Synthesis of 1,2,3,4-Tetrahydro-1,1,2,3,3,4,4-heptamethyl-6,7-dimethoxyisoquinoline and Related Compounds as Potential Hypotensive Agents

JACOB FINKELSTEIN,* ELLIOT CHIANG, AND ARNOLD BROSSI

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received January 22, 1971

It was of interest to synthesize the title compound **27a** which has 7 methyl groups in the heterocyclic moiety. Three synthetic schemes for preparing the intermediate 3,4-dihydroisoquinolines will be described. In two schemes they were obtained by the classical Bischler–Napieralski cyclization of the corresponding phenethylamides. In the third, which yielded the title compound, the carbonium ion of **21a** was treated with MeCN affording directly the dihydroisoquinoline **23a**; Grignard reaction with MeMgI, following N-methylation, gave **27a**. Details on these syntheses and the pharmacological screening results are described.

The report that 1,2,2,6,6-pentamethylpiperidine[1,2] (pempidine) is a highly active hypotensive agent directed our continuing interest in 1,2,3,4-tetrahydroisoquinolines to those compounds where the hydrogens of the hetero portion of the molecule are replaced by Me. Of 3 synthetic pathways used to prepare these derivatives, one led to the title compound, 1,2,3,4-tetrahydro-6,7-dimethoxy-1,1,2,3,3,4,4-heptamethylisoquinoline.

As per Scheme I, we found that the reported reduction of 2-(3,4-dimethoxyphenyl)-2-methylpropionitrile (**1a**) with LAH (Et_2O)[3] to give 2-(3,4,-dimethoxyphenyl)-2-methylpropylamine (**2a**) was satisfactory for the preparation of small amounts of material. However, for the large amounts required, we found that hydrogenation of the nitrile in MeOH–NH_3 in the presence of Raney Ni was more convenient and gave much higher yields. Acylation of a refluxing C_6H_6 solution of **2a** with AcCl in the presence of Et_3N gave *N*-1-[2-(3,4-dimethoxyphenyl)-2-methylpropylacetamide (**3a**), which was cyclized to 3,4-dihydro-6,7-dimethoxy-1,4,4-trimethylisoquinoline (**4a**) under Bischler–Napieralski[4] conditions with $POCl_3$ in refluxing PhMe. Reduction of **4a** with $NaBH_4$ in MeOH gave 1,2,3,4-tetrahydro-6,7-dimethoxy-1,4,4-trimethylisoquinoline (**5a**). In MeOH containing CH_2O, **4a** was reduced in the presence of Raney Ni under 3.5 kg of H_2/cm^2 to 1,2,-3,4-tetrahydro-1,2,4,4-tetramethyl-6,7-dimethoxyisoquinoline (**6a**). This compound was also prepared readily by hydrogenating **7a** (see below) over PtO_2. By heating **6a** in refluxing 48% HBr, the corresponding 6,-7-dihydroxy compound **6b** was obtained.

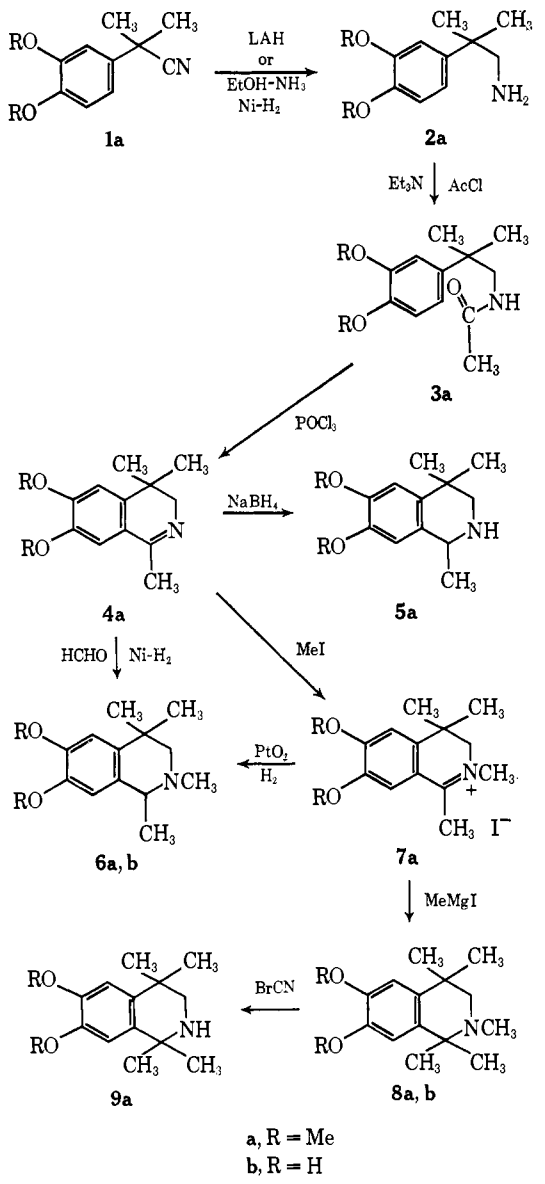
When **4a** was allowed to react with MeI (Et_2O) at room temp, 3,4-dihydro-6,7-dimethoxy-1,2,4,4-tetramethylisoquinolinium iodide (**7a**) crystallized. Quaternary salts of this type, have been reported[5-9] to alkylate or arylate at the 1 position on reaction with Grignard reagents. Thus, when **7a** was treated with a refluxing solution of MeMgI in dry Et_2O, 1,2,3,4-tetrahydro-6,7-dimethoxy-1,1,2,4,4-pentamethylisoquinoline (**8a**) was obtained. Compound **8a** was cleaved to its dihydroxy derivative **8b** by refluxing 48% HBr, and converted to its N-demethylated derivative 1,2,3,4-tetrahydro-6,7-dimethoxy-1,1,4,4-tetramethylisoquinoline (**9a**) with BrCN under conditions of the von Braun reaction.[10]

