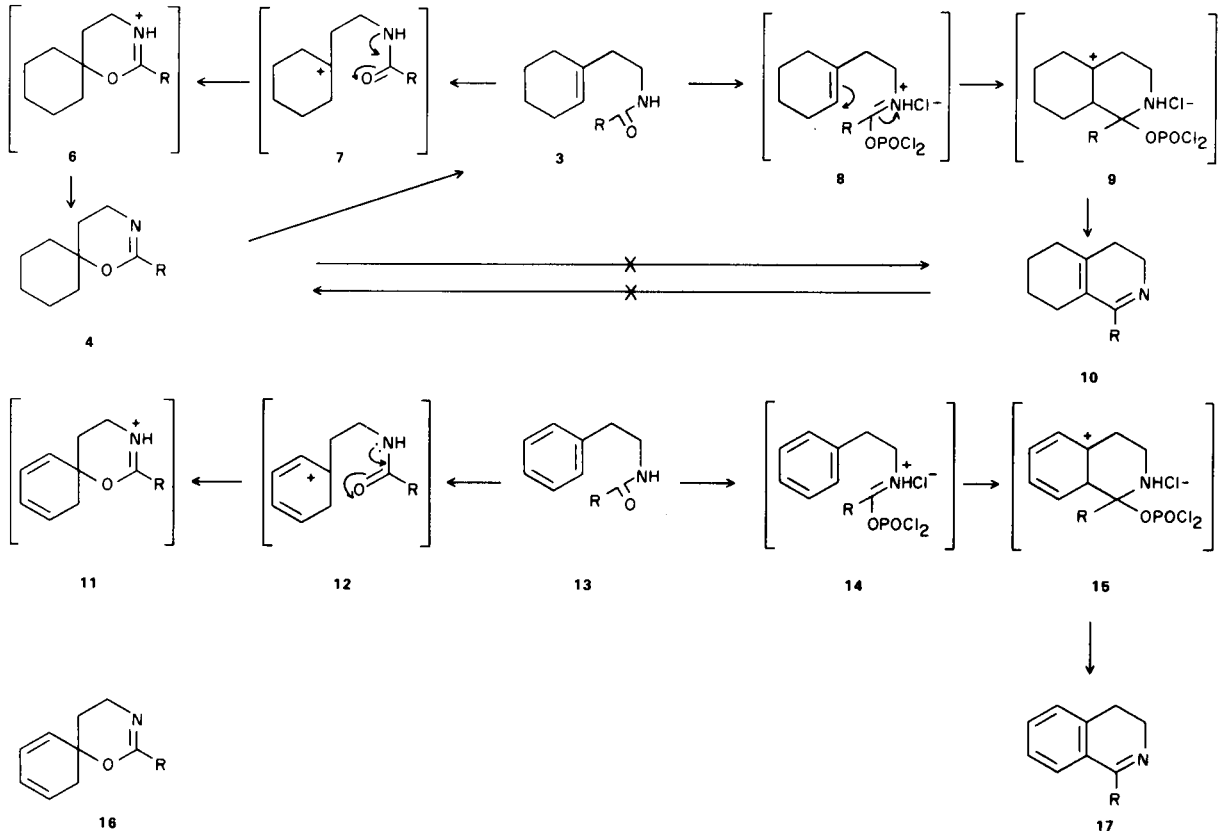
Unsaturated amides **3a-3d** were treated with phosphorus oxychloride in boiling benzene and the reaction products, without further purification, were reduced with hydrogen in the presence of Raney nickel (8) to the octahydroisoquinolines **5a-5d** in moderate yield (see Table I). The proton magnetic resonance spectra of **5a-5d**, which were transparent in the vinyl proton region (7), and the infrared spectra, which showed weak absorption bands between 1600-1700 cm^{-1}, confirmed the anticipated structural assignments. Octahydroisoquinolines **5a-5d** were further characterized by reductive alkylation to the 2-methyl derivatives **5e-5h**.

