Intramolecular Cyclization of N-(ω-Aminoalkyl)-1,2-dihydroisoquinolines

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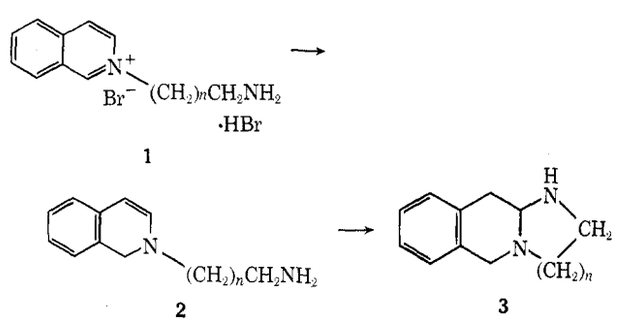
Reduction by $LiAlH_4$ of N-(2-aminoethyl)- and N-(3-aminopropyl)isoquinolinium salts leads directly to the tricyclic compounds, 1,2,3,4,5,10,10a-hexahydroimidazo[1,2-*b*]isoquinoline (**3**, $n = 1$) and 2,3,4,6,11,11a-hexahydro-1*H*-pyrimido[1,2-*b*]isoquinoline (**3**, $n = 2$). The latter compound is oxidized by mercuric acetate/EDTA to 1,3,4,11b-tetrahydro-2*H*-pyrimido[2,1-*a*]isoquinoline (**6**, R = H), identical with material obtained by treatment of N-(3-aminopropyl)isoquinolinium chloride hydrochloride with base, thus suggesting that the isoquinolinium salt is an intermediate in the oxidative transformation. An alternative unproven hypothesis proceeding *via* a macrocyclic intermediate **11** is discussed. This is given some credence by the reduction of the methiodide of **3** ($n = 2$), compound **13**, to 1,2,3,4,5,6,7,8-octahydro-2-methyl-2,6-benzodiazecine (**14**) and the failure of the N-methyl analog **9** to undergo the oxidative transformation in good yield, other oxidation products being formed concomitantly.

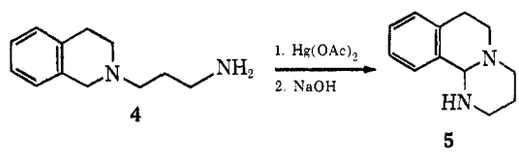
The intramolecular cyclization of 1,2-dihydroisoquinolines has been shown to be a very useful route to the Berberine alkaloids.[1]

More recently the chemistry of 1,2-dihydroisoquinolines has been the subject of extensive investigations by the groups of Dyke in England and Knabe in Germany.[2]

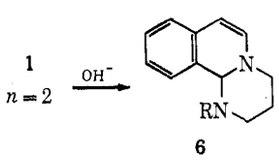
Based on the observations of these workers, it seemed possible that 1,2-dihydroisoquinolines would add other nucleophiles intramolecularly at position 3 and that this could be used to construct novel heterocyclic systems, which from our standpoint incorporated the pharmacologically significant phenethylamine moiety. To investigate this possibility, we chose to examine the reduction of a 2-(3-aminopropyl)isoquinolinium salt **1** ($n = 2$) to the 1,2-dihydroisoquinoline **2** ($n = 2$). Cyclization of **2** would yield a known member of the type of heterocycle we wished to investigate, *i.e.*, 1,3,4,6,11,11a-hexahydro-2*H*-pyrimido[1,2-*b*]isoquinoline **3** ($n = 2$).[3]



Rapid addition of the finely ground isoquinolinium salt **1** ($n = 2$), prepared in a manner analogous to that used for N-(3-dimethylaminopropyl)isoquinolinium chloride,[4] to a slurry of lithium aluminum hydride in ether, followed by rapid work-up, gave **3** ($n = 2$) directly in 53% yield. The spectra were in accord with the assigned structure and the material had a melting point (69–70°) close to that reported (70–72°).[3] As direct comparison, which would have removed any ambiguity about the direction of ring closure, could not be made,[5] the isomeric tricycle **5**, mp 83°, was prepared by the literature procedure.[6] This was not



identical with **3** ($n = 2$) based on comparison of nmr spectra. Furthermore, extraction of an aqueous solution of the isoquinolinium salt **1** ($n = 2$), which had been made thoroughly basic, gave compound **6** (R = H) in 95% yield.



