*Anal.*[16] Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.27; N, 4.65.

**Methylation of II.**—Ten milligrams of II was dissolved in 10 ml. of warm ethanol, and ethereal diazomethane was added in slight excess. After about 10 min., the solution was evaporated completely, and the residue was treated with 2.5 ml. of 0.2% aqueous NaOH. The mixture was extracted four times with chloroform. The combined extracts were washed twice with small amounts of water, dried ($Na_2SO_4$), and evaporated *in vacuo*; the last traces of chloroform were removed by addition of ethanol and complete evaporation. Addition of a few drops of hexane and seeding with authentic IV produced crystals which melted at 158°, alone or mixed with IV.

**14-Hydroxydihydromorphine (V). A. By Reduction of 14-Hydroxydihydromorphinone (I).**—A suspension of 5 g. of sodium borohydride in 400 ml. of ethanol was added in one portion to a suspension of 5 g. of I in 100 ml. of ethanol, and the mixture was kept at room temperature for about 24 hr. A flocculent precipitate formed slowly during this time. Acetone (60 ml.) was added next in small portions with cooling, to destroy the excess borohydride; the acetone produced a white curdy precipitate. Regardless of this, the mixture was concentrated *in vacuo* to about one-third volume. A solution of 45 g. of NaOH in 450 ml. of water was added, and the resulting clear liquid was boiled briefly over a free flame, cooled, and acidified with dilute HCl. It was next adjusted to slight phenolphthalein alkalinity with aqueous ammonia, a small amount of sodium dithionite was added, and the liquid was extracted repeatedly with a 2:1 mixture of chloroform and ethanol. The combined extracts were dried over sodium sulfate and evaporated under reduced pressure to a small volume. After several days, most of V crystallized (m.p. 245–249°). An additional amount of less pure material was obtained on evaporation of the mother liquors; total yield, 70–90%. This crude base can be purified by recrystallization from a large volume of ethyl acetate; it crystallizes only slowly, however, and is purified more advantageously by way of the bitartrate, obtained by adding 5 g. of tartaric acid in 10 ml. of water to crude V (5 g.) in 240 ml. of ethanol. After seeding, the salt crystallized slowly. It was filtered after about 3 days, washed with acetone, and dried; yield, 5.4 g. A charcoal-treated solution of this in ten volumes of water, made slightly ammoniacal, gave about 3 g. of pure V, with additional material obtainable on extraction of the aqueous mother liquors with chloroform–ethanol (2:1). Evaporation of the mother and wash liquids of the bitartrate gave an additional amount of the salt, which could be purified by conversion to the base and reworking *via* the bitartrate. Pure V melts at 249–250° to a red liquid which decomposes to a voluminous dark mass a few degrees above its melting point. The mixture melting point with I (dec. 248–249°) is strongly depressed. The compound yields a colorless solution with aqueous alkali and gives no color with *m*-dinitrobenzene. Aqueous $FeCl_3$ produces a pure blue color. V forms a crystalline, water-insoluble reineckate.

*Anal.* Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.38; H, 7.26.

**B. By Demethylation of 14-Hydroxydihydrocodeine B.**—Concentrated aqueous HBr (35 ml.) was preheated to 100° in a flask equipped with reflux condenser and stirrer and treated with 3.5 g. of VI. The mixture was stirred at 110–115° for 20 min. The resulting brown solution was cooled, diluted with water, and made alkaline with excess aqueous NaOH. Extraction with chloroform removed a small amount of nonphenolic material. The aqueous phase was acidified with dilute HCl, treated with charcoal, filtered, and made slightly ammoniacal, with addition of a small amount of sodium dithionite. From this solution, V was obtained by solvent extraction and purification *via* the bitartrate as described above. However, the yield of crystalline bitartrate was rather low, and the base recovered from it melted at 244°. The mixture melting point with pure V was 249–250°.

**Methylation of V.**—A slight excess of ethereal diazomethane was added to 0.2 g. of pure V, dissolved in 10 ml. of ethanol, and the mixture was kept overnight at room temperature. Evaporation under reduced pressure yielded a colorless glass which soon crystallized; yield, 0.15 g. Recrystallization from hexane gave aggregates of fine needles of m.p. 142–144°, not changed by one more crystallization from hexane. The mixture melting point with an authentic sample of VI (m.p. 145–146°), furnished by the late Dr. L. F. Small, was 143–145° (lit.[12] 145–145.5°).