Olefinic amides **3a-3d** were also treated with polyphosphoric acid at room temperature and the resultant

Scheme I



Scheme II



oxazines **4a-4d** were isolated as hydrohalide salts in good yield (see Table I). Intense iminium absorption bands in the 1670 cm^{-1} region of the infrared spectra (9) of **4a-4d** supported the structural formulations.

Even though oxazine **4d** is thermally unstable and reverts to olefinic amide **3d** upon attempted distillation at 205°, **4d** is stable in boiling benzene containing phosphorus oxychloride, conditions which effect the conversion of unsaturated amides **3** to hexahydroisoquinolines **10** (2). Hexahydroisoquinolines **10** are stable with respect to oxazines **3** in the presence of protonic acids which are utilized or generated in the usual isolation procedures of this isoquinoline synthesis (2,11) and which, as described in this paper, transform **3** to **4**. No evidence (spectral or chromatographic) for the formation of oxazine **4** from **3** and phosphorus oxychloride and hexahydroisoquinoline **10** from **3** and polyphosphoric acid or phosphoric acid was obtained. Thus, oxazines **4** and hexahydroisoquinolines **10** are formed independently and exclusively from **3**. In fact, hexahydroisoquinolines **10** corresponding to the octahydro derivatives **5c** and **5d** were isolated as picrates in 78 and 46% yields, respectively, while oxazines **4c** and **4d** were secured in 89 and 84% yields from the same precursors, **3c** and **3d**.

Formation of hexahydroisoquinolines **10** can be rationalized as occurring through phosphonoimidates **8** fabricated by interaction of phosphoryl chloride with the amide group rather than the less basic ethylene function (12). Cyclization induced by the electrophilic system as depicted in **8** followed by loss of a proton and dichlorophosphoric acid affords **10**. This scheme is analogous to the generally accepted mechanism for the elaboration of dihydroisoquinolines **17** from acylphenethylamines **13** (12), which is also catalyzed by protonic acids (13). That **13** in the presence of protonic acids yields **17** and not spirooxazine **16** is undoubtedly due to the uncompensated loss of resonance energy associated with the destruction of the aromatic system by the required protonation (**12** → **13**). This unfavorable energy situation is not obtained with **3** which gives rise to the stable tertiary carbonium ion upon protonation. Spirocyclization followed by loss of a proton yield oxazines **4**.

TABLE I

Reaction of Olefinic Amides with

Amide	Phosphorus Oxychloride Octahydroisoquinoline	Yield %	Polyphosphoric Acid 1-Oxa-3-Azaspiro[5.5]undec-2-ene	Yield %
3a	**5a**-hydrochloride	54	**4a**-hydrobromide	61
3b	**5b**-oxalate	42	**4b**-hydrochloride	65
3c	**5c**-hydrobromide	51	**4c**-hydrochloride	89
3d	**5d**-hydrobromide (10)	30	**4d**-hydrochloride	47

EXPERIMENTAL (14)

N-[2-(1-Cyclohexen-1-yl)ethyl]-3-(3-methoxyphenyl)propionamide (**3b**).

A solution of 2-(1-cyclohexen-1-yl)ethylamine (**1**) (24.0 g., 0.191 mole), 3-(3-methoxyphenyl)propionic acid (**2b**) (32.5 g., 0.191 mole) and xylene (300 ml.) was boiled under reflux with azeotropic water separation (Dean-Stark trap) for 24 hours and allowed to cool to room temperature. The reaction mixture was washed with 1*N* hydrochloric acid, water, 1*N* potassium carbonate solution and water, dried over anhydrous potassium carbonate and filtered. Distillation of the residue from an oil-jacketed flash gave 3.78 g. (69%) of amide **3b**, b.p. 210-230° (bath temperature, 0.05 mm.).

