A two-step method, reductive alkylation of benzylamine with 3-diethylamino-2,2-dimethylpropionaldehyde (I) and subsequent catalytic hydrogenolysis of the resultant distilled product II gave III in 70% over-all yield. Reductive amination of I furnished a lower yield of less pure product. In the latter procedure, a higher boiling component was obtained, which was at first assumed to be secondary amine. Its infrared spectrum, showing the presence of a C=N and absence of an NH band, indicated that it was an imine probably formed in the following manner.

$$\underset{\text{I}}{\text{RCHO}} + \text{NH}_3 \xrightarrow{-\text{H}_2\text{O}} \underset{\text{Ia}}{\text{RCH=NH}} \xrightarrow{\text{H}_2} \underset{\text{III}}{\text{RCH}_2\text{NH}_2}$$

$$\begin{matrix} \text{I} + \text{III} \\ \text{or} \\ \text{Ia} + \text{III} \end{matrix} \xrightarrow[-\text{NH}_3]{-\text{H}_2\text{O}} \underset{\text{IV}}{\text{RCH=NCH}_2\text{R}}$$

$$\text{R} = (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{C}(\text{CH}_3)_2$$

The structure of IV was confirmed by comparison with an authentic sample prepared by treating I with III. The infrared spectrum of the two products were identical. N.m.r. spectra showed each with a peak at 447 c.p.s., indicative of a proton attached to a double bonded carbon atom.[1] Each was reduced to the secondary amine (V).

Pharmacology.—Compound III, the primary amine, and the N-benzyl derivative II were tested in the antihypertensive program. Both were inactive in the cat eye test. The benzyl compound, when administered intravenously in the cat at 2 mg./kg., caused a biphasic effect. At higher doses, a fall of blood pressure was noted, but it was of short duration. Compounds IV and V were not tested.

Experimental[2]

N¹-Benzyl-N³,N³-diethyl-2,2-dimethylpropane-1,3-diamine (II).—A solution of 31.4 g. (0.2 mole) of 3-diethylamino-2,2-dimethylpropionaldehyde (I)[3] in 75 ml. of thiophene-free benzene was treated portionwise with 21.4 g. (0.2 mole) of benzylamine while keeping the temperature below 50°. When water separated, about 15 g. of anhydrous magnesium sulfate was added, and the mixture was allowed to stand for 1 hr. It was then filtered and the filter cake was washed with an additional 75 ml. of thiophene-free benzene. The solution was hydrogenated under 2 atm. of pressure in the presence of 4.0 g. of 5% platinum-on-carbon catalyst.[4] After uptake of hydrogen was complete (1–2 hr.), the solution was filtered from the catalyst. The catalyst was washed with additional solvent, and the filtrate and washings were concentrated under reduced pressure. The residue, on distillation, gave a fraction at 153–154° (5.8 mm.), n^{25}D 1.4945. It weighed 43.9 g. (90.3% yield).

Anal. Calcd. for $C_{16}H_{28}N_2$: C, 77.41; H, 11.29; N, 11.20. Found: C, 77.50; H, 11.57; N, 11.29.

N,N-Diethyl-2,2-dimethylpropane-1,3-diamine (III).—A solution of 62.0 g. (0.25 mole) of II in 150 ml. of ethyl alcohol was hydrogenated under 2 atm. pressure in the presence of 8.0 g. of 5% palladium on activated carbon.[4] Uptake of hydrogen was complete in less than 1 hr. The solution was filtered, the catalyst was washed with some solvent, and the combined filtrates were concentrated under reduced pressure. Fractionation of the residue gave III in 78.5% yield; it distilled at 67–70° (8 mm.), n^{25}D 1.4430. In other runs fractions were collected at 105° (57 mm.) and 112–116° (66 mm.). In every instance the amine absorbed carbon dioxide so rapidly that it was not possible to get good carbon values on analysis. However, it was readily converted to a dihydrochloride salt, m.p. 178–180° (cor.).

Anal. Calcd. for $C_9H_{24}Cl_2N_2$: C, 46.74; H, 10.46; Cl, 30.66; N, 12.11. Found: C, 46.92; H, 10.54; Cl, 30.23; N, 12.34.