**Acknowledgment.**—The authors are much indebted to Dr. N. B. Eddy for permission to quote his findings on the pharmacology of these compounds.

(16) Microanalyses by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

## 1,2,3,4-Tetrahydroisoquinoline Derivatives with Antihypertensive Properties

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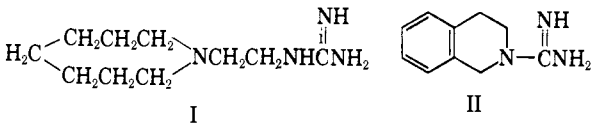
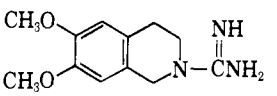
The discovery that [2-(octahydro-1-azocinyl)ethyl]-guanidine sulfate[1] (guanethidine) (I) is a clinically useful blood pressure lowering agent has stimulated the investigation of other guanidine derivatives for antihypertensive properties. Most of these newer guanidine derivatives[2] were synthesized in such a manner that they contain the characteristic structural elements of guanethidine, namely (a) a heterocyclic ring with one nitrogen, (b) an aliphatic side chain connected to this nitrogen atom, and (c) a terminal guanidine group.



I II



III

Our search for new antihypertensive guanidines was aimed at molecules of simpler structure. Among compounds of this type we found derivatives of 1,2,3,4-tetrahydroisoquinoline to be quite active. The simplest compound is 3,4-dihydro-2(1H)-isoquinolinecarboxamidine (II, Debrisoquin sulfate),[3] which is a potent antihypertensive in pharmacological tests.[4] It has also shown good clinical results with few undesirable side effects.[5]

The 6,7-dimethoxy derivative III is likewise a potent hypotensive agent. In doses of 1–4 mg./kg. it

(1) (a) R. P. Mull, U. S. Patent 2,928,829 (March 15, 1960); (b) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959); (c) R. P. Mull, M. Egbert, and M. R. Daporo, *J. Org. Chem.*, **25**, 1953 (1960); (d) R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. David, *J. Pharmacol. Exptl. Therap.*, **128**, 22 (1960).

(2) (a) R. P. Mull, U. S. Patent 3,030,378 (April 17, 1962); (b) R. P. Mull, U. S. Patent 3,036,083 (May 22, 1962); (c) R. P. Mull, U. S. Patent 3,055,883 (Sept. 25, 1962); (d) C. S. Scanley and F. H. Siegele, U. S. Patent 3,093,654 (June 11, 1963); (e) R. P. Mull, U. S. Patent 3,093,632 (June 11, 1963); (f) R. P. Mull, U. S. Patent 3,098,066 (July 16, 1963); (g) H. Wollweber, R. Hiltmann, H. Wilms, H. G. Kroneberg, and K. Stopel, Belgian Patent 611,886 (Dec. 22, 1960).

(3) Declinax®.

(4) R. A. Moe, H. M. Bates, Z. M. Palkowski, and R. Banziger, *Current Therap. Res.* **6**, 299 (1964).

(5) (a) E. D. Hurwitz, W. B. Abrams, and R. Pocelinko, *J. Newark Beth Israel Hospital*, **14**, 192 (1963); (b) N. Kakaviatos, F. A. Finnerty, Jr., V. Chupkovich, and J. Tuckman, *Circulation*, **28**, 746 (1963); (c) F. A. Finnerty, Jr., *Med. Clin. N. Am.*, **48**, 331 (1964).

produced a prolonged hypotensive effect both by oral and parenteral administration in dogs.

The chemistry of the new compounds is quite simple. The 1,2,3,4-tetrahydroisoquinoline bases are converted into the guanidines by standard methods for the syntheses of guanidines. The following procedures were used: (A) 1,2,3,4-tetrahydroisoquinoline + S-methylpseudothiourea sulfate, (B) 1,2,3,4-tetrahydroisoquinoline + S-ethylpseudothiourea hydrobromide, (C) 1,2,3,4-tetrahydroisoquinoline + O-methylpseudourea sulfate, (D) 1,2,3,4-tetrahydroisoquinoline + 3,5-dimethylpyrazole-1-carboxamidine, (E) 1,2,3,4-tetrahydroisoquinoline hydrochloride + cyanamide.