Treatment of **6** (R = H) with lithium aluminum hydride in refluxing tetrahydrofuran overnight failed to reduce the double bond, which would have given **5**. Catalytic hydrogenation converted **6** (R = H) in 95% yield to N-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**).[6] Cyclization of the amino group of the isoquinolinium salt **1** ($n = 2$) to position 1 of the isoquinoline as a prelude to reduction can therefore be excluded from consideration.

The reductive cyclization procedure also worked well on the isoquinolinium salt **1** ($n = 1$) to give an 83% yield of a crystalline product. From comparison of the nmr spectrum of this product **3** ($n = 1$) with that of compound **3** ($n = 2$) obtained previously, the new compound was clearly 1,2,3,5,10,10a-hexahydroimidazo[1,2-*b*]isoquinoline **3** ($n = 1$). It was, however, quite sensitive to autoxidation and discolored on standing in the air even in the solid state. Our investigations were therefore restricted to **3** ($n = 2$), which was more stable and, although previously synthesized,[3] had not been investigated. In view of the sensitivity to oxidation it was of interest to explore which pathway was pursued. Several oxidation conditions yielded intractable mixtures. One experiment using mercuric acetate–EDTA,[7] however, smoothly transformed **3** ($n = 2$) in 68% yield to a new com-

(1) A. R. Battersby, D. J. LeCount, S. Garratt, and R. I. Thrift, *Tetrahedron*, **14**, 46 (1961).

(2) S. F. Dyke, K. G. Kinsman, J. Knabe, and H. D. Holtje, *Tetrahedron*, **27**, 6181 (1971), and references cited therein.

(3) J. L. Neumeyer and K. K. Weinhardt, *Chem. Commun.*, 1423 (1968).

(4) A. P. Grey, W. L. Archer, D. C. Schlieper, E. E. Spinner, and C. J. Cavallito, *J. Amer. Chem. Soc.*, **77**, 3536 (1955).

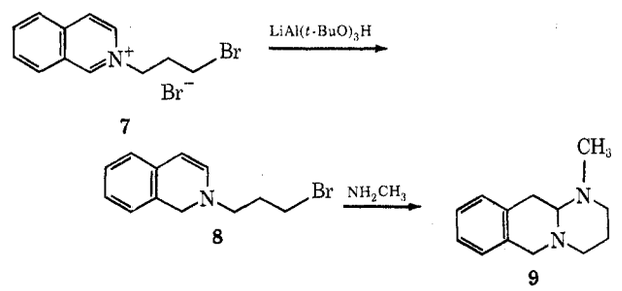
(5) Professor Neumeyer was unable to supply a sample or copies of the spectra.

(6) D. Beke and L. Toke, *Chem. Ber.*, **95**, 2122 (1962).

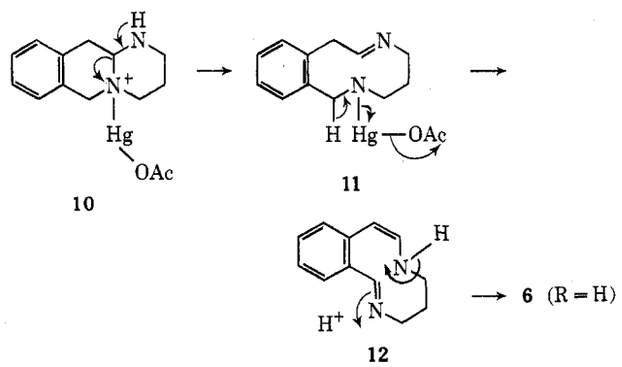
(7) J. Knabe and H. Roloff, *ibid.*, **97**, 3452 (1964).

pound, which was quickly identified *via* the cyclamate salt as the 1,3,4,11b-tetrahydro-2*H*-pyrimido[2,1-*a*]-isoquinoline **6** (R = H), obtained previously from treatment of the isoquinoline salt **1** (n = 2) with base. The mechanism of the formation of **6** (R = H) that we favor is therefore oxidation of **2** (n = 2), present in equilibrium with **3** (n = 2), to the isoquinolinium salt **1** (n = 2). This is cyclized to **6** (R = H) during the basification, which precedes extraction.