Reductive Amination of I.—A solution of 27.3 g. (0.3 mole) of I in 75 ml. of ethyl alcohol was placed in a 270-ml. high-pressure rocker-type bomb along with 10 g. of Raney nickel catalyst. The vessel was cooled in an acetone–Dry Ice bath to about −25°, and 50 ml. of liquid ammonia was added. The reaction vessel was sealed and warmed to room temperature, and the mixture was hydrogenated under 100 atm. pressure until there was no further absorption (6–7 hr.). The contents of the bomb were filtered, the catalyst was washed, and the solvent then was removed by distillation. About 43% of III was collected at 105–110° (47 mm.), n^{25}D 1.4420, and at 114° (47 mm.), n^{25}D 1.4408. From the index of refraction it appeared that the first fraction might be satisfactory. However, dihydrochloride salts of each gave unsharp melting points, indicative of impurities. A much higher boiling fraction (IV) was also collected at 117–120° (0.8 mm.), n^{25}D 1.4513; λ_{max}^{film} 6.0 μ strong (C=N), no band for NH; yield, about 11%. Its n.m.r. spectrum showed the presence of CH=N by the peak at 447 c.p.s.

Anal. Calcd. for $C_{18}H_{39}N_3$: C, 72.66; H, 13.21; N, 14.21. Found: C, 72.44; H, 13.31; N, 14.43.

N¹,N¹,N⁹,N⁹-Tetraethyl-3,3,7,7-tetramethyl-1,5,9-triaza-4-nonene.—The following procedure yielded an authentic sample of IV. A solution of 15.7 g. (0.1 mole) of 3-diethylamino-2,2-dimethylpropionaldehyde in 50 ml. of thiophene-free benzene (analytical grade) and 15.8 g. (0.1 mole) of III in 50 ml. of the same solvent were mixed and allowed to stand for 30–45 min. When the separation of water appeared to be complete, the mixture was treated with a drying agent as in the preparation of II. The solution was divided in two portions. One was concentrated to dryness, and the residue was distilled under reduced pressure. Although much foaming occurred, a portion was collected at 134° (2.5 mm.), n^{25}D 1.4507. It was redistilled at 119–125° (1 mm.), n^{25}D 1.4511. N.m.r. and infrared spectra of the authentic sample and the previously mentioned product were identical. The second portion gave similar results.

1,1,9,9-Tetraethyl-3,3,7,7-tetramethyl-1,5,9-triazanonane (V).—A solution of 5.4 g. (0.84 mole) of IV in 100 ml. of ethyl alcohol was hydrogenated under 2 atm. of pressure in the presence of 0.1 g. of platinum oxide. No uptake beyond theory occurred (30 min.). The solution, after removal of the catalyst, was concentrated and the residue was fractionated. The fraction distilling at 130–135° (1.5–2.0 mm.), n^{25}D 1.4502, weighed 2.9 g. (53%). The infrared and n.m.r. spectra showed no unsaturation.

Anal. Calcd. for $C_{18}H_{41}N_3$: C, 72.17; H, 13.80; N, 14.02. Found: C, 71.96; H, 13.79; N, 14.13.

(1) The n.m.r. spectrum of IV will be the subject of an article submitted to another journal.

(2) Microanalyses were carried out by Mr. O. F. Kolsto and his associates; infrared examinations were conducted by Mr. A. Kammer and Mr. W. Washburn; n.m.r. spectra were run by Mr. R. Kriese of this laboratory on a Varian A60 spectrometer in carbon tetrachloride solution at 60 Mc./sec. with tetramethylsilane as internal standard.

(3) Available from Aldrich Chemical Co., Milwaukee, Wis.

(4) Purchased from Engelhard Industries, Newark, N. J.

Derivatives of Morphine. IV.[1] 14-Hydroxymorphine and 14-Hydroxydihydromorphine

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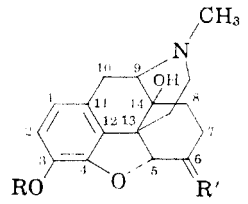
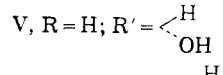
Introduction of a hydroxyl group into position 14 of the morphine skeleton often leads to compounds with improved pharmacological properties. The observation[2] that the intense analgesic action (~ ten times that

(1) Paper III: F. E. Stynler and U. Weiss, *J. Med. Chem.*, **7**, 105 (1964).

