1-ALKYL- AND 1-ARYL- SUBSTITUTED-3-AMINOMETHYL-3-METHYL-3,4-DIHYDROISOQUINOLINES AND RELATED COMPOUNDS[1)]

by

Akira TERADA

SYNOPSIS

As part of search for a potential new type of antimalarial, a number of amine and diamine derivatives were prepared from the reaction of 1-alkyl- and 1-aryl-substituted-3-bromomethyl-3-methyl-3,4-dihydroisoquinolines with amines and with diamines. For the structural proof of these 3,4-dihydroisoquinolines, some attempted syntheses have successfully been done by conversion of the above starting materials, bromides, into more fundmental 3,4-dihydroisoquinolines upon the reductive debromination using triphenyltin hydride.

1. INTRODUCTION

Previously, one of our papers has shown a possible synthetic route of 3, 4-dihydroisoquinoline rings. In the paper, it was reported that the addition of halogen to olefinic compounds, such as allylbenzene and safrole, in alkyl- and arylnitrile media in the presence of Lewis acid afforded 3,4-dihydroisoquinolines containing an additional halogen function, which can be converted to other functional groups by nucleophilic substitution.[2)]

In connection with our search for a potential new type of antimalarial and our broad research program on the stereospecific introduction of nitrogen function into organic compounds, a number of amine and diamine derivatives of tetrazoles[3)] and of 3,4-dihydroisoquinolines have been prepared. Because of the compounds possessing a significant therapeutic effect against malaria shows to have a rigid ring portion containing nitrogen atom and a high electron density such as quinoline ring together with a less rigid side chain which is often an aminoalkanol or diaminoalkylamine.

2. RESULTS AND DISCUSSION

A number of aliphatic and alicyclic mono- and di-amine derivatives of 1-benzyl-3-bromomethyl-3-methyl-3,4-dihydroisoquinoline (I), 1,3-dimethyl-3-bromomethyl-3,4-dihydroisoquinoline (II) and 1-phenyl-3-bromomethyl-3-methyl-3,4-dihydroisoquinoline (III) were prepared.

The starting materials, II and III, were obtained following the methods reported by R. Gault.[4)] Also one of the starting materials, I, was similarly prepared using benzylnitrile as the solvent of the reaction.

Since the structural proof of these 3-bromomethyl-3-methyl-3,4-dihydroisoquinolines have not been accomplished yet, the bromide III was converted into 1-phenyl-3,3-dimethyl-3,4-dihydroisoquinoline (V) by the reductive debromination using triphenyltin hydride. The debromination did not occure at room temperature, but took place smoothyl under reflux in benzene. The product V could also be obtained, through another pass way, by a dehydrative ring closure of N-benzyl-α,α-dimethyl-β-phenylethylamine (VII) in the presence of polyphosphoric acid. The compound VII was obtained in a 78.5% yield from a Ritter reaction of methallylbenzene in benzonitrile, which had been prepared by Ritter and Murphy from α,α-dimethyl-β-phenethyalcohol[3)]

For the same purpose, another bromide, II, also easily gave 1,3,3-trimethyl-3,4-dihydroisoquinoline by the similar procedure.

The bromides I,II and III were easily converted into their corresponding amine derivatives on reflux with a large amount of amine. However, in the case of γ-acetoxypropylamine, 3-(γ-hydroxypropylamino)methyl-3-methyl-3,4-dihydroisoquinolines were always given. This was due to an acetyl group migration between the ester and the primary amino groups in the original amine molecule at elevated temperature during reaction.

All the amine products obtained here are very hygroscopic in their hydrohalide salts, and this character is much more in the salts of the polyamino compounds.

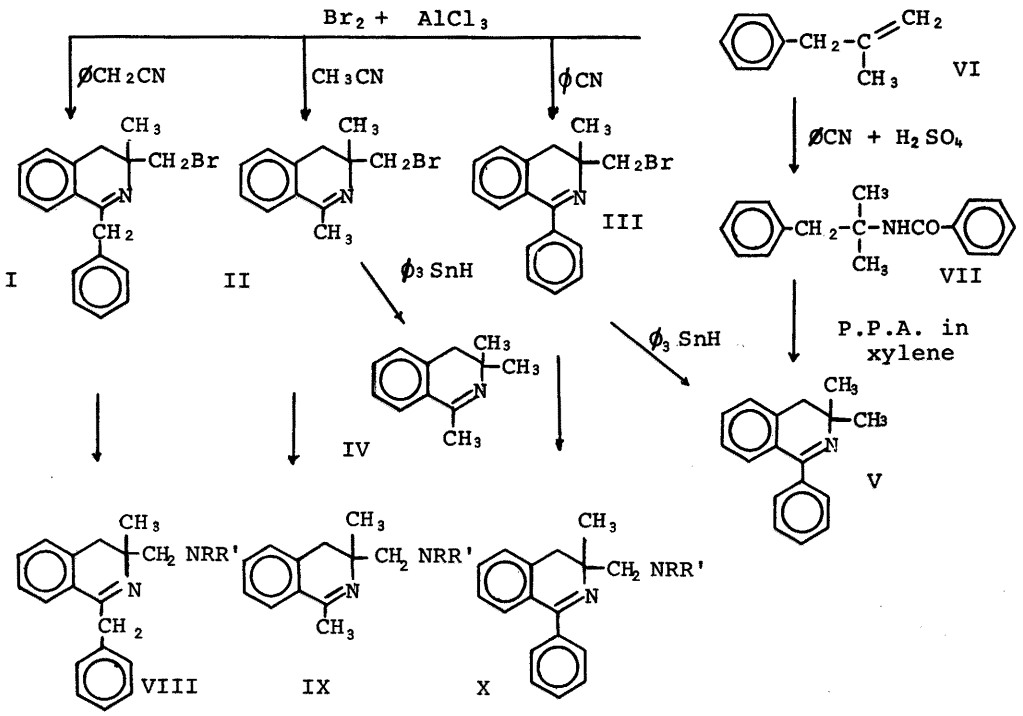
3. EXPERIMENTAL

3.1 Materials.

γ-Acetoxypropylamine, dimethylamine, morpholine, piperidine and pyrrolidine were available commercially as reagent grade, and were used without exceptional purification. The δ-pyrrolidinobutylamine was obtained by an LAH-reduction of the corresponding nitrile as reported in one of our previous papers.[3] 2-Amino-5-diethylaminopentane (b.p. 74°C/20 mmHg), 2-diethylaminoethylamine (b.p. 55-56°C/30 mmHg), 3-diethylaminopropylamine (b.p. 96-100°C/61 mmHg), and 1-amino-3-diethylamino-2-propanol of commercial grade reagents were furnished by the U.S. Army, Water Reed Medical Center, and were purified by usual vacuum distillation.