To increase the generality of the synthetic method an alternate route was devised so that other amino functions could be introduced. Lithium aluminum tri-*tert*-butoxyhydride reduction of *N*-(3-bromopropyl)-isoquinolinium bromide (**7**) yielded the 1,2-dihydroisoquinoline **8** as an oil, which decomposed on heating but was otherwise no less stable than the other intermediates. Reaction of this compound with ethanolic methylamine yielded the *N*-methyl analog of **3** (n = 2), compound **9**.

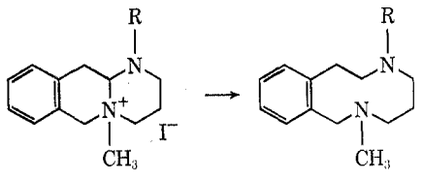


Compound **9**, 2,3,4,6,11,11a-hexahydro-1-methylpyrimido[1,2-*b*]isoquinoline, is a crystalline, readily characterizable compound. Application of the mercuric acetate oxidation conditions to **9** gave a complex product mixture, containing about 25% of an isocarbostyril (C=O in ir, low-field proton in nmr). The nmr spectrum resembled more that of the mixture of products obtained by extraction of a basified aqueous solution of 2-(3-dimethylaminopropyl)isoquinolinium chloride hydrochloride, which does not have the possibility to cyclize and perforce yields a pseudobase and products derived therefrom (*e.g.*, an isocarbostyril is also present). One interesting possibility[8] to account for the difference in the behavior of **9** and **3** (n = 2) would be that **3** (n = 2) has a pathway open to **6** (R = H) other than *via* the isoquinolinium salt.

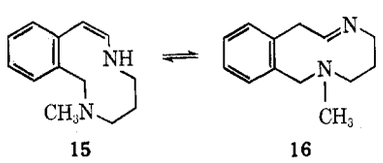


Attempts to provide substantiation for this hypothesis by demonstrating the stability of **6** (R = H) under reaction conditions gave inconclusive results. Nevertheless, some credence was provided by the observation that the methiodide of **3** (n = 2), compound **13** (R = H), on reduction with lithium aluminum hydride gave in 52% yield the macrocycle **14** (R = H) derived from an intermediate analogous to **11**.

Similarly **13** (R = CH_3) could be reduced to **14** (R = CH_3) by sodium borohydride. A related transformation was reported recently,[9] and a dimethoxybenzodiazecine related to **14** has been described by an alternative route.[10]



Further evidence for the propensity of the central bond to cleave in the methiodide **13** (R = H) was obtained by examination of the nmr spectrum in DMSO–D_2O and adding NaOD. On standing three peaks developed in the olefin region. This resembled an AB pattern with a further broad peak superimposed over one doublet of the AB at δ 5.98 and the other doublet at 5.18 (J = 6 Hz). This is what one might anticipate from some equilibrium between **15** and **16**.



Experimental Section[11]

***N*-(2-Aminoethyl)isoquinolinium Bromide Hydrobromide, 1** (n = 1).—Isoquinoline (50 g, 0.39 mol) was dissolved in isopropyl alcohol (800 ml), 2-bromoethylamine hydrobromide (80 g, 0.39 mol) was added, and the mixture was heated to reflux. After reflux overnight the precipitate was collected, washed, and dried to yield **1** (n = 1) (105 g, 80%): mp 281–283°; ν_{max} 1646 (m), 1100 (m), 834 cm^{-1} (m); λ_{max}^{MeOH} 232 mμ (ϵ 47,430), 278 (2980), 338 (4310).

Anal. Calcd for $C_{11}H_{14}Br_2N_2$: C, 39.55; H, 4.23; N, 8.39. Found: C, 39.67; H, 4.24; N, 8.22.