For the compounds shown in Scheme II, we started with 3-(3,4-dimethoxyphenyl)-3-methyl-2-butanone (**10a**), obtained from **1a** and MeMgI. This reaction required 3 equiv of the Grignard reagent and reasonably high dilution; no reaction took place with equiv amounts of reactants. The oxime **11a** was obtained from **10a** in the usual manner. Reduction of **11a** to 2-amino-3-(3,4-dimethoxyphenyl)-3-methylbutane (**12a**) was effected by hydrogenation (Raney Ni) in EtOH–NH_3 at high pressure and elevated temp according to the method of Sheppard, *et al.*,[11] since reduction with $NaBH_4$, LAH (Et_2O), and H_2 (Pt) at 3.5 kg/cm^2 failed. The remaining compounds in this scheme were prepared as indicated in analogy with the methods used in Scheme I, except that, since N-debenzylation could be achieved more readily than N-demethylation, 1,2,-3,4-tetrahydro-6,7-dimethoxy-1,1,3,4,4-pentamethylisoquinoline (**18a**) was obtained *via* the *N*-benzyl derivatives **16a** and **17a**.

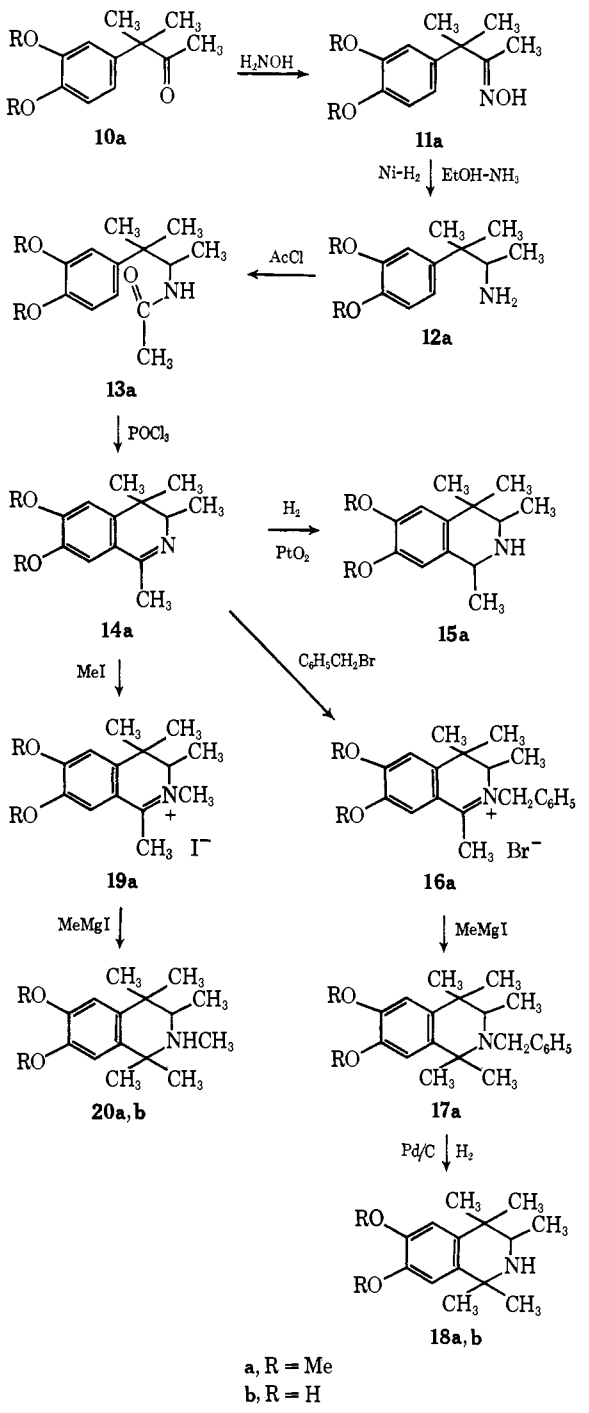
For the compounds shown in Scheme III, we started with 3-(3,4-dimethoxyphenyl)-2,3-dimethyl-2-butanol (**21a**) which was obtained from **10a** and MeMgI. Although this product was contaminated with **10a** (nmr), it was suitable for use in the next reaction. Pure **21a** could be obtained from **10a** and MeLi. When **21a** was caused to react with MeCN under conditions of the Ritter reaction,[12] the expected amide **22a** was not obtained. This was indicated by ir, uv, and nmr data which, along with the elementary analysis, clearly showed that the product was 3,4-dihydro-6,7-dimethoxy-1,3,3,4,4-pentamethylisoquinoline (**23a**). Further confirmation was obtained by formation of its hydrochloride, its methiodide **26a**, and the other transformations shown in Scheme III. Thus, reduction of **23a** with $NaBH_4$ gave 1,2,3,4-tetrahydro-6,7-dimethoxy-1,3,3,4,4-pentamethylisoquinoline (**24a**). Catalytic reductive-methylation of both **23a** and **24a** in the presence of CH_2O gave 1,2,3,4-tetrahydro-6,7-dimethoxy-1,2,3,3,4,4-hexamethylisoquinoline (**25a**). Reaction of methiodide **26a** gave the title compound, 1,2,3,-4-tetrahydro-6,7-dimethoxy-1,1,2,3,3,4,4-heptamethyl-