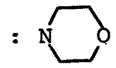
Benzylnitrile (Aldrich chemicals, reagent) was also purified by vacuum distillation over phosphorous pentoxide, b.p. 156-162°C/138 mmHg.

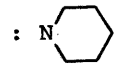
The other starting materials, compounds II and III, were prepared as previously reported.[4]

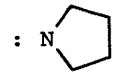


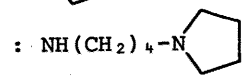
Where

a NRR' : $N(CH_3)_2$

b : 

c : 

d : 

e : $NH(CH_2)_4$- 

f NRR' : $NH(CH_2)_3OH$

g : $NH(CH_2)_2N(C_2H_5)_2$

h : $NH(CH_2)_3N(C_2H_5)_2$

i : $NHCH_2-\underset{\underset{OH}{|}}{CH}-CH_2N(C_2H_5)_2$

j : $NH-\underset{\underset{CH_3}{|}}{CH}-(CH_2)_3N(C_2H_5)_2$

3.2 Structural Proof of 1-Substituted-3-bromomethyl-3-methyl-3,4-dihydroisoquinolines.

3.2.1 *N*-Benzoyl-α,α-dimethyl-β-phenethylamine (VII).

To a mixture of 10.0 g. (0.1 mole) of conc. sulfuric acid and 50 ml. of glacial acetic acid, was added 11.4 g. (0.11 mole) of benzonitrile portionwise at 20°C, and then methallylbenzene (13.2 g., 0.1 mole) added dropwise below 20°C. After standing overnight at room temperature, the mixture was poured into ice-water. The crystals precipitated were gathered on a filter and repeatedly washed with water and air-dried. *N*-benzoyl-α, α-dimethyl-β-phenethylamine. m.p. 113-114°C, 19.715 g. (78.5%), (lit., m.p. 112.5-113°C[6]. 112-113°C[7]). ν_{max}^{KBr}: 3367 (NH) : 3049 (ϕ) ; 2976, 2924, 2874 (CH_2, CH_3) ; 1642 (amide, C = O) ; 728, 711, 699, 690 cm^{-1} (monosubstituted benzenes).

3.2.2 1-Phenyl-3,3-dimethyl-3, 4-dihydroisoquinoline (V).

A mixture of 2.00 g. of the above obtained amide, 20 g. of phosphorus oxychloride, 10 g. of phosphorus pentoxide in 50 ml. of xylene was refluxed for 11 hr., treated with ice-water, alkalized with sodium hydroxide and extracted with benzene. The benzene solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual oil was extracted with dilute hydrochloric acid. The acid extract was washed with benzene, alkalized strongly with sodium hydroxide, and extracted with benzene again. This benzene solution, on work up as usual, finally gave 81 mg. of crude crystals, m.p. 114-118°C. Recrystallization from petroleum benzine gave an analytical sample of V, m.p. 121-123°C.

Anal. Calcd. for $C_{17}H_{17}N$: C, 86. 77 ; H, 7.28. Found : C, 86. 99 ; H, 7.34. ν_{max}^{KBr} : 3077, 3030 (ϕ); 2985, 2941, 2882 (CH_2, CH_3), 1618 (C = N) ; 1570 (ϕ) ; 1377 (CH_3) ; 784, 739, 714 (3,4-dihydroisoquinoline ring) ; 739, 701 cm^{-1} (monosubstituted benzene).

V-Picrate : Usual picrate formation and subsequent recrystallization from benzene gave yellow crystals, m.p. 178-178. 5°C.

Anal. Calcd. for $C_{23}H_{20}N_4O_7$: C, 59.48 ; H, 4.34 ; N, 12.06. Found : C, 59. 64 ; H, 4.37 ; N, 13.09.

3.2.3 Reductive Debromination of 1-Phenyl-3-bromomethyl-3-methyl-3,4-dihydroisoquinoline by Triphenyltin hydride.

A sample of 395 mg. (1 mmole) of III-hydrobromide was dissolved in a few ml. of water, alkalized with 2*N* sodium hydroxide and immediately extracted with benzene. The benzene solution was dried over anhydrous magnesium sulfate and gave 343 mg. of free amine (III) on solvent removal. All of this amine was dissolved again in 4 ml. of benzene, and to this 446 mg. (1.27 mmole) of triphenyltin hydride prepared by the method of Kuivila et al[8] was added and refluxed for 24 hr. After concentration and extraction with dil. hydrochloric acid, crystals, m.p. 116-121°C, resulted. This product was a crude triphenyltin bromide (lit., m.p. 121°C[9]).

From the hydrochloric acid-extract, after concentration and subsequent recrystallization from acetone, 1-phenyl-3,3-dimethyl-3,4-dihydroisoquinoline hydrochloride, m.p. 228-232°C was obtained, 110 mg., (40.5%).

Free Amine V: Was prepared as usual, m.p. 123-124°C. This did not depress the melting point of the authentic sample obtained above on mixed melting point test.