An analytical sample, prepared by chromatography on alumina followed by distillation, had b.p. 215° (bath temperature, 0.3 mm.); ν max 3390 (NH), 2780 (CH_3O), 1655 (C=O), 1590, 1510 (aromatic) cm^{-1}; λ max 272 nm (ϵ, 1,860), 229 (1,720); δ 1.3-3.5 (multiplet, 16H, $-CH_2-$), 3.74 (singlet, 3H, CH_3O-), 5.38 (multiplet, 1H, vinyl proton), 6.03 (multiplet, 1H, -NH-), 6.6-7.3 (multiplet, 4H, aromatic) cm^{-1}.

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 74.93; H, 8.82; N, 4.98.

The gas-liquid chromatogram (2% XE-60-on-Gas Chrom Z 80/100, column temperature 215°) exhibited one band.

N-[2-(1-Cyclohexen-1-yl)ethyl]-3-(3,4-dimethoxyphenyl)propionamide (**3c**).

Amide **3c** was prepared by the procedure described for **3b**. From amine **1** (62.5 g., 0.500 mole), 3-(3,4-dimethoxyphenyl)-propionic acid (**2c**, 105 g., 0.500 mole) and xylene (1.5 l.), there was obtained 123 g. (75%) of amide **3c**, m.p. 84-85°; ν max 3460 (NH), 2840 (CH_3O), 1669 (C=O), 1610, 1594, 1515 (aromatic) cm^{-1}; λ max 229 nm (ϵ, 8,100), 280 (3,030); λ inf 285 nm (ϵ, 2,440); δ 1.3-3.5 (multiplet, 16H, $-CH_2-$), 3.81 (singlet, 6H, CH_3O-), 5.38 (multiplet, 1H, vinyl proton), 5.90 (multiplet, 1H, -NH-), 6.73 (singlet, 3H, aromatic) ppm.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.65; H, 8.59; N, 4.62.

2-Phenethyl-1-oxa-3-azaspiro[5.5]undec-2-ene Hydrobromide (**4a**).

A mixture of the amide **3a** (4.70 g., 0.0183 mole) (5), 85% phosphoric acid (35 ml.) and phosphorus pentoxide (35 g.) was stirred at room temperature for 2 days. The reaction mixture was poured on to ice-potassium hydroxide (excess) and extracted with methylene chloride. The organic extracts were dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure. The residual oil was dissolved in ether and the solution was added to excess ethereal hydrogen bromide. The precipitate was collected, washed with ether and recrystallized from acetonitrile-ether (1:3); yield 3.75 g. (61%) of oxazine hydrobromide **4a**, m.p. 123-124°; ν max 1670 ($C=\overset{+}{N}$), 1611, 1497 (aromatic) cm^{-1}; λ max end-absorption; δ 1.6-3.6 (multiplet, 18H, $-CH_2-$), 7.25 (singlet, 5H, aromatic), 13 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H<$) ppm.

Anal. Calcd. for $C_{17}H_{24}BrNO$: C, 60.36; H, 7.15; Br, 23.62; N, 4.14. Found: C, 60.19; H, 7.22; Br, 23.68; N, 4.12.

2-(3-Methoxyphenethyl)-1-oxa-3-azaspiro[5.5]undec-2-ene Hydrochloride (**4b**).

1-Oxa-3-azasprio[5.5]undec-2-ene (**4b**) was prepared by the procedure described above. From propionamide **3b** (10.0 g., 0.0349 mole), 85% phosphoric acid (70 ml.) and phosphorus pentoxide (70 g.) there was obtained 7.0 g. (65%) of oxazine **4b** as the hydrochloride, m.p. 99-100°; ν max 2860 (CH_3O), 1675 ($C=\overset{+}{N}$), 1605, 1493 (aromatic) cm^{-1}; λ max 273 nm (ϵ, 2,000), 280 (1,840); δ 1.59 (multiplet, 10H, cyclohexane $-CH_2-$), 1.99 (multiplet, 2H, $-CH_2CH_2NH-$), 3.15 (multiplet, 4H, CH_2CH_2-). 3.56 (multiplet, 2H, $-CH_2\overset{+}{N}H<$), 3.81 (singlet, 3H, CH_3O-), 7.0 (multiplet, 4H, aromatic), 14.1 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H-$) ppm.