(1) A. Spinks and E. H. P. Young, *Nature (London)*, **181**, 1397 (1958).
(2) G. E. Lee, W. R. Wragg, S. I. Corne, N. D. Edge, and H. W. Reading, *ibid.*, **181**, 1717 (1958).
(3) J. Knabe and J. Kubitz, *Naturwissenschaften*, **48**, 669 (1961).
(4) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).
(5) M. Freund and I. Brode, *Ber.*, **42**, 1746 (1909).
(6) K. Wiesner, Z. Valenta, A. J. Mason, and F. W. Stone, *J. Amer. Chem. Soc.*, **77**, 675 (1955).
(7) E. Hoft, A. Rieche, and H. Schultze, *Justus Liebigs Ann. Chem.*, **697**, 181 (1966).
(8) E. Schmitz, *Ber.*, **91**, 1133 (1958).
(9) J. Knabe and A. Schepers, *Arch. Pharm. (Weinheim)*, **295**, 481 (1962).
(10) H. A. Hageman, *Org. React.*, **7**, 198 (1953).
(11) E. R. Sheppard, J. F. Noth, H. D. Porter, and E. K. Simmons, *J. Amer. Chem. Soc.*, **74**, 4611 (1952).
(12) L. I. Krimen and D. J. Costa, *Org. React*, **17**, 213 (1969).

SCHEME I



SCHEME II



isoquinoline (**27a**), which was cleaved with refluxing 48% HBr to give its 6,7-dihydroxy derivative **27b**.

Biological Results.—Pharmacological screening tests were performed for blood pressure, analgetic, and antiedema effects. Various compounds exhibited analgtic activity in the writhing[13] and/or hot[14] plate tests, but at dose levels with unfavorable therapeutic indices. The same observations were made regarding the weak antiedema activity in the carrageenin-induced test.[15] The blood pressure screens were performed in dogs anesthetized by pentobarbital at 4–10 mg per kg iv. The two most active compounds are: **17a** at 10 mg/kg lowered blood pressure 30 mm for 50 min, and **20a** at 4 mg/kg produced a drop of 30 mm for 60 min. The title compound **27a** produced a drop of 35 mm at 4 mg/kg for 5 min, and its dihydroxy derivative, 35 mm for 30 min at 10 mg/kg.

The acute 24-hr toxicity (LD_{50}) determined in mice ip did not reveal any noteworthy toxicity.

Experimental Section[16]

2-(3,4-Dimethoxyphenyl)-2-methylpropylamine (2a).—A suspension of 41 g (0.2 mole) of 2-(3,4-dimethoxyphenyl)-2-methylpropionitrile (**1a**) in 160 ml of MeOH contg **17 g** of NH_3 and **80 g** of Raney Ni was reduced under H_2 (35 kg/cm²) at 30° in a rock-

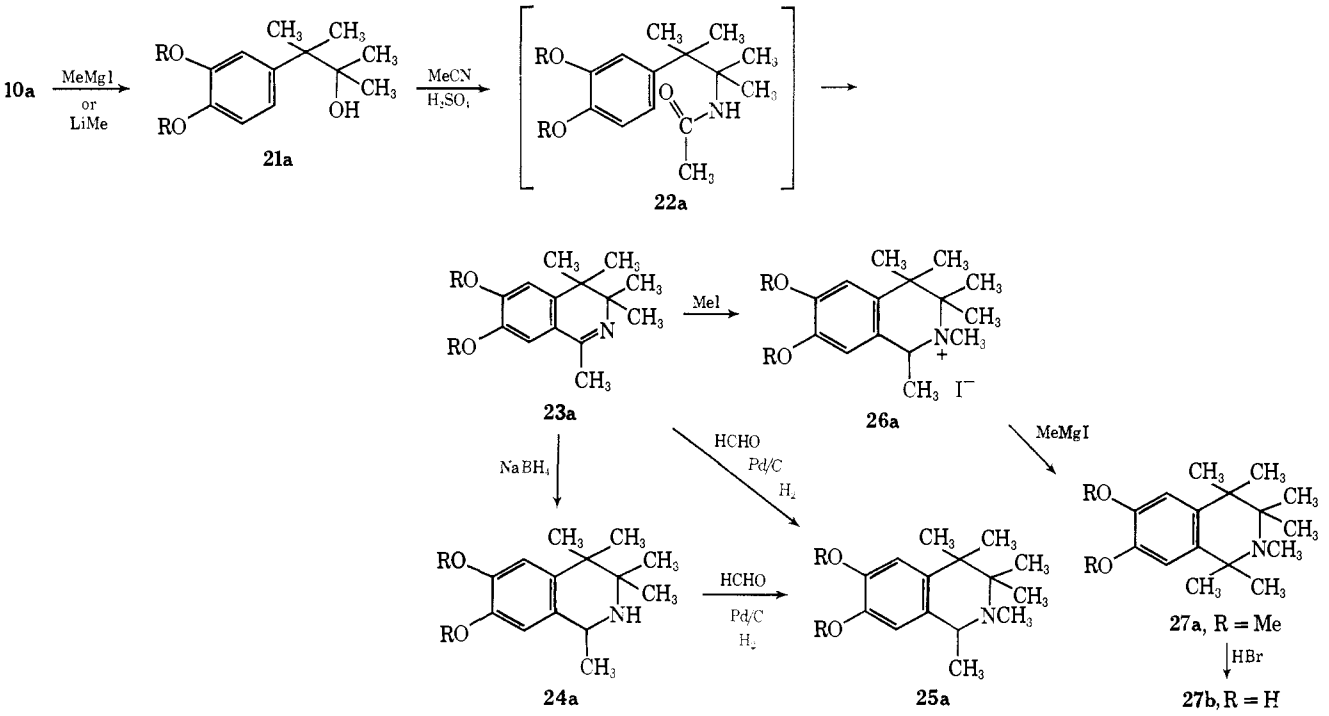
(13) E. Sigmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957).