3.2.4 Reductive Debromination of 1,3-Dimethyl-3-bromomethyl-3,4-dihydroisoquinoline.

A solution of 1.264 g. (5.3 mmole) of II and 2.1 g. (6 mmole) of triphenyltin hydride in 10 ml. of benzene was refluxed for 24 hr. After work up as usual, 1,3,3-trimethyl-3,4-dihydroisoquinoline hydrobromide, 482 mg. (33.4%) was obtained. After recrystallization from acetone the melting point raised up to 197-198°C, IV-HBr.

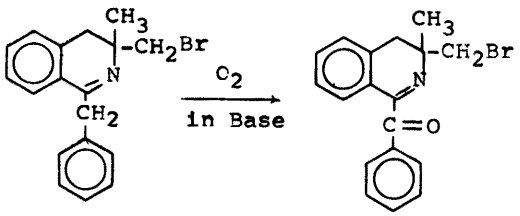
Anal. Calcd. for $C_{12}H_{16}NBr\text{-}H_2O$: C, 55.39 ; H, 6.46 ; N, 5.38 ; H_2O, 2.82. Found : C, 55.11; H, 6.40 ; N, 5.20; H_2O, 3.00. ν_{max}^{KBr} : 3436 (OH, NH, broad); 3040-2494 (amine hydrobromide, broad); 1658 (C = N); 1608, 1570, 1515 (ϕ); 1374 (CH_3): 768, 740, 711 cm^{-1} (3,4-dihydroisoquinoline).

3.3 1-Benzyl-3-bromomethyl-3-methyl-3, 4-dihydroisoquinoline (I).

To a solution of 6.40 g. (0.048 mole) of anhydrous aluminum chloride in 100 ml. of benzylnitrile, 2.40 ml. (0.048 mole) of bromine was added during 30 min. at -10°C, and the system was continuously stirred and kept at room temperature for 48 hr. After addition of 40 ml. of water at 0°C, the water layer was removed and the organic layer was repeatedly extracted with dil. hydrochloric acid. The acid extract was alkalized with dil. sodium hydroxide, and the free amine was taken up in benzene. The benzene solution was washed repeatedly with water and dried over anhydrous magnesium sulfate. On solvent removal, 4.981 g. (32.3%) of an oil (I) was obtained.

ν_{max}^{liquid} :No sign of NH and OH; 3096, 3049 (ϕ); 3003, 2959, 2915, 2857 (CH); 1678 (conjugated phenyl ketone, weak); 1631 (C = N); 1605, 1575, 1497 (ϕ), 1453, 1429 (CH_2, CH_3); 1374 (CH_3); 803, 769, 732, 718 (3,4-dihydroisoquinoline); 750, 700 cm^{-1} (monosubstituted benzene).

The 1678 cm^{-1} band should be due to an existence of some air-oxidation product usually formed in alkali media as illustrated below.



From the residue of the above acid extraction, 104 g. of crude benzylnitrile (b.p. 87-91°C /2 mmHg) was recovered.

I-Hydrobromide : Was prepared as usual. Recrystallization from ethanol gave 2.146 g. of the analytical sample melting at 219-222°C.

Anal. Calcd. for $C_{18}H_{19}NBr_2$: C, 52. 83 ; H, 4.68 ; N, 3.42. Found : C, 52.86 ; H, 4.83 ; N, 3.60. ν_{max}^{KBr} : 3484 (NH) ; 3106, 3040 (ϕ) ; 2967, 2865, 2817 (CH_3, CH_2) ; 2646 (amine hydrobromide, broad) ; 1645 (C = N), 1608, 1570, 1497 (ϕ) : 1453, 1425 (CH_3, CH_2) ; 1383 (CH_3) ; 772, 762, 718 (3,4-dihydroisoquinoline) ; 738, 708 cm^{-1} (monosubstituted benzene).

The hydrochloride of I had been shown to have a melting point of 206-212°C by Robert Arnold.[10]

3.3.1 1-Benzyl-3-dimethylaminomethyl-3-methyl-3,4-dihydroisoquinoline (VIIIa).

A mixture of 409 mg (1 mmole) of I-hydrobromide and 10 ml. of 33% ethanolic dimethylamine in a glass sealed tube was heated in a steam bath for 24 hr. After working up as usual, 266 mg (91%) of an oily product (VIIIa) was obtained. This showed a negative Beilstein test of halogen. However, its infrared spectrum showed a strong band assignable to a conjugated carbonyl group at 1678 cm^{-1}.

ν_{max}^{liquid} : No sign of NH and OH; 3086, 3049 (ϕ); 2941, 2874, 2833 (CH_3, CH_2); 2778 (N-CH_3); 1678 (ϕ-C(=O)-C = C, strong); 1621 (C = N); 1603, 1572, 1493 (ϕ); 1453, 1429 (CH_3, CH_2); 1372 (CH_3); 1044 (dimethylamino-, liquid state); 767, 718 (3,4-dihydroisoquinoline ring); 746, 699 cm^{-1} (monosubstituted benzene).

VIIIa-Dihydrobromide : Was prepared as usual. Crystallization from an acetone-benzene-ethanol mixture gave a crude product, m.p. 218-220°C. Another recrystallization gave an analytical sampe of m.p. 225-227°C.

Anal. Calcd. for $C_{20}H_{26}N_2Br_2$: C, 52.88 ; H, 5.77. Found : C, 50.05 ; H, 8.08.

3.3.2 1-Benzyl-3-morpholinomethyl-3-methyl-3,4-dihydroisoquinoline (VIIIb).

A sample of 409 mg. (1 mmole) of I-hydrobromide was heated in 3 ml. of morpholine under reflux for 24 hr. Working up as usual gave 318 mg. (95%) of an oil. The Beilstein test was negative.

ν_{max}^{liquid} : No sign of NH and OH; 3096, 3058 (ϕ); 2985, 2950, 2874, 2825 (CH_3, CH_2); 2778 (morpholino-, sh); 1692 (conjugated ketone, w); 1634 (C = N); 1608, 1580, 1499 (ϕ); 1458 (CH_3, CH_2); 1370 (CH_3); 1136, 1117 (morpholino-); 768, 717 (3,4-dihydroisoquinoline); 748, 698 cm^{-1} (monosubstituted benzene).