Anal. Calcd. for $C_{18}H_{26}ClNO_2$: C, 66.76; H, 8.09; Cl, 10.95; N, 4.32. Found: C, 66.96; H, 8.31; Cl, 10.97; N, 4.56.

2-(3,4-Dimethoxyphenethyl)-1-oxa-3-azaspiro[5.5]undec-2-ene Hydrochloride (**4c**).

1-Oxa-3-azaspiro[5.5]undec-2-ene (**4c**) was also prepared by the method described for **4a**. Propionamide **3c** (10.0 g., 0.0315 mole), phosphorus pentoxide (70 g.) and 85% phosphoric acid (70 g.) gave 9.80 g. (89%) of oxazine **4c** as the hydrochloride, m.p. 117-118°; ν max 2840 (CH_3O), 1670 ($C=\overset{+}{N}$), 1606, 1514 (aromatic) cm^{-1}; λ max 229 nm (ϵ, 7,820), 280 (3,110); λ inf 284 nm (ϵ, 2,650); δ 1.1-3.6 (multiplet, 18H, $-CH_2-$), 3.69, 3.76 (singlets, 6H, CH_3O-), 6.6 (multiplet, 3H, aromatic), 13.6 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H<$) ppm.

Anal. Calcd. for $C_{19}H_{28}ClNO_3$: C, 64.49; H, 7.98; Cl, 10.02; N, 3.96. Found: C, 64.21; H, 7.99; Cl, 9.93; N, 4.05.

Spirocyclization of *N*-[2-(1-Cyclohexen-1-yl)ethyl]-2-(2-methoxyphenyl)acetamide (**3d**).

A. In the Presence of Polyphosphoric Acid.

2-(2-Methoxybenzyl)-1-oxa-3-azaspiro[5.5]undec-2-ene hydrochloride (**4d**) was prepared by the general procedure outlined above. A mixture of acetamide **3d** (10) (10.1 g., 0.0370 mole), 85% phosphoric acid (70 ml.) and phosphorus pentoxide (70 g.) afforded 5.40 g. (47%) of oxazine **4d** as the hydrochloride, m.p.

119-120°; ν max 2850 (CH_3O), 1675 ($C=\overset{+}{N}$), 1593, 1495 (aromatic) cm^{-1}; λ max 272 nm (ϵ, 2,330), 278 (2,330); δ 1.0-3.7 (multiplet, 14H, ring $-CH_2-$), 3.82 (singlet, 3H, CH_3O-), 4.19 (singlet, 2H, ϕCH_2-), 6.7-7.6 (multiplet, 4H, aromatic), 14.1 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H\lessdot$) ppm.

Anal. Calcd. for $C_{17}N_{24}ClNO_2$: C, 65.90; H, 7.81; Cl, 11.44; N, 4.52. Found: C, 65.81; H, 7.87; Cl, 11.23; N, 4.34.

B. In the Presence of 85% Phosphoric Acid.

A solution of acetamide **3d** (10.0 g., 0.0366 mole) and 85% phosphoric acid (100 ml.) was allowed to stand at room temperature for two days. The reaction mixture was poured on to ice-potassium hydroxide (200 g.) and extracted with dichloromethane. The combined organic extracts were washed with saturated sodium hydroxide solution, dried over anhydrous potassium carbonate, filtered and evaporated. The residual oil was dissolved in anhydrous ether (100 ml.) and was treated with excess ethereal hydrogen bromide. The precipitate was collected and recrystallized from acetonitrile-ether (3:1) to give 10.8 g. (83%) of oxazine **4d** as the hydrobromide, m.p. 142-144°; ν max (chloroform) 1660 ($C=\overset{+}{N}$), 1595, 1495 (aromatic) cm^{-1}; λ max 272 nm (ϵ, 1,950), 278 (1,950); δ 1.0-2.2 (multiplet, 12H, ring $-CH_2-$), 3.5-3.9 (multiplet, 5H, CH_3O-, $-CH_2N\lessdot$), 4.12 (singlet, 2H, $-CH_2-$), 6.5-7.4 (multiplet, 4H, aromatic), 13.0 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H\lessdot$) ppm.