(14) N. B. Eddy, C. F. Touchbeny, and J. E. Lieberman, *J. Pharmacol. Exp. Ther.*, **90**, 121 (1950).

(15) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(16) Melting points were determined on a Uni-Melt Thomas-Hoover capillary melting point apparatus, and are corrected. Ir spectra were determined on a Beckman IR-9 or Perkin-Elmer 621 spectrophotometer, and uv spectra on a Cary spectrophotometer (Model 41). The nmr spectra were obtained with a Varian A-60 or HA-100. These spectra were taken in sequence to confirm the expected chemical changes. The yields reported are not optimized. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

SCHEME III



ing autoclave for approximately 30 min. After cooling, filtering, and concg the filtrate, the product was obtd as a clear dist: bp 117–118° (1 mm); yield 39 g (93%). *Anal.* ($C_{12}H_{19}NO_2$) C, H, N.

***N*-1-[2-(3,4-Dimethoxyphenyl)-2-methylpropyl]acetamide (3a).**—To a stirring soln of 4.2 g (0.02 mole) of **2a** and 3 g (0.03 mole) of Et_3N in 40 ml of dry C_6H_6 at 10°, a soln of 1.6 g (0.02 mole) of AcCl in 20 ml of dry C_6H_6 was added dropwise and slowly. The reaction was completed by refluxing for 2 hr. The cooled soln was dild with 30 ml of H_2O, and the org layer was washed with dil HCl, dried, and concd at 30° *in vacuo* to give an oil which soon crystd: yield 4 g (80%); a sample from petr ether (bp 30–60°) had mp 95.5–97°. *Anal.* ($C_{14}H_{21}NO_3$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1,4,4-trimethylisoquinoline·HCl (4a·HCl).—A mixt of 2.5 g (0.01 mole) of **3a** and 6 ml of $POCl_3$ in 30 ml of dry $C_6H_5CH_3$ was refluxed for 3 hr. The reaction mixt was carefully decompd with ice water, and the layer was sepd, made alk to pH ~ 9 by adding a soln of NaOH, and extd with $CHCl_3$. The dried ext was concd to leave an oil which was converted into its cryst hydrochloride: mp 190–192° (EtOH–EtOAc). *Anal.* ($C_{14}H_{19}NO\cdot HCl$) C, H, N.

When the reaction was repeated with 25 g (0.1 mole) of **3a**, 17 g (63%) of the product was obtained.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,4,4-trimethylisoquinoline·HCl (5a·HCl).—To a stirred soln of 2.7 g (0.01 mole) of **4a** in 50 ml of MeOH at 24–30°, 1.5 g (0.04 mole) of $NaBH_4$ was added in several portions. After additional stirring for 1 hr, the soln was concd at 35° *in vacuo* to a white solid. This was broken up with the aid of 30 ml of H_2O extd with Et_2O, and dried. Upon evapn of the Et_2O, the residual product was converted into its hydrochloride, and crystd from EtOH–EtOAc: mp 214–215°; yield 2 g (74%). *Anal.* ($C_{14}H_{21}NO_2\cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-1,2,4,4-tetramethyl-6,7-dimethoxyisoquinoline·HCl (6a·HCl). A.—A soln of 4.1 g (0.015 mole) of **4a** in 250 moles of MeOH containing 1.4 g (0.017 mole) of 37% formalin and 1 tablespoon of Raney Ni was reduced under 3.5 kg/cm² of H_2. After filtering the catalyst, the filtrate was evapd at 30° *in vacuo*, and the residual oil was dild with 30 ml of H_2O and made alk with a soln of NaOH, and the base was extd with $CHCl_3$. The dried ext was evapd to yield 3.5 g (82%) of the oily product, which was converted into its hydrochloride: mp 229–230.5° (EtOH–EtOAc). *Anal.* ($C_{15}H_{23}NO_2\cdot HCl$) C, H, N.

B.—A soln of 3.8 g (0.01 mole) of **7a** (see below) in 200 ml of MeOH and 150 mg of PtO_2 was reduced under 3.5 kg/cm² of H_2. After filtering the catalyst, the filtrate was evapd *in vacuo* at 35°, and the oily residue was taken up into 20 ml of H_2O, and made alk with a dil NaOH soln. The base was extd with Et_2O, dried, and treated with $Et_2O\cdot HCl$ to form the hydrochloride; mp 230–231° (EtOH–EtOAc): yield 2.25 g (79%); indistinguishable from the product obtained by method A. *Anal.* ($C_{15}H_{23}NO_2\cdot HCl$) C, H, N.