VIIIb-Dihydrobromide : Was prepared as usual. Recrystallization from acetone-ethanol gave 361 mg. (72%) of crystals, m.p. 228-230°C. Another recrystallization raised the melting point to 231-232°C.

Anal. Calcd. for $C_{22}H_{28}N_2OBr_2$: C, 53. 24 ; H, 5.69. Found : C, 52.92 ; H, 5.54.

3.3.3 1-Benzyl-3-methyl-3-piperidinomethyl-3,4-dihydroisoquinoline (VIIIc).

One mmole of I-hydrobromide in 3 ml. of piperidine was refluxed for 15 hr. After work up as usual, 316 mg. (95%) of an oily product was obtained. This showed a negative Beilstein reaction of bromine.

VIIIc-Dihydrobromide : Was obtained as usual. Recrystallization from acetone-ethanol gave an analytical sample of m.p. 212.5-213.5°C.

Anal. Calcd. for $C_{23}H_{30}N_2Br_2$: C, 55.88 ; H, 6.12. Found : C, 56.34; H, 6.02. ν_{max}^{KBr} : 3425 (NH); 3049 (ϕ) ; 2933, 2857, 2833 (CH_3, CH_2); 2703, 2653, 2525 (amine hydrobromide); 1621 (C = N); 1595, 1567, 1493 (ϕ); 1451, 1442, 1433 (CH_3, CH_2); 1377 (CH_3); 765, 731 (3.4-dihydroisoquinoline); 745, 696 cm^{-1} (monosubstituted benzene).

3.3.4 1-Benzyl-3-methyl-3-pyrrolidinomethyl-3,4-dihydroisoquinoline (VIIId).

A mixture of 288 mg. (0.7 mmole) of I-hydrobromide and 3 ml. of pyrrolidine gave 205 mg. (91.5%) of an oily product (VIIId).

VIIId-Dihydrobromide : Was obtained as usual, m.p. 195-197°C.

Anal. Calcd. for $C_{22}H_{28}N_2Br_2$: C, 55.01 ;H, 5.88. Found : C, 55.26 : H, 6.07. ν_{max}^{KBr} : 3460 (NH); 3086 (ϕ, sh); 2976, 2950. 2849, 2801 (CH) ; 2778 (*N*-alkyl pyrrolidino, sh); 2688. 2625 (amine salt, broad) ; 1634 (C = N) ; 1608, 1567, 1499 (ϕ) ; 1453, 1412 (CH) ; 1387 (CH_3) ; 778, 765, 716 (3,4-dihydroisoquinoline) : 746, 706 cm^{-1} (monosubstituted benzene).

3.3.5 1-Benzyl-3-(γ-hydroxypropylamino)methyl-3-methyl-3,4-dihydroisoquinoline (VIIIf).

A sample of 167 mg. (0.409 mmole) of I-hydrobromide and 1.5 ml. of 3-acetoxypropylamine was heated on a steam bath for 24 hr. Work up as usual gave 149 mg. of yellow oil. The

Beilstein reaction of halogen was negative.

ν_{max}^{liquid} : 3356 (NH, OH, broad); 2994 (ϕ) ; 2985, 2950, 2925 (CH_3, CH_2); no carbonyl peak at 1818-1667 region; 1631 (C = N); 1115 (OH, strong and broad); 766, 717 (dihydroisoquinoline); 746, 698 cm^{-1} (monosubstituted benzene).

3.3.6 1-Benzyl-3-(β-diethylaminoethylamino)methyl-3-methyl-3,4-dihydroisoquinoline (VIIIg).

A mixture of 730 mg. (2 mmole) of I-hydrochloride in 10 ml. of β-diethylaminoethylamine was heated for 24 hr. After usual work up, 930 mg. (76.8%) of the product, trihydrobromide, m.p. 229.5-231°C, was obtained.

Anal. Calcd. for $C_{24}H_{33}N_3$-3HBr : C, 47.54; H, 5.99. Found : C, 47.41; H, 6.20. ν_{max}^{KBr}: 3413 (NH) ; 3049 (ϕ); 2950, 2924 (CH_3, CH_2); 2778-2326 (amine hydrobromide, broad); 1634 (C = N); 1597, 1563, 1513, 1486 (ϕ); 1024, 1013, 808 ; 769, 752, 718 (3,4-dihydroisoquinoline); 736, 696 cm^{-1} (monosubstituted benzene).

3.3.7 1-Benzyl-3-(γ-diethylaminopropylamino)methyl-3-methyl-3,4-dihydroisoquinoline (VIIIh).

A mixture of 730 mg. (2 mmole) of I-hydrochloride in 10 ml. of γ-diethylaminopropylamine under reflux for 30 hr. After usual work up and hydrobromide formation, recrystallization from an *n*-butanol-benzene-acetone mixture gave 837 mg. of crystals (67.5%), m.p. 239.5-240°C, trihydrobromide.

Anal. Calcd. for $C_{25}H_{35}N_3$-3HBr : C, 48.40; H, 6.17. Found : C, 48.25 ; H, 6.28. ν_{max}^{KBr} : 3425 (NH); 3030 (ϕ , sh); 2941 (CH_3, CH_2, broad); 2778 -2353 (amine hydrobromide, broad); 1637 (C = N); 1595, 1563, 1515, (ϕ); 1029, 807 ; 773, 734, 719 (3,4-dihydroisoquinoline); 751, 696 cm^{-1} (monosubstituted benzene).

3.3.8 1-Benzyl-3-(β-hydroxy-γ-diethylaminopropylamino)methyl-3-methyl-3,4-dihydroisoquinoline (VIIIi).

A mixture of 730 mg. (2 mmole) of I-hydrochloride and 15 ml. of β-hydroxy-γ-diethylaminopropylamine was refluxed for 30 hr. After work up as usual and the hydrobromide formation, 539 mg. (42.3%) of the trihydrobromide, m.p. 228-230°C (obtained by a trituration in acetone).