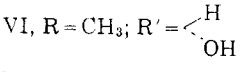
(2) N. B. Eddy, *J. Chronic Diseases*, **4**, 59 (1956).



I, R = H; R′ = O

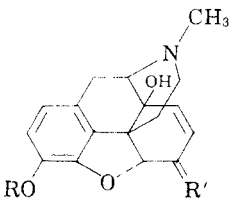


V, R = H; R′ = H, OH



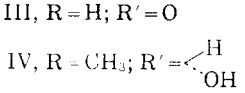
VI, R = CH_3; R′ = H, OH

VII, R = CH_3; R′ = O



II, R = H; R′ = H, OH

III, R = H; R′ = O



IV, R = CH_3; R′ = H, OH

of morphine) of 14-hydroxydihydromorphinone (I)[3] is not accompanied by the shortening of the effect usually observed with strongly acting analgesics may serve as an example.

While a fair number of 14-hydroxy derivatives of the morphine–codeine series have been prepared, the parent compound, 14-hydroxymorphine (II), has, so far, not been described; indeed, only two hydroxymorphines, 2-hydroxymorphine[4] and 10-hydroxymorphine,[5] are known. Preparation of II and of related substances thus seemed of interest. While it is well known[6] that compounds with a secondary hydroxy group in position 6 (*e.g.*, morphine itself) have a less powerful analgetic effect, on a weight basis, than related compounds lacking this group (*e.g.*, 6-keto or 6-deoxy compounds), the loss in potency to be expected for II compared to I or other analgesics devoid of this hydroxyl might be offset by other advantages.

Compound II was obtained by reduction of the corresponding ketone III[7] with sodium borohydride in ethanol. The resulting base dissolves in aqueous sodium hydroxide, giving a colorless solution, in contrast to the yellow color produced by III under these circumstances. In aqueous medium, II, like other morphine derivatives with a free phenolic hydroxyl at C-3 and intact oxygen bridge, gives a blue color with ferric chloride. The identity of II was established by methylation with diazomethane to the known[8] 14-hydroxycodeine (IV). Since IV has been shown[8a,b] to have the same configuration[9] at C-6 as morphine (hydroxyl in α-orientation), this reaction also demonstrates that II is 14-hydroxymorphine rather than its epimer, 14-hydroxy-α-isomorphine, and shows that the hydride reduction of an α,β-unsaturated ketone has, as usual in this series, given the epimer having the α-configuration at C-6 (*cf.*, *e.g.*, the exclusive formation of codeine on hydride reduction of codeinone[10] and 1-bromocodeinone[11] and of IV from 14-hydroxycodeinone).[8b]

(3) U. Weiss, *J. Am. Chem. Soc.*, **77**, 5891 (1955).

(4) H. Wieland and P. Kappelmeier, *Ann.*, **382**, 306 (1911).

(5) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, **77**, 6359 (1955).

(6) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

(7) U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).

(8) (a) L. J. Sargent, L. H. Schwartzman, and L. F. Small, *ibid.*, **23**, 1247 (1958); (b) A. C. Currie, J. Gillon, G. F. Newbold, and F. S. Spring, *J. Chem. Soc.*, 773 (1960); (c) U. Weiss, U. S. Patent 3,007,932 (1960); *Chem. Abstr.*, **56**, 4810*b* (1961).

(9) Further evidence for this configuration comes from a comparison of the n.m.r. spectrum of IV with spectra of codeine and isocodeine (T. J. Batterham and U. Weiss, unpublished). The spectrum of IV shows the expected analogies to that of codeine, but is quite different from that of isocodeine.

(10) M. Gates, *J. Am. Chem. Soc.*, **75**, 4340 (1953).

(11) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

Repeated attempts to prepare II by demethylation of IV with hydrobromic acid or pyridine hydrochloride were uniformly unsuccessful.