Anal. Calcd. for $C_{17}H_{24}BrNO_2$: C, 57.63; H, 6.83; Br, 22.55; N, 3.95. Found: C, 57.55; H, 6.94; Br, 22.74; N, 3.81.

The picrate had m.p. 156-157°; ν max (Nujol) 1640 ($C=\overset{+}{N}$), 1625, 1610 (aromatic), 1560, 1365 (NO_2); λ max 364 nm (ϵ, 16,000); δ (deuteriodimethylsulfoxide) 0.8-2.2 (multiplet, 12H, $-CH_2-$), 3.3-4.0 (multiplet, 7H, CH_3O, $-CH_2\overset{+}{N}=CCH_2-$), 6.7-7.4 (multiplet, 4H, aromatic), 8.55 (singlet, 2H, aromatic), 12 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H\lessdot$) ppm.

In a second experiment the residual oil (1 g.) was placed in the pot of a one piece distillation apparatus and heated to 205° at 0.1 mm. At this temperature the oil solidified. Recrystallization of the solid from cyclohexane gave 0.82 g. (82%) of olefinic amide **3d**, m.p. 91-92° alone or admixed with an authentic sample.

Anal. Calcd. for $C_{23}H_{26}N_4O_9$: C, 54.97; H, 5.22; N, 11.15. Found: C, 54.79; H, 5.24; N, 11.26.

1,2,3,4,5,6,7,8-Octahydro-1-phenethylisoquinoline Hydrochloride (**5a**).

A solution of amide **3a** (4) (257 g., 1.00 mole), phosphorus oxychloride (250 ml.), benzene (3 l.) and ethanol (2 ml.) was heated under reflux for 2 hours and allowed to stand at room temperature for 1 day. The reaction mixture was concentrated. Water (1 l.) was added to the residue; the solution was boiled for 15 minutes, allowed to cool to room temperature and extracted with chloroform. The organic extract was washed with 5% potassium carbonate solution and water, dried over anhydrous potassium carbonate and filtered. Evaporation of the filtrate gave 220 g. of a yellow oil. A mixture of the residual oil, ethanol (1.2 l.) and Raney nickel (8) (50 g.) was hydrogenated on a Parr shaker at room temperature and an initial pressure of 40 psi. After 24 hours, the theoretical quantity of hydrogen was absorbed and there was no additional uptake. The catalyst was collected on a filter, washed with ethanol and the filtrate was concentrated under reduced pressure. The residual oil (217 g.) was dissolved in ether (1 l.) and the solution was added to a solution of hydrogen chloride (33 g.) and ether (1 l.). The precipitate was collected and recrystallized from ethanol; yield 136 g. (54%) of the octahydroisoquinoline hydrochloride **5a**, m.p. 197-198° (lit. (4) m.p. 197-198°); ν max 3370 (NH_2), 1600 (C=C), 1590 (NH_2), 1490 (aromatic) cm^{-1}; λ max 253 nm (ϵ, 166), 259 (201), 264 (156), 268 (133); δ 1.0-4.0 (multiplet, 17H, $-CH_2-$, $\gtrless CH-NH_2-$), 7.14 (singlet, 5H, aromatic), 9.7 (deuterium oxide-exchangeable broad signal, 2H, $-\overset{+}{N}H_2-$) ppm.

2-Methyl-1,2,3,4,5,6,7,8-octahydro-1-phenethylisoquinoline (**5e**).