Anal. Calcd. for $C_{25}H_{35}N_3O$-3HBr : C, 47.18; H, 6.02. Found: C, 47.10; H, 6.14. ν_{max}^{KBr} : 3448, 3322 (NH, OH); 3030 (ϕ, sh) ; 2985, 2941 (CH_3, CH_2, broad); 2778-2381 (amine hydrobromide, broad); 1637 (C = N); 1600, 1563, 1493 (ϕ) ; 1031, 1010 ; 772, 733, 718(3,4-dihydroisoquinoline); 750, 696 cm^{-1} (monosubstituted benzene).

3.4.1 1,3-Dimethyl-3-dimethylaminomethyl-3,4-dihydroisoquinoline (IXa).

A mixture of 675 mg. (2.83 mmole) of II and 20 ml. of 33% dimethylamine-ethanol solution in a sealed glass tube was heated in a steam bath for 24 hr. After concentration and alkalization with *N* sodium hydroxide, an oily product separated was taken up in benzene and dried over anhydrous magnesium sulfate. After benzene removal, 450 mg. (74.4%) of an oil (IXa) was obtained. This showed a negative Beilstein reaction of halogen.

ν_{max}^{liquid} : no NH or no OH band ; 3055, 3015 (ϕ) ; 2960, 2888 (CH_3, sh); 2930, 2845 (CH_2); 2808, 2758 (*N*-CH_3) ; 1631 (C=N) ; 1608, 1577 (ϕ) ; 1376 (CH_3); 1041 (dimethylamino-, liquid state); 762 (*o*-disubstituted benzene).

IXa-Dihydrobromide : Was prepared by the usual treatment with conc. hydrobromic acid and concentration, m.p. 231°C (ethanol) ; 647 mg. (60.5%). Another recrystallization from ethanol did not raise the melting point.

Anal. Calcd. for $C_{14}H_{22}N_2Br_2$: C, 44.46 ; H, 5.86. Found : C, 44.92 ; H, 6.18. ν_{max}^{KBr} : 3448 (NH) ; 3030 (ϕ, sh) ; 2967 (CH_3) ; 2915, 2849 (CH_2) ; 2732 (N-CH_3) ; 2688, 2326 (amine hydrobromide, vs and broad); 1634 (C=N); 1600, 1567, 1513 (ϕ) ; 1481, 1449 (CH_3, CH_2) ; 1393, 1377 (CH_3, doublet); 743 cm^{-1} (*o*-disubstituted benzene).

3.4.2 1,3-Dimethyl-3-morpholinomethyl-3,4-dihydroisoquinoline (IXb).

A mixture of 268 mg. (1.12 mmole) of II and 3 ml. of morpholine was refluxed for 24 hr. After working up as usual, 232 mg. (80%) of free amine was obtained. This showed a negative Beilstein reaction.

ν_{max}^{liquid} : NO NH and OH bands ; 3030 (ϕ) ; 2985, 2915, 2874 (CH_3, CH_2) ; 2786, 2732 (morpholino) ; 1645 (C = N) ; 1585, 1497 (ϕ) ; 1582, 1449 (CH_3, CH_2) ; 1376 (CH_3); 804, 763, 738, 714 (3,4-dihydroisoquinoline).

IXb-Dihydrobromide : Was prepared as usual. Recrystallization from benzene-ethanol gave 270 mg. of crude crystals, m.p. 217-220°C. Further recrystallization from ethanol gave an analytical sample of dihydrobromide, m.p. 219.5-220°C.

Anal. Calcd. for $C_{16}H_{24}N_2OBr_2$: C, 45.73 ; H, 5.76. Found : C, 45.67 ; H, 5.91. ν_{max}^{KBr} : 3472 (NH) ; 3049 (ϕ , sh) ; 2976, 2941, 2857 (CH_3, CH_2, broad), 2703, 2611, 2463 (amine hydrobromide, broad) ; 1637 (C=N) ; 1608, 1567, 1517 (ϕ) ; 1456, 1422, 1385, 1361 (CH_3, CH_2) ; 777, 746, 714 cm^{-1} (3,4-dihydroisoquinoline).

Another procedure using 553 mg. of II and 6 ml. morpholine gave 571 mg., dihydromide, m.p. 218-220°C.

3.4.3 1,3-Dimethyl-3-piperidinomethyl-3,4-dihydroisoquinoline (IXc).

A solution of 865 mg. (3.63 mmole) of II in 2 ml. of piperidine was refluxed for 24 hr. Working up as usual gave 778 mg. (83.7%) of an oil, which showed a negative Beilstein reaction.

ν_{max}^{liquid} : No sign of NH and OH bands ; 3106, 3049 (ϕ , sh) ; 2950, 2874 (CH_3, CH_2) ; 2801, 2762 (piperidino, sh) ; 1631 (C=N) ; 1456, 1443 (CH_3, CH_2) ; 1374 (CH_3) ; 762, 734, 714 cm^{-1} (3,4-dihydroisoquinoline).

IXc-Dihydrobromide: Was obtained as usual. Recrystallization from ethanol gave 1.016 g. (66.9%) of crude crystals, m.p. 243-247.5°C. Further recrystallization from acetone-ethanol gave an analytical sample, m.p. 238°C (decomp.). This was obtained as monohydrate crystals.

Anal. Calcd. for $C_{17}H_{26}N_2Br_2$-H_2O : C, 46.80 ; H, 6.47 ; N, 6.42 ; H_2O, 4.13. Found : C, 46.83, 46.87 ; H, 6.31, 6.73 ; N, 6.35 ; H_2O, 4.14%. ν_{max}^{KBr} : 3534 (sh), 3401 (NH) ; 3030 (ϕ) ; 2950, 2890. 2857, 2801 (CH_3, CH_2) ; 2770, 2717 (piperidino, sh) ; 2604 (amine hydrobromide, broad) ; 1634 (C=N) ; 1605, 1565, 1517 (ϕ) ; 1443, 1420 (CH_3, CH_2) ; 1376 (CH_3) ; 787, 780, 741, 711 cm^{-1} (3,4-dihydroisoquinoline).