Borohydride reduction of I similarly yielded 14-hydroxydihydromorphine (V) as colorless crystals. The compound was also obtained by demethylation of its methyl ether, the 14-hydroxydihydrocodeine B (VI) of Lutz and Small,[12] but the samples obtained in this manner proved difficult to purify. Diazomethane reconverted V to VI; since the latter compound has been shown[8a,b] to have the codeine (α) configuration at C-6, V is the 6α-epimer. Hydride (or catalytic[12]) reduction of 14-hydroxydihydrocodeinone (VII), the methyl ether of I, has been shown[8b] to yield both VI and its 6-epimer 14-hydroxydihydrocodeine C (the latter, at least in the case of catalytic reduction, as a minor product only). The hydride reduction of I might thus have yielded some 14-hydroxydihydro-α-isomorphine, the as yet undescribed 6-epimer[13] of V. No indication for the presence of this compound was obtained; however, no systematic search for it has been made.

Pharmacology.—Pharmacological tests on II[14] in mice on subcutaneous administration showed an analgetic action of moderate strength (ED_{50} 2.9 mg./kg.) and average duration (167 min.).

In contrast, V exhibited[14,15] increased activity (ED_{50} 1.1 mg./kg.), about twice that of morphine, and, interestingly, of markedly prolonged duration (246 min.). Clinical tests led to similar observations, the effect on oral administration being particularly satisfactory.

Experimental

14-Hydroxymorphine (II).—A suspension of 3.8 g. of finely powdered III in about 100 ml. of ethanol was added in small portions during 45 min. to a solution of 8 g. of sodium borohydride in 240 ml. of ethanol. The yellow color shown by III in ethanolic solution[7] disappeared rapidly after every addition. The mixture was left overnight. Regardless of the presence of a white, flocculent precipitate, acetone was added next to decompose the excess borohydride, and the mixture was concentrated *in vacuo* to about half its volume. Sodium hydroxide (40 ml., 10%) was added, and the resulting clear, colorless solution was rapidly brought to boiling over a free flame, and kept boiling for a few minutes. After cooling, the liquid was acidified with aqueous HCl, treated with charcoal, and filtered. The filtrate was made weakly basic (light pink color on phenolphthalein paper) with dilute NH_4OH and was extracted repeatedly with a 2:1 mixture of chloroform and ethanol. A white crystalline precipitate which sometimes appeared during this operation did not interfere. It contained boron and apparently none of the desired base; it was not investigated further. The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was evaporated completely under reduced pressure, leaving a yellowish, microcrystalline precipitate (approximately 3.5 g.). Recrystallization from boiling ethanol gave pure II as colorless crystals which discolor above 200° and form a red mass at about 250°. 14-Hydroxymorphine (II) is relatively soluble in water, insoluble in chloroform, and slightly soluble in ethanol. It dissolves in benzyl alcohol, which can be used for isolation instead of the chloroform–ethanol mixture. It is not precipitated from aqueous, acidic solution by picric or perchloric acids. The reineckate is crystalline and water insoluble. The hydrochloride is precipitated in crystalline form from its aqueous solution by excess acetone.

(12) R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939).

(13) Pharmacological properties of this compound and of II and V, are listed by I. Seki, H. Taragi, and S. Kobayashi, *Yakugaku Zasshi*, **84**, 280 (1964).

(14) N. B. Eddy, personal communication.

(15) *Cf.* also Table I in ref. 8a.

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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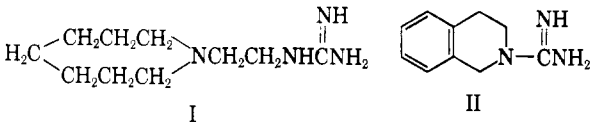
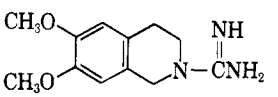
The discovery that [2-(octahydro-1-azocinyl)ethyl]-guanidine sulfate[1] (guanethidine) (I) is a clinically useful blood pressure lowering agent has stimulated the investigation of other guanidine derivatives for antihypertensive properties. Most of these newer guanidine derivatives[2] were synthesized 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).