A solution of 1,2,3,4,5,6,7,8-octahydro-1-phenethylisoquinoline (**5a**) (92.0 g., 0.382 mole), obtained from the hydrochloride by basification with potassium hydroxide solution followed by extraction with ether, 37% formaldehyde solution (36 ml., 0.46 mole) and ethanol (600 ml.) was allowed to stand at room temperature for 1.5 hours. Raney nickel (8) (50 g.) was added and the mixture was shaken on a Parr Pressure Reaction Apparatus at room temperature and an initial pressure of 44 psi. After about 24 hours, the theoretical quantity of hydrogen was absorbed and there was no additional uptake. The catalyst was collected and the filtrate was evaporated under reduced pressure. A 76 g.-sample of the residual oil (87.5 g.) was dissolved in ether (1.2 l.) and the solution was added to a solution of oxalic acid (31.4 g., 0.348 mole) and ethanol (250 ml.). The solid was collected and recrystallized from 2-propanol; yield 86.0 g. (65%) of isoquinolinium **5e** oxalate, m.p. 144-145° (lit. (4) m.p. 145°).

The oxalate (3.0 g., 0.0087 mole) was dissolved in water, basified with 85% potassium hydroxide and extracted with ether. The ether extracts were dried over anhydrous potassium carbonate, filtered and evaporated. Distillation of the residue from an oil-jacketed flask at 0.3 mm. gave 2.0 g. (90%) of **5e**, b.p. 125° (bath temperature); ν max 1602 (C=C), 1595 (aromatic) cm^{-1}; λ max 258 nm (ϵ, 373); δ 1.0-3.0 (multiplet, 20H, $-CH_2-$, $\gtrless\overset{+}{C}HNCH_3$), 7.2 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.80; H, 9.57; N, 5.47.

The gas-liquid chromatogram (2% XE-60-on-Gas Chrom Z 80/100, column temperature 135°) showed one symmetrical band.

1-(3-Methoxyphenethyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline Oxalate (**5b**).

The octahydroisoquinoline **5b** was prepared by the procedure described for **5a**. Propionamide **3b** (188 g., 0.653 mole), phosphorus oxychloride (160 ml., 1.76 mole), benzene (2 l.) and ethanol (2 ml.) gave 172 g. of an oil which was dissolved in ethanol (600 ml.) and hydrogenated at room temperature and an initial pressure of 40 psi in the presence of Raney nickel (8) (20 g.) to **5b**, isolated as the oxalate (42% yield) m.p. 167-169°; ν max (Nujol) 1700 (CO_2H), 1615 (CO_2^-), 1605, 1493 (aromatic) cm^{-1}; λ max 272 nm (ϵ, 2,080), 279 (1,880); δ (deuteriomethanol) 1.4-4.0 (multiplet, 20H, $-CH_2-$, $-CH=$, CH_3O-), 7.0 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.56; H, 7.48; N, 3.84.

The free base had b.p. 150-160° (bath temperature 0.05 mm.), λ max 3660 (NH), 2880 (CH_3O), 1600 (C=C), 1585, 1494 (aromatic) cm^{-1}; λ max 273 nm (ϵ, 2,050), 280 (1,900), δ 1.2-3.3 (multiplet, 18H, $-CH_2$, $\gtrless CHNH-$), 3.75 (singlet, 3H, CH_3O-), 7.0 (multiplet, 4H, aromatic) ppm.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.90; H, 9.36; N, 5.57.

The gas-liquid chromatogram (2% XE-60-on-Gas Chrom Z 80/100, column temperature 135°) showed one symmetrical band.