3.4.4 1,3-Dimethyl-3-pyrrolidinomethyl-3,4-dihydroisoquinoline (IXd).

A mixture of 250 mg. (1.05 mmole) of II in 2 ml. of pyrrolidine gave 290 mg. of an oily product. The following infrared spectra showed this had been contaminated with a little amount of pyrrolidine.

ν_{max}^{liquid} : 3333 (NH, v.w) ; 3030 (ϕ) ; 2994, 2950 (CH_3, CH_2) ; 2841 (pyrrolidino) ; 1645 (C = N) ; 1603, 1587, 1495 (ϕ) ; 1462, 1443 (CH_3, CH_2) ; 1374, (CH_3) ; 762, 735, 714 cm^{-1} (3,4-dihydroisoquinoline).

IXd-Dihydrobromide : Was obtained as usual. Recrystallization from acetone-ethanol gave 251 mg. of crude crystals. Further repeated recrystallizations gave an analytical sample, IXd-2HBr, m.p. 232-233°C.

Anal. Calcd. for $C_{16}H_{24}N_2Br_2$: C, 47.54 ; H, 5.99. Found : C, 47.17 ; H, 6.34. ν_{max}^{KBr} : 3484 (NH) ; 3106 (ϕ, sh) ; 2924, 2874, 2825 (CH_3, CH_2) ; 2755 (pyrrolidino) ; 2667, 2597, 2475, 2370 (amine hydrobromide) ; 1639 (C=N) ; 1608, 1572, 1522 (ϕ) ; 1458, 1441, 1425, 1414 (CH_3, CH_2) ; 1381, 1377 (CH_3) ; 773, 739, 710 cm^{-1} (3,4-dihydroisoquinoline).

3.4.5 1,3-Dimethyl-3[(ɗ-pyrrolidinobutylamino)methyl] -3,4-dihydroisoquinoline (IXe).

A mixture of 473 mg. (1.98 mmole) of II and 1.637 g. (11.5 mmole) of ɗ-pyrrolidinobutylamine in 5 ml. of dioxane was refluxed for 24 hr. After usual work up, 563 mg. (91%) of an oily product was obtained, which showed a negative Beilstein reaction.

ν_{max}^{liquid} : 3333 (NH) ; 3077, 3040 (ϕ, sh) ; 2899 (sh), 2809, 2717, (CH_3, CH_2) ; 2755, 2725 (pyrrolidino, both sh) ; 1634 (C=N) ; 1577 (ϕ) ; 1456 (CH_3, CH_2, broad) : 1370 (CH_3) ; 808 (broad), 762, 740, 713 cm^{-1} (3,4-dihydroisoquinoline).

The salt formation with hydrochloric, fumaric or tartaric acid failed to give any clear crystals. A chromatographic separation of the free amine on aluminum oxide was therefore carried out, and a chromatographically pure sample was recovered in a yield more than 71%. However, this showed the same infrared spectrum with the original sample before the above chromatography.

IXe-Trihydrobromide: Was successfully obtained as usual. Repeated recrystallizations from benzene-*n*-butanol gave an analytical sample, m.p. 186-187°C.

Anal. Calcd. for $C_{20}H_{34}N_3Br_3$: C, 43.18 ; H, 6,16. Found : C, 44.01 ; H, 6.16. ν_{max}^{KBr} : 3448 (NH) ; 3058 (ϕ) ; 2915, 2793 (CH_3, CH_2, sh) ; 2717 (*N*-alkylpyrrolidino) ; 1647 (C = N) ; 1608, 1488, 1458 (ϕ) ; 830, 772, 764.5, 742, 709 cm^{-1} (3,4-dihydroisoquinoline).

IXe-Tripicrate : m.p. 119-122°C., (from benzene-acetone).

Anal. Calcd. for $C_{38}H_{40}N_{12}O_{21}$: C, 45.60 ; H, 4.03. Found : C, 48.63 ; H, 4.29.

3.4.6 1,3-Dimethyl-3(γ-hydroxypropylamino)methyl-3,4-dihydroisoquinoline (IXf).

A mixture of 323 mg. (1.28 mmole) of II and 2 ml. of 3-acetoxypropylamine was heated in a steam bath for 24 hr. Work up as usual gave 302 mg. (95%) of an orange yellow oil, which showed a negative Beilstein reaction and no carbonyl peak at 1818-1667 cm^{-1} region on the ir inspection.

ν_{max}^{liquid} : 3333 (NH, OH, Broad) ; 2967 (ϕ) ; 2924, 2793 (CH_3, CH_2) ; 1634 (C=N) ; 1115 (C-O, s) ; 763, 738, 713 cm^{-1} (3,4-dihydroisoquinoline).

3.4.7 1,3-Dimethyl-3-(β-diethylaminoethylamino)methyl-3,4-dihydroisoquinoline (IXg).

A mixture of 1.436 g. (5.69 mmole) of II in 10 ml. of β-diethylaminoethylamine was refluxed for 24 hr. Work up as usual gave 1.863 g. of an oil, free amine. Upon hydrobromide formation, 1.877 g. (62%) of the trihydrobromide, m.p. 207-209°C, was obtained.

Anal. Calcd. for $C_{18}H_{29}N_3$-3HBr : C, 40.77 ; H, 5.51. Found : C, 40.92 ; H, 6.20. ν_{max}^{KBr} : 3425 (NH), 3030 (ϕ, sh) ; 2967, 2890 (CH_3, CH_2) ; 2849-2326 (amine hydrobromide, broad) 1639 (C=N) ; 1600 (ϕ) ; 1038, 1018 ; 801, 778, 744, 732, 710 cm^{-1} (3,4-dihydroisoquinoline).

3.4.8 1,3-Dimethyl-3-(γ-diethylaminopropylamino)methyl-3,4-dihydroisoquinoline (IXh).