6,7-Dihydroxy-1,2,3,4-tetrahydro-1,2,4,4-tetramethylisoquinoline (6b).—A soln of 1.5 g (0.006 mole) of **6a** in 30 ml of 48% HBr was refluxed for 6 hr, and concd *in vacuo* at 40–50°. The residue was dild with H_2O, made alk with concd NH_4OH to give a ppt which was filtered, washed with H_2O, and crystd from C_6H_6: mp 164–169°; yield 600 mg (45%). *Anal.* ($C_{13}H_{19}NO_2$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1,2,4,4-tetramethylisoquinolinium Iodide (7a).—A soln of 2 g (0.0086 mole) of **4a** and 3 ml of MeI in 50 ml of dry Et_2O was kept at room temp overnight, and the product was crystd from EtOH: yield 2 g (62%); mp 194–196°. *Anal.* ($C_{14}H_{19}NO_2\cdot CH_3I$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,1,2,4,4-pentamethylisoquinoline·HCl (8a·HCl).—To a Griguard soln prepd from 4.8 g of Mg turnings and 28.4 g (0.2 mole) of MeI in 1 l. of dry Et_2O 2.5 g (0.007 mole) of **7a** was added in several portions over 15 min and the mixt was then refluxed with stirring for 24 hr. The cooled reaction mixt was poured onto crushed ice contg 16 g of NH_4Cl in 160 ml of H_2O. The mixt was then made alk with concd NH_4OH, extd with Et_2O, and the dried Et_2O soln was treated with a soln of $Et_2O\cdot HCl$ to give the salt: yield 1.2 g (61%); mp 249–250° (*i*-PrOH). *Anal.* ($C_{16}H_{25}NO_2\cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dihydroxy-1,1,2,4,4-pentamethylisoquinoline·HBr (8b·HBr).—A soln of 1.5 g (0.0057 mole) of **8a** in 30 ml of 48% HBr was refluxed for 6 hr and evapd *in vacuo* at 35–40°, and the residue was crystd from EtOH: yield 900 mg (45%); mp 112–115°, dried at 95° (1 mm); the nmr indicated the presence of EtOH of crystn which was confirmed by elemental analyses. *Anal.* ($C_{14}H_{21}NO\cdot HBr\cdot EtOH$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,1,4,4-tetramethylisoquinoline·HCl (9a·HCl).—A soln of 0.53 g (0.005 mole) of BrCN in 20 ml of dry $CHCl_3$ was added to 1.0 g (0.4 mole) of **8a** in 30 ml of $CHCl_3$ and refluxed with stirring for 4 hr. The cooled soln was washed with 20 ml of 5% HCl, dried, and concd *in vacuo* at 25°. The residual oil (0.9 g) was refluxed in 15 ml of 3 *N* HCl for 10 hr, cooled, made alk with 4 *N* NaOH, and extd with Et_2O. The dried ext was treated with an $EtOH\cdot HCl$ soln to give a ppt which was crystd from EtOH; yield 200 mg (19%); mp 270–272°. *Anal.* ($C_{15}H_{23}NO_2\cdot HCl$) C, H, N.

3-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone (10a).—To the Grignard reagent prepd from 2.9 g (0.12 g-atom) of Mg and 17 g (0.12 mole) of MeI in 80 ml of dry Et_2O a soln of 8.2 g (0.04

mole) of **1a** in 100 ml of dry Et_2O was added at a rate to sustain gentle refluxing, and the mixt was heated for 48 hr at reflux. The cooled reaction mixt was carefully dild with 20 ml of cold H_2O, and then poured onto a mixt of 250 g of chipped ice contg 30 ml of concd HCl. The org layer was combined with subsequent Et_2O ext, dried, and concd to give 7.7 g of crude product. This residue was dissolved in C_6H_6, and passed through a 6 in. × 2.0 cm column of neutral Al_2O_3. The eluate was concd to give 6 g of an oil, which was distd: bp 130–131° (2 mm). Repeating this prepn, from 41 g (0.2 mole) of **1a**, 25.0 g (56%) of the product was obtd as a colorless oil. *Anal.* ($C_{13}H_{18}O_3$) C, H, N.

3-(3,4-Dimethoxyphenyl)-3-methyl-2-butanone Oxime (11a).—From 17.6 g (0.08 mole) of **10a**, 6.08 g (0.08 mole) of $H_2NOH \cdot HCl$, and 8.0 g (0.1 mole) of NaOAc in 25 ml of 70% EtOH, 14.7 g (77%) of product was obtd: mp 87.5–89° (petr ether 30–60°); white cryst. *Anal.* ($C_{13}H_{19}NO_3$) C, H, N.

3-(3,4-Dimethoxyphenyl)-3-methyl-2-aminobutane·HBr (12a·HBr).—A shaking autoclave was charged with 17 g (0.072 mole) of **11a**, 450 ml of 50% EtOH·NH_3, and 5 g of Raney Ni. Under 350 kg/cm³ of H_2 at 120°, the reduction was completed in 8 hr. After filtering and concg the filtrate *in vacuo* at 30°, the residual oil was extd with Et_2O, dried, and treated with HBr to give the cryst salt: yield 19 g (87%); mp 198–200° (EtOH–EtOAc). *Anal.* ($C_{13}H_{21}NO_2 \cdot HBr$) C, H, N.