***N*-(3-Aminopropyl)isoquinolinium Bromide Hydrobromide, 1** (n = 2).—Isoquinoline (12.9 g, 0.1 mol) was dissolved in isopropyl alcohol (80 ml). 3-Bromopropylamine hydrobromide (21.9 g, 0.1 mol) was added and the mixture was refluxed. During 3 hr the insoluble hybrobromide dissolved; soon thereafter a solid precipitated from the refluxing solution. This was collected, washed, and dried to give **1** (n = 2) (26.5 g, 76%): mp 207–209°; ν_{max} 1644 (m), 828 (s), 762 cm^{-1} (s); λ_{max}^{MeOH} 233 mμ (ϵ 50,600), 278 (2950), 337 (4270).

Anal. Calcd for $C_{12}H_{16}Br_2N_2$: C, 41.41; H, 4.63; N, 8.05. Found: C, 41.37; H, 4.63; N, 7.88.

1,2,3,5,10,10a-Hexahydroimidazo[1,2-*b*]isoquinoline, 3 (n = 1).—The isoquinolium salt **1** (n = 1) (17.3 g, 0.051 mol) was ground to a dust and added rapidly to a well-stirred slurry of $LiAlH_4$ (5.6 g, 0.147 mol) in ether (200 ml). The mixture was stirred at room temperature for 25 min. The excess $LiAlH_4$ was decomposed with a saturated solution of potassium sodium tartrate. The salts were removed by filtration and washed with

(8) Suggested by Professor Peter Yates.

(9) M. Davis, P. Knowles, B. W. Sharp, R. J. A. Walsh, and K. R. H. Wooldridge, *J. Chem. Soc. C*, 2449 (1971).

(10) T. Yamazaki, *Yakugaku Zasshi*, **79**, 1014 (1959); *Chem. Abstr.*, **54**, 5680 (1960).

(11) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument as $CDCl_3$ solutions and ir spectra as Nujol mulls, unless otherwise indicated. Mass spectra were obtained on a M.S.9 instrument, at 70 eV.

ether. The ethereal filtrate was washed, dried ($MgSO_4$), and removed to give **3** (n = 1) as a colorless, crystalline solid (7.4 g, 83%). This material could be recrystallized from ether, but showed a sensitivity to autoxidation. The analytical sample was obtained by sublimation (0.05 mm, 50°): mp 66–69°; ν_{max} 3222 (m), 1166 (m), 908 (m), 740 cm^{-1} (s); nmr δ 7.08 (br s, 4), 4.24 (d, 1, J = 6 Hz), 3.98 (d, 1, J = 6 Hz).

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.59; H, 8.04; N, 16.04.

1,3,4,6,11,11a-Hexahydro-2*H*-pyrimido[1,2-*b*]isoquinoline, 3 (n = 2).—The isoquinolinium salt **1** (n = 2) (60 g, 0.172 mol) was treated and worked up in an analogous manner as above with $LiAlH_4$ (9.8 g, 0.258 mol) in ether (1 l.). The ethereal filtrate yielded a colorless solid **3** (n = 2) (17.3 g, 53%), mp 68–70°, which could be recrystallized (water). An analytical sample was prepared by sublimation (0.05 mm, 50°), yielding material of mp 69–70° (lit.[3] mp 70–72°); ν_{max} 3275 (m), 1102 (m), 738 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr δ 7.10 (s, 4), 3.84 (d, 1, J = 14 Hz).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.87; H, 8.35; N, 14.74.

1,3,4,6,11,11a-Hexahydro-5-methyl-2*H*-pyrimido[1,2-*b*]isoquinolinium Iodide, 13 (R = H).—Compound **3** (n = 2) (2 g, 0.0106 mol) was dissolved in ice-cold CH_2Cl_2, which contained CH_3I (1.67 g, 0.0117 mol). After standing at 0° for 30 min, the solid was collected, washed (ether), and dried. The product was **13** (R = H) (1.4 g, 28%): mp 187–189°; ν_{max} 3270 (m), 1235 (m), 750 (s), 728 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr[12] (D_2O) δ 7.34 (m, 4), 4.78 (q, 1), 4.58 (AB, 2, J = 16 Hz), 2.94 (s, 3), in DMSO/D_2O/NaOD, δ 5.98 (br s), 5.18 (d, J = 6 Hz).