Since S-methylpseudothiourea sulfate is commercially available, method A is the most convenient procedure. 1,2,3,4-Tetrahydroisoquinoline and S-methylpseudothiourea sulfate in aqueous solution react rather easily even at room temperature. At slightly higher temperatures the reaction is finished in a few hours, and on cooling the sulfate of II crystallizes from the reaction mixture. In addition to the sulfate several other salts which are described in the Experimental section were made. The free base is very soluble in water and alcohol, but less soluble in other organic solvents.

The results of these investigations show that useful blood pressure lowering properties are not restricted to the almost exclusively explored compounds closely related to guanethidine, but may also be found in guanidine derivatives of different structure.

## Experimental

Melting points were determined by the capillary tube method using the Thomas-Hoover apparatus. The calibrated thermometer showed no need for correction when tested against standard compounds.

**3,4-Dihydro-2(1H)-isoquinolinecarboxamidine (II). A. Preparation of the Sulfate of IV with S-Methylpseudothiourea Sulfate.**—1,2,3,4-Tetrahydroisoquinoline (1000 g.) was stirred with 3000 ml. of water at 30–35°. To the homogeneous solution was added within a few minutes a solution of 1075 g. of S-methylpseudothiourea sulfate in 5000–6000 ml. of water. The mixture remained homogeneous and immediately started to evolve methyl mercaptan, which was absorbed in NaOH solution. The reaction mixture was stirred for about 30 min. and was then allowed to stand at room temperature. After a few hours crystals started to form, and at this point stirring was resumed to avoid formation of a solid crystalline cake. After 24 hr. the mixture was cooled with ice water, and the crystals were filtered and washed with 1000–2000 ml. of ice-cold water. The crude compound was recrystallized from water, using about 5 parts of water for 1 part of material. The hot solution was treated with activated carbon to remove the last traces of methyl mercaptan. On cooling the pure sulfate crystallized. It was filtered, washed with ice-cold water and dried. The yield was 900–950 g. (53.4–56.4%), m.p. 274–276°, which may vary within a few degrees in different batches, depending on crystal size.

*Anal.* Calcd. for $(C_{10}H_{12}N_2)_2 \cdot H_2SO_4$: C, 53.55; H, 6.29; N, 18.74. Found: C, 53.15; H, 6.04; N, 18.48.

**B. Preparation of II·Hydrobromide with S-Ethylpseudothiourea Hydrobromide.**—1,2,3,4-Tetrahydroisoquinoline (13 g.) and 17 g. of S-ethylpseudothiourea hydrobromide were dissolved in 500 ml. of water. The clear solution which formed on shaking was heated to 70–80° for 3 hr. The solution was then evaporated to dryness *in vacuo*, leaving a crystalline residue which was triturated with 200 ml. of acetone and filtered. The crude hydrobromide weighed 20–21 g. (80–84%). Recrystallization from about 100 ml. of water yielded pure 3,4-dihydro-2(1H)-isoquinolinecarboxamidine hydrobromide, m.p. 175–176°.

*Anal.* Calcd. for $C_{10}H_{12}N_2 \cdot HBr$: C, 46.89; H, 5.51; N, 16.40. Found: C, 47.71; H, 5.84; N, 16.50.

**C. Preparation of II Sulfate with O-Methylpseudouare Sulfate.**—1,2,3,4-Tetrahydroisoquinoline (13.5 g.) and 12 g. of O-methylpseudourea sulfate[6] were dissolved at room temperature in 100 ml. of water. After standing at about 25° for 24 hr., the solution was refluxed for 20 hr. On cooling with ice water for several hours, crystals separated which were filtered. The filtrate was evaporated to dryness, the residue was stirred up with alcohol, and the undissolved material was filtered. It was recrystallized from a small amount of water, to yield 4 g. (17.6%) of the pure sulfate, m.p. 274–275°.

*Anal.* Calcd. for $(C_{10}H_{12}N_2)_2 \cdot H_2SO_4$: C, 53.55; H, 6.29; N, 18.71. Found: C, 53.74; H, 6.14; N, 18.97.