The hydrochloride of **5b** had m.p. 130-131°; ν max 2300-

2900 ($\overset{+}{N}H_2$), 1600 (C=C, aromatic) 1586 ($\overset{+}{N}H_2$), 1498 (aromatic) cm^{-1}; λ max 272 nm (ε, 2,120), 279 (1,960); δ 1.2-4.0 (multiplet, 20H, $-CH_2-$, $>CH\overset{+}{N}<$ CH_3O), 6.8 (multiplet, 4H, aromatic), 9.6 (deuterium oxide-exchangeable broad signal, 2H, $-\overset{+}{N}H_2-$) ppm.

Anal. Calcd. for $C_{18}H_{26}ClNO$: C, 70.23; H, 8.51; Cl, 11.52; N, 4.55. Found: C, 70.47; H, 8.60; Cl, 11.58; N, 4.59.

1-(3-Methoxyphenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline Hydrobromide (**5f**).

2-Methyloctahydroisoquinoline **5f** was prepared by the procedure outlined for **5e**. Octahydroisoquinoline **5b** (5.00 g., 0.0184 mole), 37.5% formalin solution (1.76 ml., 0.0234 mole) and ethanol (35 ml.) was hydrogenated (room temperature and initial pressure of 40 psi) in the presence of Raney nickel (8) (0.5 g.); yield 4.40 g. (65%) of **5f**-hydrobromide, m.p. 143-144°; ν max 2820 (CH_3O), 1600 (C=C), 1585, 1485 (aromatic) cm^{-1}; λ max 273 nm (ε, 1,980), 280 (1,830); δ 1.3-3.7 (multiplet, 23H, $-CH_2-$, $>CH\overset{+}{N}HCH<$ CH_3O-), 6.8 (multiplet, 4H, aromatic), 10.2 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H<$) ppm.

Anal. Calcd. for $C_{19}H_{28}BrNO$: C, 62.29; H, 7.70; Br, 21.81; N, 3.82. Found: C, 62.33; H, 7.62; Br, 21.86; N, 3.92.

1-(3,4-Dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline Hydrobromide (**5c**).

Octahydroisoquinoline **5c** was also prepared by the procedure described for **5a**. From propionamide **3c** (159 g., 0.501 mole), phosphorus oxychloride (125 ml., 1.37 mole) benzene (1.5 l.) and ethanol (1 ml.), there was obtained 153 g. of an oil which was dissolved in ethanol (900 ml.) and reduced with hydrogen (room temperature and an initial pressure of 40 psi) in the presence of Raney nickel (8) (40 g.) to **5c** isolated as the hydrobromide, m.p. 183-184°; ν max 2400-2700 ($\overset{+}{N}H_2$), 1605 (C=C, aromatic), 1580 ($\overset{+}{N}H_2$), 1512 (aromatic) cm^{-1}; λ max 229 nm (ε, 8,880), 279 (3,060), λ inf 284 nm (ε, 2,560); δ 1.2-4.0 (multiplet, 23H, $-CH_2-$, $>CH-$, CH_3O-), 6.88 (multiplet, 3H, aromatic), 9.4 (deuterium oxide-exchangeable broad signal, 2H, $-\overset{+}{N}H_2-$) ppm in 51% yield.

Anal. Calcd. for $C_{19}H_{28}BrNO_2$: C, 59.69; H, 7.38; Br, 20.90; N, 3.66. Found: C, 59.40; H, 7.47; Br, 21.00; N, 3.96.

The free base **5c** obtained from the hydrobromide by basification (potassium hydroxide solution), extraction (ether) and recrystallization (Skelly B), had m.p. 53-54°; ν max 1600 (C=C), 1590, 1510 (aromatic) cm^{-1}; λ max 229 nm (ε, 9,100), 279 (3,100); λ inf 283 nm (ε, 2,660); δ 1.2-3.9 (multiplet, 24H, $-CH_2-$, $>CHNH-$, CH_3O), 6.77 (singlet, 3H, aromatic) ppm.

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.63; H, 9.09; N, 4.67.

The gas-liquid chromatogram (2% XE-60-on-Gas Chrom Z 80/100 column temperature 190°) exhibited one symmetrical band.