Anal. Calcd for $C_{13}H_{19}N_2I$: C, 47.27; H, 5.75; N, 8.48. Found: C, 47.19; H, 5.67; N, 8.35.

***N*-(3-Aminopropyl)-1,2,3,4-tetrahydroisoquinoline (4).**—2-(3-Aminopropyl)isoquinolinium bromide hydrobromide, **1** (n = 2) (20.5 g, 0.059 mol), was dissolved in water (50 ml) and methanol (50 ml) was added. An aqueous solution of sodium borohydride (6 g in 60 ml) was added slowly to the well-stirred and cooled (ice bath) mixture. After addition, the mixture was stirred for 30 min, then made strongly basic (20% KOH) and continuously extracted with ether. The ether was dried ($MgSO_4$) and removed to give a colorless oil **4** (5.8 g, 52%), nmr δ 7.06 (s, 4), 3.60 (s, 2).

Solution in ethanolic HCl and precipitation by ether gave 6.8 g of HCl salt, mp 263–265° (lit.[6] mp 261°). Recrystallization from ethanol gave an analytical sample, mp 263–265°, ν_{max} 2670, 2560, 1602 (m), 1168 (m), 766 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{18}N_2 \cdot 2HCl$: C, 54.80; H, 7.67; N, 10.65. Found: C, 54.61; H, 7.67; N, 10.43.

1,3,4,6,7,11b-Hexahydro-2*H*-pyrimido[2,1-*a*]isoquinoline (5).—*N*-(3-Aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**, 2.83 g, 0.015 mol) was dissolved in 4% aqueous acetic acid (50 ml). Mercuric acetate (9.6 g, 0.03 mol) was added, and the mixture was warmed for 6 hr at 50° and then stirred overnight at room temperature. It was then filtered. The filtrate was basified (20% KOH) and extracted (ether). The ether extracts were washed (water), dried ($MgSO_4$), and removed to give a white solid, which was recrystallized from petroleum ether (bp 30–60°) to give **5** (760 mg, 27%): mp 74–76°; ν_{max} 3230 (m), 2800 (m), 2740 (m), 1294 (s), 1135 (s), 736 cm^{-1} (s); ν_{max}^{MeOH} benzenoid absorption; nmr δ 7.58 (m, 1), 7.08 (m, 3), 3.88 (s, 1).

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.66; H, 8.68; N, 15.03.

Compound **5** was identical (mixture melting point and spectra) with material prepared by the literature procedure.[6]

1,3,4,11b-Tetrahydro-2*H*-pyrimido[2,1-*a*]isoquinoline, 6 (R = H).—Compound **3** (n = 2) (10 g, 0.053 mol) was added to a well-stirred solution of mercuric acetate (16.9 g, 0.053 mol) and ethylenediaminetetraacetic acid disodium salt (19.8 g, 0.053 mol) in 2% aqueous acetic acid (100 ml) at room temperature under nitrogen. A gray precipitate separated rapidly from the initial solution. The mixture was stirred overnight at room temperature, and the precipitate was removed. The filtrate was made basic (20% KOH) and extracted (ether). The ethereal extracts were washed (water), dried ($MgSO_4$), and concentrated. The residue was an oil (6.8 g, 68%), which from the nmr spectrum was exclusively **6** (R = H). This was characterized as the biscyclamate salt: mp 154–155° (acetone); ν_{max} 3250 (m), 1224 (s), 1158 (s), 1028 cm^{-1} (s); λ_{max}^{MeOH} 231 mμ (ε 47,040), 277 (3010), 335 (4120); nmr (of free base) δ 7.02 (m, 4), 6.0 (d, 1, J = 7 Hz), 5.34 (d, 1, J = 7 Hz), 5.20 (s, 1).