A mixture of 782 mg. (3.1 mmole) of II and 10 ml. of β-diethylaminopropylamine was refluxed for 24 hr. After work up as usual, the following hydrobromide formation, and recrystallization from an acetone-benzene-*n*-butanol mixture gave 1.179 g. (66%) of the trihydrobromide. The melting point was 114-119°C and decomposition temperature was 138-141°C.

Anal. Calcd. for $C_{19}H_{31}N_3$-3HBr : C, 41.93 ; H, 6.30. Found : C, 41.70 ; H, 6.45. ν_{max}^{KBr} : 3401 (NH) ;3040 (ϕ) ; 2959, 2924 (CH_3, CH_2) ; 2809-2353 (amine hydrobromide, broad) : 1637 (C = N) ; 1595, 1563, 1511(ϕ) ; 1029, 772, 743, 709 cm^{-1} (3,4-dihydroisoquinoline).

3.4.9 1,3-Dimethyl-3-(γ-diethylamino-β-hydroxypropylamino)methyl-3,4-dihydroisoquinoline (IXi).

A mixture of 1.280 g. of II and 15 ml. of γ-diethylamino-β-hydroxypropylamine was refluxed for 32 hr. After work up as usual, 644 mg. of the free amine product was obtained. Usual hydrobromide formation gave 668 mg. of a powder, m.p. 185-195°C (decomp.).

Anal. Calcd. for $C_{19}H_{34}N_3OBr_3$: C, 40.73 ; H, 6.12, N, 7.50. Found : C, 42.75 ; H, 6.62 ; N, 8.09.

These analytical values show that this product was contaminated greatly with the by-product, such as $C_{19}H_{29}N_3$-3HBr (Anal. Calcd. C, 42.09 ; H, 5.95 ; N, 7.75%) by dehydration in the presence of conc. hydrobromic acid upon the above salt formation.

ν_{max}^{KBr}: 3400 (NH, OH) ; 2938 (CH_2) ; 2800-2470 (amine hydrobromide) ; 1620, 1570, 1440,

1380, 1090, 1020 (C—O) ; 760 cm^{-1} (3,4-dihydroisoquinoline).

3.5.1 1-Phenyl-3-dimethylaminomethyl-3-methyl-3,4-dihydroisoquinoline (Xa).

A mixture of 395 mg. (1 mmole) of III-hydrobromide and 10 ml. of 25% aqueous dimethylamine was heated in a sealed tube placed in a steam bath for 55 hr. Work up as usual gave 265 mg. (95%) of an oily product, which showed a negative result upon Beilstein test of halogen and no sign of NH and OH bands upon the ir inspection.

ν_{max}^{liquid} : 3086, 3058 (phenyl); 2994 (sh), 2950, 2882, 2841, 2786 (CH_3, CH_2); 2740 (N-CH_3, sh) ; 1610 (C=N) ; 1565, 1497 (phenyl) ; 1453, 1429 (CH_3, CH_2) ; 1381 (sh), 1372 (CH_3) ; 1044 ((CH_3)$_2$N-, in liquid state) ; 762, 717 (3,4-dihydroisoquinoline) ; 746, 698 cm^{-1} (monosubstituted benzene).

Xa-Dihydrobromide : Was obtained as usual. m.p. 161-165°C (from acetone-ethanol), 317 mg. (72%). Recrystallization from ethanol gave an analytical sample, m.p. 164—166°C and 212-214°C (decomp.). This salt has two melting points.

Anal. Calcd. for $C_{19}H_{24}N_2Br_2$: C, 51.83 ; H, 5.50. Found : C, 52.00 ; H, 5.74.

3.5.2 1-Phenyl-3-methyl-3-morpholinomethyl-3,4-dihydroisoquinoline (Xb).

One mmole of III-hydrobromide and 3 ml. of morpholine gave 270 mg. (84.5%) of a yellow oily product (Xb). The Beilstein reaction was negative.

Xb-Dihydrobromide : Was obtained as usual, and 60.5% of crude crystals, 71.5% in another run, was obtained. Repeated recrystallizations from acetone-ethanol gave an analytical sample, m.p. 241—242°C.

Anal. Calcd. for $C_{21}H_{26}N_2OBr_2$: C, 52.30 ; H, 5.43. Found : C, 52.45 ; H, 5.54.

3.5.3 l-Phenyl-3-methyl-3-piperidinomethyl-3,4-dihydroisoquinoline (Xc).

The same procedure using piperidine under 20 hr. -reflux as above gave 308 mg. (96.8%) of a dark yellow oil (Xc), which showed no sign on Beilstein test of halogen.

Xc-Dihydrobromide : Was obtained as usual, 326 mg. (82.5%). An analytical sample was obtained by recrystallization from ethanol, m.p. 250-255°C (decomp.).

Anal. Calcd. for $C_{22}H_{28}N_2Br_2$: C, 55.01 ; H, 5.88. Found : C, 55.13 ; H, 5.99.

ν_{max}^{KBr} : 3472 (NH) ; 3030 (phenyl, sh) ; 2959, 2882 (CH_3, CH_2) ; 2667 (amine hydrobromide, broad) ; 1631 (C=N) ; 1610, 1572, 1497 (phenyl) ; 1456, 1441, 1427 (CH_3, CH_2) ; 794, 763, 719 (3,4-dihydroisoquinoline) ; 747, 694 (monosubstituted benzene).

3.5.4 1-Phenyl-3-methyl-3-pyrrolidinomethyl-3,4-dihydroisoquinoline (Xd).

The same procedure using pyrrolidine as above gave 277 mg. (91%) of an oily product (Xd), which showed a negative Beilstein reaction.

Xd-Dihydrobromide : Was obtained as usual, 287 mg. Recrystallization from benzene-ethanol gave an analytical sample, m.p. 152-155°C and 208-210°C (decomp.). This amine salt changed into yellow on heating above 100°C and seemed to have two melting points as in the case of Xa.