3-(3,4-Dimethoxyphenyl)-3-methyl-2-acetamidobutane (13a).—A mixt of 11 g (0.05 mole) of **12a** in 80 ml of dry C_6H_6 was stirred with 3.4 g (0.03 mole) of Na_2CO_3 while 4.2 g (0.055 mole) of AcCl was added. After refluxing for 5 hr, the solvent was removed *in vacuo*, and the residue was dild with 100 ml of H_2O and extd with Et_2O. The dried Et_2O soln was evapd to leave an oil, which crystd upon trituration with petr ether: mp 101–103° (petr ether 60–90°); yield 7.7 g (55%). *Anal.* ($C_{15}H_{23}NO_3$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1,3,4,4-tetramethylisoquinoline·HCl (14a·HCl).—A mixt of 24.8 g (0.093 mole) of **13a** in 300 ml of dry $C_6H_5CH_3$ and 56 ml of $POCl_3$ was refluxed for 4 hr, cooled, and poured into 300 ml of ice H_2O. The org layer was sepd and discarded. The aq layer was made alk by the addn of a 30% NaOH soln and extd with $CHCl_3$. The dried ext was evapd to leave an oily residue, which was treated with $Et_2O \cdot HCl$ to form the salt: yield 25.3 g (96%); mp 199–201° (EtOH–EtOAc). *Anal.* ($C_{15}H_{21}NO \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,3,4,4-tetramethylisoquinoline·HCl (15a·HCl).—A soln of 2.5 g (0.01 mole) of **14a** in 100 ml of MeOH in the presence of 100 mg of PtO_2 was reduced under 3.5 kg/cm² of H_2. After filtering the catalyst, the solvent was evapd, the residue was dissolved in 20 ml of H_2O and made alk with an aq NaOH soln, and the oil was extd with Et_2O. The dried Et_2O soln was treated with $Et_2O \cdot HCl$ to form the salt: yield 2.0 g (71%); mp 264–265° (EtOH). *Anal.* ($C_{15}H_{23}NO_2 \cdot HCl$) C, H, N.

2-Benzyl-3,4-dihydro-6,7-dimethoxy-1,3,4,4-tetramethylisoquinolinium Bromide (16a).—A soln of 18 g (0.07 mole) of **14a** and 15.4 g (0.09 mole) of benzyl bromide in 300 ml of EtOAc was refluxed for 1 hr. After cooling, the cryst product was cryst from *i*-PrOH: mp 203–204°; yield 17.1 g (58%). *Anal.* ($C_{22}H_{28}BrNO_2$) C, H, N.

2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1,1,3,4,4-pentamethylisoquinoline·HCl (17a·HCl).—To the Grignard reagent prepd from 12.2 g (0.8 g-atom) of Mg turnings in 500 ml of dry Et_2O and 114 g (0.8 mole) of MeI in 500 ml of dry Et_2O 17 g (0.044 mole) of **16a** was added, and the mixt was refluxed for 20 hr with stirring and worked-up as for **8a·HCl**: yield 7.5 g (44%); mp 303–305° (*i*-PrOH). *Anal.* ($C_{23}H_{31}NO_2 \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,1,3,4,4-pentamethylisoquinoline·HCl (18a·HCl).—A soln of 4.3 g (0.012 mole) of **17a** in 250 ml of MeOH was reduced at 3.5 kg of H_2/cm² in the presence of 100 mg of 10% Pd/C at room temp. After filtering, the filtrate was evapd at 30° *in vacuo* to a solid residue, which was dild with H_2O, made alk with a NaOH soln, and the base extd with Et_2O. The dried Et_2O soln was treated with $Et_2O \cdot HCl$, and concd to crystn: mp 310–311° (EtOH); yield 2.6 g (72%). *Anal.* ($C_{16}H_{25}NO_2 \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dihydroxy-1,1,3,4,4-pentamethylisoquinoline·HBr (18b·HBr).—A soln of 1.4 g (0.0053 mole) of **18a** in 50 ml of 48% HBr was refluxed for 16 hr, concd *in vacuo* at 35°, and the residue was crystd from EtOH: mp 300–302°; yield 1.4 g (88%). *Anal.* ($C_{14}H_{21}NO_2 \cdot HBr$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1,2,3,4,4-pentamethylisoquinolinium Iodide (19a).—A soln of 12 g (0.05 mole) of **14a** and 20 ml of MeI in 300 ml of dry Et_2O was kept at room temp for 16 hr, and the solid was filtered: mp 226.5–227.5° (EtOH); yield 14.5 g (76%). *Anal.* ($C_{16}H_{24}INO_2$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,1,2,3,4,4-hexamethylisoquinoline·HCl (20a·HCl).—To a Grignard reagent prepd from 4.8 g (0.2 g-atom) of Mg and 28.4 g (0.2 mole) of MeI in 300 ml of dry Et_2O 2.5 g (0.007 mole) of **19a** was added, and refluxed for 24 hr. The reaction was worked-up as for **8a·HCl**: mp 230–232° (EtOH–EtOAc). *Anal.* ($C_{17}H_{27}NO \cdot HCl$) C, H, N.

In a similar manner from 22.5 g (0.06 mole) of **19a**, 13.8 g (37%) of product was obtained.

1,2,3,4-Tetrahydro-6,7-dihydroxy-1,1,2,3,4,4-hexamethylisoquinoline·HBr (20b·HBr).—A soln of 5 g (0.018 mole) of **20a** in 120 ml of 48% HBr was refluxed for 6 hr and concd *in vacuo* at 35°, and the solid was crystd from EtOH–EtOAc: mp 264–266°; yield 5.2 g (86%). *Anal.* ($C_{15}H_{23}NO_2 \cdot HBr$) C, H, N.

3-(3,4-Dimethoxyphenyl)-2,3-dimethyl-2-butanol (21a). A.—To the Grignard reagent, prepd from 5.7 g (0.24 g-atom) of Mg turnings and 34.1 g (0.24 mole) of MeI in 200 ml of dry Et_2O, 8.9 g (0.04 mole) of **10a** dissolved in 200 ml of dry Et_2O was added and the mixt was refluxed and stirred for 48 hr. The cooled reaction mixt was decompd with 300 ml of 10% NH_4Cl soln, and the org layer was sepd and dried. The soln was passed through a column of neutral alumina, 10 × 1.875 cm, and the eluate was evapd to leave an oily residue: bp 129–130° (1 mm); colorless liquid; yield 7.8 g (82%); nmr showed ketone impurity. *Anal.* ($C_{14}H_{22}O_3$) C, H, N.