Anal. Calcd for $C_{12}H_{14}N_2 \cdot 2C_6H_{13}NO_3S$: C, 52.93; H, 7.40; N, 10.29. Found: C, 53.29; H, 7.27; N, 10.15.

1,3,4,11b-Tetrahydro-2*H*-pyrimido[2,1-*a*]isoquinoline, 6 (R = H).—2-(3-Aminopropyl)isoquinolinium bromide hydrobromide (**1**, n = 2) (10 g, 0.028 mol) was dissolved in water (40 ml). The solution was covered with benzene (40 ml) and stirred; 20% aqueous KOH was added until the aqueous phase was strongly basic. The mixture was stirred at room temperature for 10 min. The benzene layer was separated, washed (water), dried ($MgSO_4$), and removed to yield an oil **6** (R = H) (5.1 g, 95%) identical by nmr spectroscopy with that obtained from the experiment above.

The oil was characterized as the biscyclamate salt, bp 154–156°. There was no depression in melting point on admixture with the biscyclamate from the experiment above. The two compounds were identical by ir spectroscopy.

***N*-(3-Bromopropyl)isoquinolinium Bromide (7).**—Isoquinoline (200 g, 1.55 mol) was dissolved in toluene (1 l.). 1,3-Dibromopropane (600 g, 2.96 mol) was added and the mixture was stirred at 60° for 21 hr. The resulting precipitate was collected well, washed with toluene, and dried to yield **7** (384 g, 75%): ν_{max} 1650 (m), 1194 (m), 854 cm^{-1} (m); λ_{max}^{MeOH} 232 mμ (ε 52,380), 277 (3050), 337 (4200).

Anal. Calcd for $C_{12}H_{13}Br_2N$: C, 43.53; H, 3.96; N, 4.23. Found: C, 43.92; H, 4.04; N, 4.16.

***N*-(3-Bromopropyl)-1,2-dihydroisoquinoline (8).**—*N*-(3-Bromopropyl)isoquinolinium bromide (90 g, 0.262 mol) was crushed to a fine dust and added to a well-stirred solution of lithium tri-*tert*-butoxyaluminum hydride (100 g, 0.394 mol) in dry tetrahydrofuran (500 ml) under nitrogen, in an ice bath. The mixture was stirred for 45 min, then concentrated to dryness *in vacuo*. The residue was shaken with an ether–water mixture and filtered through Celite, and the ethereal layer was separated. The ether was dried ($MgSO_4$) and removed to yield a pale yellow oil **8** (44.6 g, 68%); attempts at distillation gave decomposition. It was characterized by nmr: δ 6.90 (m, 4), 6.06 (d, 1, J = 7 Hz), 5.20 (d, 1, J = 7 Hz), 4.16 (s, 2), 3.36 (t, 2), 3.04 (t, 2), 1.96 (quintet, 2).

2,3,4,6,11,11a-Hexahydro-1-methylpyrimido[1,2-*b*]isoquinoline (9).—The above yellow oil **8** (44.6 g, 0.178 mol) was dissolved in ethanol (650 ml). Methylamine was slowly bubbled through the solution at room temperature overnight. The ethanol was removed. The residue was partitioned between ether and water. The aqueous solution was made basic (20% KOH). The ethereal layer was separated, washed (water), dried ($MgSO_4$), and removed. The residue was crystallized from petroleum ether to give **9** (25.34 g, 70%), mp 50–52°. Alternatively, the residue may be distilled to give a colorless main fraction, bp 94° (0.1 mm), which solidifies on standing: ν_{max} 2790 (m), 2750 (m), 1284 (m), 1138 (m), 744 (s); λ_{max}^{MeOH} benzenoid absorption; nmr δ 7.0 (m, 4), 3.80 (d, 1, J = 15 Hz), 3.28 (d, 1, J = 15 Hz), 2.26 (s, 3).

Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.45; H, 8.96; N, 13.78.