Anal. Calcd. for $C_{21}H_{26}N_2Br_2$: C, 54.09 ; H, 5.62. Found : 53.93 ; H, 5.74.

ν_{max}^{KBr} : 3448 (NH) ; 3058 (phenyl) ; 2959, 2849 (CH_3, CH_2) ; 2564, 2475 (amine hydrobromide) ; 1631 (C=N) ; 1605, 1565, 1495 (phenyl) ; 1453 (CH_2) ; 787, 768, 720 (3,4-dihydroisoquinoline) ; 745, 695 cm^{-1} (monosubstituted benzene).

3.5.5 1-Pheny-3-methyl-3-(δ-pyrrolidinobutylaminomethyl)-3,4-dihydroisoquinoline (Xe).

A mixture of 395 mg. (1 mmole) of III-hydrobromide and 1.179 g. (83 mmole) of δ-pyrrolidinobutylamine was heated on a steam bath for 24 hr. The excess amine was removed by vacuum distillation. After alkalization of the residue with sodium hydroxide, the isolated oil was taken up in benzene and the benzene layer was washed repeatedly with water to completely

remove the excess of δ-pyrrolidinobutylamine, and dried over potassium hydroxide pellets. After a complete evaporation of the solvent under reduced pressure, 454 mg. of a yellow oil remained. It showed no Beilstein reaction of halogen.

ν_{max}^{liquid} : 3311, (NH) ; 3067, 3030 (φ) ; 2941, 2874, 2793 (CH_3, CH_2) ; 2747, 2725 (*N*-alkylpyrrolidino, both sh) ; 1616 (C=N) ; 1567, 1479 (φ) ; 1456, 1447 (CH_3, CH_2) ; 1125 (pyrrolidino, in liquid state) ; 786, 762, 717 (3,4-dihydroisoquinoline) ; 746, 697 cm^{-1} (monosubstituted benzene).

Xe-Tripicrate : m.p. 197.5-199°C (from acetone-benzene).

Anal. Calcd. for $C_{43}H_{42}N_2O_{21}$: C, 48.59 ; H, 3.98. Found : C, 48.44 ; H, 4.16.

ν_{max}^{KBr}: 3460, 3115, 2941, 2865, 2770, 1637, 1613, 1563, 1541, 1493, 1433, 1366, 1342—1312 (broad) , 1271, 1164, 1080, 943, 924 (sh), 911, 838, 788, 763, 744, 717, 709, 698 cm^{-1}.

3,5,6 1-Phenyl-3-(β-diethylaminoethylamino)methyl-3-methyl-3,4-dihydroisoquinoline (Xg).

A mixture of 870 mg. (2.77 mmole) of III in 5 ml. of β-diethylaminoethylamine was refluxed for 24 hr. After vacuum concentration, the reaction system was treated and dissolved in dil. hydrochloric acid and decolorized with an active carbon and filtered. Alkalization with sodium hydroxide and subsequent extraction with benzene, and usual work up gave 809 mg. of oil.

The hydrobromide formation as usual and recrystallization from ethanol gave white crystals, Xg-3HBr, m.p. 168—169°C (decomp.), 80 mg.

Anal. Calcd. fo $C_{23}H_{31}N_3$·3HBr : C, 46.64 ; H, 5.79. Found : C, 46.57 ; H, 5.94.

ν_{max}^{KBr} : 3413 (NH) ; 3049 (phenyl) ; 2941-2646 (amine hydrobromide, broad); 2315 (diethylamino); 1616 (C = N) ; 1595, 1560, 1495 (phenyl, sh); 795, 764, 718 (3,4-dihydroisoquinoline) ; 750, 694 cm^{-1} (monosubstituted benzene).

3.5.7 1-Phenyl-3-(γ-diethylaminopropylamino)methyl-3-methyl-3,4-dihydroisoquinoline (Xh).

A mixture of 942 mg (3.34 mmole) of III in 10 ml. of γ-diethylaminopropylamine was refluxed for 30 hr. After work up as usual 862 mg. (47.4%) of the trihydrobromide was obtained. The trihydrobromide crystals (Xh-3HBr) melted above 100°C and decomposed at 131-136°C.

Anal. Calcd. for $C_{24}H_{33}N_3$·3HBr : C, 47.54 ; H, 5.99 ; N, 6.93. Found : C, 46.49 ; H, 5.98 ; N, 6.94.

ν_{max}^{KBr} : 3333 (NH) ; 3030 (phenyl, sh) ; 2950, 2933 (CH_3, CH_2, broad) ; 2778-2392 (amine hydrobromide, broad) ; 1610 (C = N) ; 1595, 1558 (φ) ; 1020 ; 794, 765, 721 (3,4-dihydroisoquinoline) ; 739, 696 cm^{-1} (monosubstituted benzene).

3.5.8 1-Phenyl-3-[(δ-diethylamino-α-methylbutyl)amino]methyl-3-methyl-3,4-dihydroisoquinoline (Xi).

A sample of 826 mg. (2.63 mmole) of III in 10 ml. of 2-amino-5-diethylaminopentane was heated at 130°C for 24 hr. The reaction mixture was poured into a large amount of water and extracted with benzene. The benzene layer was extracted with dil. hydrochloric acid. The acid layer was alkalized with conc. sodium hydroxide to make the amine product free. Work up as usual gave 1.150 g. of an oil. Subsequent hydrobromide formation gave 1.200 g. of a yellow amorphous solid, which decomposed at 140-145°C.

Anal. Calcd. for $C_{26}H_{40}N_3Br_3$: C, 49.23 ; H, 6.36 ; N, 6.63. Found : C, 48.21 ; H, 6.29 N, 6.97.

ν_{max}^{KBr}: 3448 (NH) ; 3077-2370 (amine hydrobromide, broad) ; 1631 (C=N) ; 1563, 1453, 1393, 1333, 1206, 1164, 1042 ; 794, 766, 718 (3,4-dihydroisoquinoline) ; 746, 696 cm^{-1} (monosubstituted benzene).

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