**D. Preparation of the II Nitrate with 3,5-Dimethylpyrazole-1-carboxamidine Nitrate.**—1,2,3,4-Tetrahydroisoquinoline (13.3 g.) and 20 g. of 3,5-dimethylpyrazole-1-carboxamidine nitrate[7] were refluxed overnight in 200 ml. of absolute alcohol. The solvent was removed by distillation *in vacuo*, leaving a crystalline residue. On triturating with 60 ml. of alcohol at room temperature, part of the material dissolved. The mixture was filtered, and the crystals were washed with ice-cold alcohol. They were recrystallized from alcohol to yield 7 g. (29.4%) of pure 3,4-dihydro-2(1H)-isoquinolinecarboxamidine nitrate, m.p. 146–148°.

*Anal.* Calcd. for $C_{10}H_{12}N_2 \cdot HNO_3$: C, 50.42; H, 5.92; N, 23.52. Found: C, 50.72; H, 6.18; N, 23.29.

**E. Preparation of II·Hydrochloride from Cyanamide.**—1,2,3,4-Tetrahydroisoquinoline hydrochloride (8.5 g.) and 2 g. of cyanamide were suspended in 50 ml. of toluene. The mixture was stirred vigorously and heated to reflux temperature for 6 hr. It was then cooled to room temperature and allowed to stand for 15 hr. Crystals separated and were filtered by suction. They were recrystallized from 60 ml. of absolute alcohol, to yield 4.9 g. (47.3%) of pure 3,4-dihydro-2(1H)-isoquinolinecarboxamidine hydrochloride, m.p. 179–181°.

*Anal.* Calcd. for $C_{10}H_{12}N_2 \cdot HCl$: C, 56.73; H, 6.67; N, 19.87. Found: C, 56.96; H, 6.63; N, 19.63.

**F. Free Base of II.**—The sulfate (44.85 g., method A) was dissolved in 1000 ml. of water. To the solution, 18.94 g. of finely ground barium hydroxide was added. The mixture was shaken mechanically for 24 hr. The precipitated barium sulfate was filtered, and the clear filtrate was evaporated to dryness *in vacuo*. A colorless viscous oil remained, which, when kept for many days in an evacuated desiccator solidified slowly to a soft crystalline mass. The base absorbs $CO_2$ from the air. If freshly prepared samples are sealed in ampoules, the base crystallizes on standing. It melts, in the sealed ampoule at 60–63° without decomposition, and solidifies slowly again on cooling. Recrystallization of the free base from common solvents was not possible.

**G. Carbonate of II.**—The sulfate (2 g., method A) was dissolved in the minimum amount of water at room temperature. The solution was cooled with ice-water and an excess of 10% NaOH solution was added. The clear alkaline solution was extracted repeatedly with ether and the combined ether extracts were dried over potassium carbonate. The filtered solution was saturated with $CO_2$, causing 1 g. (47.3%) of 3,4-dihydro-2(1H)-isoquinolinecarboxamidine carbonate to crystallize. It was filtered off and dried, m.p. 136–138°.

*Anal.* Calcd. for $C_{10}H_{12}N_2 \cdot H_2CO_3$: C, 55.68; H, 6.37; N, 17.71. Found: C, 56.32; H, 6.60; N, 17.42.

**6,7-Dimethoxy-3,4-dihydro-2(1H)-isoquinolinecarboxamidine (III).**—1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline (39 g.) was dissolved in 200 ml. of methanol and a solution of 27.9 g. of S-methylpseudothiourea sulfate in 150 ml. of water was added. The mixture was kept at room temperature for 2 hr. and was then warmed on a steam bath for 2 hr. The solvents were distilled *in vacuo*, and the residue was slurried with alcohol and filtered. The undissolved material weighed 40 g. It was recrystallized first from methanol, then from 90% alcohol. In this manner, 23 g. (40.1%) of pure 6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinolinecarboxamidine sulfate, m.p. 261–262°, was obtained.

*Anal.* Calcd. for $(C_{12}H_{17}N_2O_2)_2 \cdot H_2SO_4$: C, 50.70; H, 6.38; N, 14.78. Found: C, 50.56; H, 6.61; N, 14.40.

**Acknowledgment.**—The author is indebted to Dr. A. Steyermark for the microanalyses.

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(7) J. Thiele and E. Dralle, *Ann.*, **302**, 275, 294 (1898).