1-(3,4-Dimethoxyphenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline Oxalate (**5g**).

2-Methyloctahydroisoquinoline **5g** was also prepared by the procedure outlined for **5e**. Octahydroisoquinoline **5c** (43.0 g., 0.143 mole), 37.5% formalin (13.6 ml., 0.182 mole) and ethanol (200 ml.) was reduced with hydrogen (room temperature and an initial pressure of 40 psi) in the presence of Raney nickel (8) (10 g.) to give **5g** isolated as the oxalate, m.p. 120-121°; ν max 1779 (CO_2H), 1690-1610 (C=C, CO_2^-, aromatic) cm^{-1}; λ max 229 nm (ε, 9,100), 280 (3,240); λ inf 283 nm (ε, 2,940); δ 1.3-4.0 (multiplet, 26H, $-CH_2-$, $>\overset{+}{C}H\overset{+}{N}HCH_2-$, CH_3O-), 6.78 (singlet, 3H, aromatic), 11.3 (deuterium oxide-exchangeable broad signal, 2H, $-CO_2H$, $-\overset{+}{N}H-$) ppm in 83% yield.

Anal. Calcd. for $C_{22}H_{31}NO_6$: C, 65.16; H, 7.71; N, 3.45. Found: C, 65.05; H, 7.97; N, 3.70.

The base **5g**, obtained from **5g**-oxalate by the usual procedure, had b.p. 175° (bath temperature, 0.3 mm.); ν max 1599 (C=C), 1580, 1510 (aromatic) cm^{-1}; λ max 229 nm (ε, 9,100), 280 (3,250); λ inf 283 nm (ε, 2,860); δ 1.2-2.4 (multiplet, 20H, $-CH_2-$, $>CHNCH_2-$), 3.80, 3.82 (singlets, 6H, CH_3O-), 6.72 (singlet, 3H, aromatic) ppm.

Anal. Calcd. for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.42; H, 9.32; N, 4.62.

The gas-liquid chromatogram (2% XE-60-on-Gas Chrom Z 80/100 column temperature 195°) showed one symmetrical band.

The hydrobromide had m.p. 123-124°; ν max 1610 (C=C), 1595, 1518 (aromatic) cm^{-1}; λ max 229 nm (ε, 8,800), 279 (3,200); λ inf 284 nm (ε, 2,760); δ 1.5-4.0 (multiplet, 26H, $-CH_2-$, $>CHNCH_2-$, CH_3O-), 6.75 6.98 (doublet, 3H, aromatic); 11.2 (deuterium oxide-exchangeable broad signal, 1H, $-\overset{+}{N}H<$) ppm.

Anal. Calcd. for $C_{20}H_{30}BrNO_2$: C, 60.60; H, 7.63; Br, 20.16; N, 3.53. Found: C, 60.88; H, 7.75; Br, 20.05; N, 3.56.

Treatment of 2-(2-Methoxybenzyl)-1-oxa-3-azaspiro[5.5]undec-2-ene (**4d**) with Phosphorus Oxychloride.

A solution of oxazine **4d** (3.00 g., 0.120 mole), obtained from the hydrobromide by basification (potassium hydroxide solution) and extraction (dichloromethane), phosphorus oxychloride (1.68 g.) and benzene was heated under reflux for 21 hours under a nitrogen atmosphere. Water (20 ml.) was added to the cooled reaction mixture and the solution was stirred for 18 hours and then extracted with chloroform. The organic extracts were washed with saturated sodium carbonate solution, dried over anhydrous sodium sulfate, filtered and evaporated. The residual oil (2.8 g.) was dissolved in ethanol (50 ml.) and treated with saturated ethanolic picric acid solution. The precipitate was collected. Recrystallization from ethanol gave 2.35 g. of unchanged oxazine **4d** as the picrate, m.p. 154-155°, alone or admixed with the authentic sample.

The infrared spectra of the two samples were superimposable.

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