B. LiMe Method.—To 75 ml (0.17 mole) of 2.3 *M* soln of LiMe[17] in dry Et_2O, a soln of 28.1 g (0.127 mole) of **10a** dissolved in 250 ml of dry Et_2O was added at a rate to maintain a gentle reflux. It was stirred and refluxed for 17 hr. While cooling in an ice bath, 150 ml of H_2O was added carefully, and the Et_2O layer was sepd, washed, dried, and evapd to give an oil: bp 138–141° (1 mm); yield 26 g (86%). Ir shows absence of C=O absorption. *Anal.* ($C_{14}H_{22}O_3$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1,3,3,4,4-pentamethylisoquinoline·HCl (23a·HCl).—While cooling 9.3 g (0.227 mole) of MeCN at 10–20°, a soln of 30 ml of concd H_2SO_4 and 30 ml of AcOH was added, followed by 35.7 g (0.15 mole) of **21a**. The reaction mixt was heated at 75° for 2 hr, cooled, and poured onto chipped ice, made alk by the addn of an NaOH soln and extd with Et_2O. The dried ext was treated with $Et_2O \cdot HCl$ and 29 g (64%) of product was obtained: mp 199–201° (EtOH); ν_{max}^{KBr} multiple bands centered at 2600, 1950, 1648 cm⁻¹; $\lambda_{max}^{i\text{-PrOH}}$ 210 (10,400), 256 (19,800), 309 (9250), 362 mμ (8700); nmr (TFA) δ 7.29 (1 H, aromatic), 7.52 (1 H, aromatic), 4.10 (3 H, CH_3O), 4.15 (3 H, CH_3O), 2.88 (3 H, $CH_3C{=}N$), 1.43 (6 H, $2[CH_3]_2C$), 1.54 (6 H, $2[CH_3]_2C$. *Anal.* ($C_{16}H_{23}NO_2 \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,3,3,4,4-pentamethylisoquinoline·HCl (24a·HCl).—A soln of 3 g (0.01 mole) of **23a** was stirred in a soln of 50 ml of MeOH at room temp, 1.5 g (0.04 mole) of $NaBH_4$ was added within 15 min, and the mixt was stirred for an additional 1 hr. The reaction mixt was concd *in vacuo* at 25°, the residue was triturated with H_2O and extd with Et_2O. The dried ext was treated with $Et_2O \cdot HCl$ and the product was crystd from EtOH: mp 269–271°; yield 1.2 g (40%). *Anal.* ($C_{16}H_{25}NO_2 \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-1,2,3,3,4,4-hexamethyl-6,7-dimethoxyisoquinoline·HCl (25a·HCl). A.—A soln of 2.4 g (0.009 mole) of **24a** in 100 ml of MeOH was added to a soln of 1.0 g (0.012 mole) of 37% formalin in 100 ml of MeOH and reduced under 3.5 kg/cm² of H_2 in the presence of 1.0 g of 10% Pd/C at room temp. When the reaction was completed, the filtrate was concd *in vacuo* at 25°, and the reddish oil, suspended in 25 ml of H_2O, was made alk with a NaOH soln and extd with Et_2O. The dried ext was treated with $Et_2O \cdot HCl$ and the gummy ppt was cryst from EtOH–EtOAc; mp 189–191°; yield 1.5 g (54%).

B.—**23a** (4 g, 0.015 mole) dissolved in 250 ml of MeOH contg 1.8 g (0.018 mole) of 37% formalin was reduced under 3.5 kg/cm² of H_2 in the presence of 2 g of 10% Pd/C at room temp. Worked-up as above, 3.4 g (72%) of product was obtd: mp 190–191°; no depression on mmp with the compd obtained above. *Anal.* ($C_{17}H_{27}NO_2 \cdot HCl$) C, H, N.

3,4-Dihydro-6,7-dimethoxy-1,2,3,3,4,4-hexamethylisoquinolinium Iodide (26a).—A soln of 12 g (0.05 mole) of **23a** in 300 ml of dried Et_2O was treated with 20 ml of MeI and refluxed for 17 hr.

(17) Alfa Inorganics, Inc., Beverly, Mass.

The ppt quaternary salt was filtered; the filtrate was treated with an addnl 10 ml of MeI and refluxed for an addnl 24 hr, and the ppt was filtered. This treatment with MeI was carried out 3 times to give a total of 10.2 g (51%) of product: mp 194–195.5° (EtOH); ν_{max}^{KBr} 1625 cm^{-1} (C=N$^+$=); $\lambda_{max}^{i\text{-PrOH}}$ 217 (22,400), 247 (19,400), 310 (9200), 364 (9450); nmr (TFA) δ 7.25 (1 H, arom), 7.55 (1 H, arom), 4.15 (3 H, CH_3O), 4.18 (3 H, CH_3O), 3.78 (3 H, CH_3N^+), 3.02 (3 H, CH_3C=N), 1.43 (6 H, $[CH_3]_2C$), 1.55 (6 H, $[CH_3]_2C$). *Anal.* ($C_{16}H_{23}NO_2 \cdot CH_3I$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,1,2,3,3,4,4-heptamethylisoquinoline·HCl (27a·HCl).—To a Grignard reagent prepd from 24 g (1 g-atom) of Mg turnings, 700 ml of dry Et_2O, and 142 g (1 mole) of MeI in 1.4 l. of dry Et_2O 20.1 g (0.05 mole) of **26a** was added in 30 min. The mixt was then stirred and refluxed for 20 hr, cooled, poured into 900 ml of ice H_2O contg 90 g of NH_4Cl, and then made alk by the addn of NH_4OH. The product was extd with Et_2O and dried, and the Et_2O soln was treated with dry HCl to form the hydrochloride: yield 9.4 g (61%); mp 232–234° (EtOH–EtOAc). *Anal.* ($C_{18}H_{29}NO_2 \cdot HCl$) C, H, N.