1,2,3,4,5,6,7,8-Octahydro-2-methyl-2,6-benzodiazecine, 14 (R = H).—The methiodide **13** (R = H) (7.2 g, 0.0218 mol) was added to a suspension of $LiAlH_4$ (3 g) in ether (200 ml). The mixture was refluxed overnight, the excess $LiAlH_4$ was decomposed, and the mixture was filtered (Celite). The ethereal layer was separated, washed (water), dried ($MgSO_4$), and removed to yield an oil **14** (R = H) (2.4 g, 54%) which was by nmr spectroscopy essentially homogeneous. The oil was characterized as the biscyclamate: mp 113–116°; ν_{max} 3220 (m), 1588 (m), 1280 (m), 1220 (m), 1160 (m), 1032 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr (free base) δ 7.12 (m, 4), 3.56 (s, 2), 2.96 (s, 4), 2.26 (s, 3).

Anal. Calcd for $C_{13}H_{20}N_2 \cdot 2C_6H_{13}NO_3S$: C, 53.43; H, 8.25; N, 9.97. Found: C, 53.41; H, 8.32; N, 9.85.

1,2,3,4,5,6,7,8-Octahydro-2,6-dimethyl-2,6-benzodiazecine, 14 (R = CH_3).—Compound **9** (6 g, 0.0297 mol) was dissolved in CH_2Cl_2 (60 ml) and cooled in an ice bath. Methyl iodide (4.3 g, 0.03 mol) in CH_2Cl_2 (10 ml) was added dropwise during 20 min. The mixture was stirred at room temperature for 2 hr. The CH_2Cl_2 was removed. The residue was dissolved in water and washed with ether. The aqueous part was then treated with excess aqueous sodium borohydride overnight. The mixture

(12) We wish to acknowledge the assistance of Dr. J. Karliner, CIBA-GEIGY Corp., Ardsley, who obtained these spectra on a Varian XL100 instrument.

was extracted (CH_2Cl_2, 3 × 60 ml) and the extract was concentrated. The residue was partitioned between 2 *N* HCl and ether. The 2 *N* HCl fraction was basified (20% KOH) and reextracted (ether). Removal of the ether gave an oil (3.34 g, 52%), which was essentially **14** (R = CH_3) from nmr spectroscopy. This was characterized as the biscyclamate: mp 126–128°; ν_{max} 3240 (m), 1584 (m), 1290 (s), 1270 (s) 1208 (s), 1170 (s), 1030 cm^{-1} (s); λ_{max}^{MeOH} benzenoid absorption; nmr (free base) δ 7.10 (q, 4), 3.64 (s, 2), 2.24 (s, 3), 2.04 (s, 3).

Anal. Calcd for $C_{14}H_{22}N_2 \cdot 2C_6H_{13}NO_3S$: C, 54.15; H, 8.39; N, 9.72. Found: C, 53.89; H, 8.66; N, 9.60.

Attempted Catalytic Reduction of 6 (R = H) to 5.—Compound **6** (R = H) (2.07 g, 0.011 mol) was hydrogenated (room temperature and pressure) in ethanol over PtO_2 (100 mg). Hydrogen was consumed (410 ml), the reaction mixture was filtered through Celite, and the ethanol was removed. The residue was an oil (0.02 g), identical (nmr, ir) with 2-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinoline (**4**) prepared by $NaBH_4$ reduction of **1** (*n* = 2). The dihydrochloride melting point (263–265°) was identical with that of material above.

Attempted Reduction of 6 (R = H) to 5.—Compound **6** (R = H) (3.74 g, 0.02 mol) was dissolved in dry THF (30 ml) and added to a well-stirred slurry of $LiAlH_4$ (1.9 g) in THF (100 ml) under nitrogen. The mixture was refluxed overnight. The excess reagent was decomposed with saturated sodium potassium tartrate and the mixture was filtered through Celite. The filtrate was diluted with ether, well washed (saturated salt solution), dried ($MgSO_4$), and concentrated to yield an oil (3.31 g) identical (ir, nmr) with the starting material **6** (R = H).

Mercuric Acetate–EDTA Oxidation of Compound 9.—Compound **9** (700 mg, 0.0035 mol) was added to a solution of mercuric acetate (1.14 g, 0.0035 mol) and EDTA disodium salt (1.3 g, 0.0035 mol) in 2% aqueous acetic acid (50 ml). After 2 days at room temperature, the mixture was made basic (20% KOH) and extracted (ether). The ether was washed (saturated NaCl solution), dried ($MgSO_4$), and removed. The resulting oil (420 mg) was distilled in a hot box (0.05 mm). The distilled material (380 mg) was examined: ν_{max} 1650 cm^{-1} (m), 1620 (m); nmr δ 8.34 (d, ~0.25), 6.18 (d, ~0.5), 5.34 (d, ~0.5); mass spectrum *m/e* 216, 200, 187, 157, 129; 200 → 157 is loss of $\cdot CH_2{=}NCH_2$, linked by a metastable peak at 123.2; 157 → 129 is loss of C_2H_4 linked by a metastable peak at 106.0.

Registry No.—**1** (*n* = 1), 37384-28-4; **1** (*n* = 2), 37384-29-5; **3** (*n* = 1), 37394-04-0; **3** (*n* = 2), 21139-96-8; **4**, 5596-87-2; **5**, 37393-84-3; **6** (R = H, biscyclamate), 37393-83-2; **7**, 37413-11-9; **8**, 37393-85-4; **10**, 37393-86-5; **13** (R = H), 37393-87-6; **14** (R = H, biscyclamate), 37393-88-7; **14** (R = CH_3, biscyclamate), 37393-89-8.

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A Novel Approach to the Synthesis of Nitrogen Analogs of the Tetrahydrocannabinols

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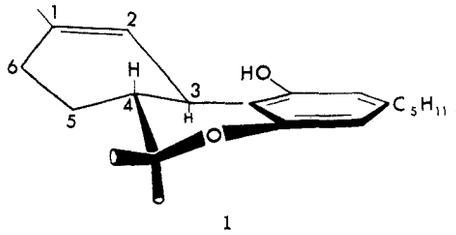
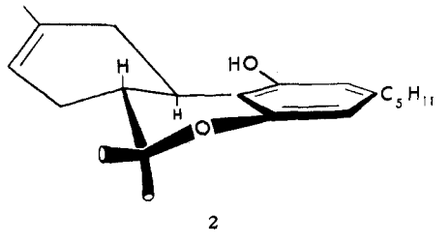
An approach to the synthesis of nitrogen analogs of the tetrahydrocannabinols which preserves the integrity of the trans ring fusion and a natural location of the double bond is reported in the present study. The condensation of *o*-anisylidenemethylamine (**10**) and glutaric anhydride yielded *trans*- and *cis*-1-methyl-5-carboxy-6-(*o*-methoxyphenyl)-2-piperidones (**11** and **12**). Subsequent O-demethylation and cyclodehydration of the trans diastereomer provided the tricyclic lactone **16**, which was converted into the corresponding *gem*-dimethyl alcohol **18**. Cyclodehydration of **18** gave the key tricyclic intermediate **23**, which was also obtained independently *via* the methyl ester **13** of **11**. Treatment of the trans ester **13** with CH_3MgBr yielded the tertiary alcohol **24**, which on treatment with BBr_3 gave the trans bromide **25**. Dehydrohalogenation of **25** provided a mixture of olefins **26** and **27**, which could be cyclized to the key intermediate **23** in CF_3COOH. Configurational and conformational assignments were made by nmr spectroscopy. Subsequent methylations and reductions of **23** provided the corresponding carbinolamines, enamines, and amines.

It has been shown that the biologically active constituents of *Cannabis* are Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC) **1**[2] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol



1

($\Delta^{1(6)}$-THC) **2**.[3] The absolute configurations of Δ^1-THC and $\Delta^{1(6)}$-THC at C-3 and C-4 are R.[4]



2
(monoterpenoid numbering)

In view of the generally recognized psychotropic activity of the THC's,[5] a striking structural feature of these molecules is the absence of nitrogen. However, a number of THC nitrogen analogs have been reported. Thus far, the synthesis of most of these nitrogen analogs has been based on the early work of Adams and Todd and their collaborators,[6] who con-

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