1,2,3,4-Tetrahydro-6,7-dihydroxy-1,1,2,3,3,4,4-heptamethylisoquinoline·HBr (27b·HBr).—A soln of 3.6 g (0.012 mole) of **27a** in 30 ml of 48% HBr was refluxed for 6 hr, and concd *in vacuo* at 35° to dryness. The solid residue was crystd from EtOH–EtOAc: mp 248–250°; yield 3.4 g (80%). *Anal.* ($C_{16}H_{25}NO_2 \cdot HBr$) C, H, N.

Acknowledgment.—We gratefully acknowledge the cooperation of the following members of our Physical Chemistry Department headed by Dr. P. Bommer: Dr. T. Williams (nmr), Dr. V. Toome (uv), and Mr. M. S. Traiman (ir); Dr. F. Scheidl and his associates (microanalyses). The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories.

Central Nervous System Depressants. 9.[1] Benzodiazepine Sulfonamides

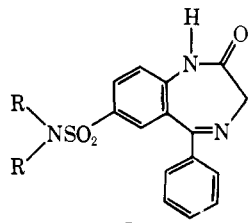
ROBERT BRUCE MOFFETT* AND ALLAN D. RUDZIK

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

Received September 12, 1970

Four 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones with a sulfonamide group in the 7 position (**3**, **6**, **16**, and **17**) and a number of intermediates and by-products are reported. Several of these have been found to be CNS depressants in animals.

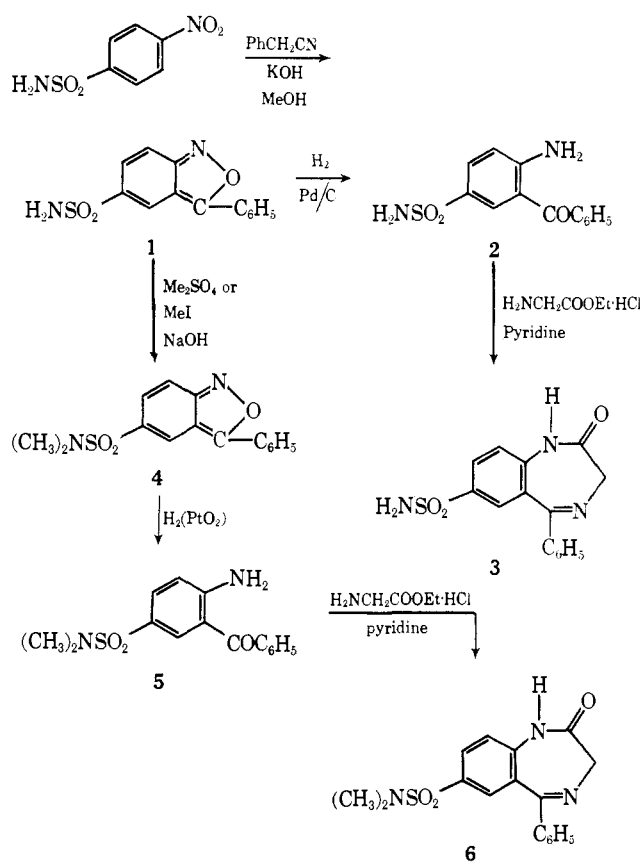
A large number of 1*H*-1,4-benzodiazepines have been prepared and their structure–activity relationships as CNS drugs have been extensively studied.[2] One conclusion from these studies was that an electron-withdrawing group in the 7 position was desirable.[3] Since sulfonamides are compatible with biological systems and are present in many drugs it was thought that compounds of type I might have desirable properties as CNS depressants.



I

Two compounds of this type (R = H, **3**; and R = CH_3, **6**) were prepared as outlined in Scheme I. The preparation of the substituted benzophenones (**2** and **5**) represents modification of the elegant method used by Davis and Pizzini,[4] and Walker[5] for other aminobenzophenones, and the condensations with glycine Et ester are similar to the general method of Sternbach, *et al.*[6] The anthranil **4** was also prepared directly by the condensation of *N*,*N*-dimethyl-*p*-nitrobenzenesulfonamide (**7**) with $PhCH_2CN$. Hydrogenation of anthranil **4** with Pd/C led to the corresponding *o*-aminobenzhydrol

SCHEME I



8 but with Adam's catalyst the desired aminobenzophenone **5** was obtained. Attempts to prepare **5** by selectively acetylating the amine of benzophenone **2** followed by methylation of the sulfonamide group led instead to mixtures from which four new acetylated and/or

(1) Paper 8 of this series: R. B. Moffett, *J. Med. Chem.*, **11**, 1251 (1968).

(2) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, Chapter 6.

(3) Reference 2, p 247.

(4) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **25**, 1884 (1960).

(5) G. N. Walker, *ibid.*, **27**, 1929 (1962).

(6) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).