

TABLE III
 5,5-DISUBSTITUTED HYDANTOIN-3-ACETAMIDE DERIVATIVES

R	R'	R''	M.P., °C.	Formula	Calcd. % N	Found % N
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	H	209-211	C ₁₁ H ₁₃ N ₃ O ₃	17.41	17.26
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	C ₆ H ₅	175-176.5	C ₁₇ H ₂₃ N ₃ O ₃	13.24	13.06
CH ₃	C ₆ H ₅	H	199.5-200	C ₁₂ H ₁₃ N ₃ O ₃	17.00	17.11
CH ₃	C ₆ H ₅	C ₆ H ₅	220.5-221.5 ^a	C ₁₈ H ₁₇ N ₃ O ₃	13.00	12.97
CH ₃	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	199.5-201	C ₁₉ H ₁₅ N ₃ O ₃	12.46	12.24
CH ₃	<i>p</i> -ClC ₆ H ₄	H	204-206	C ₁₂ H ₁₂ ClN ₃ O ₃	14.92	14.75
CH ₃	<i>p</i> -ClC ₆ H ₄	C ₆ H ₅	230-232	C ₁₇ H ₁₆ ClN ₃ O ₃	11.75	11.71
C ₂ H ₅	C ₆ H ₅	H	188	C ₁₃ H ₁₅ N ₃ O ₃	16.08	15.93
C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	180-181 ^b	C ₁₉ H ₁₉ N ₃ O ₃	12.46	12.46
<i>n</i> -C ₃ H ₇	C ₆ H ₅	H	192 ^c	C ₁₄ H ₁₇ N ₃ O ₃	15.26	15.28
C ₆ H ₅	C ₆ H ₅	H	248-250 ^c	C ₁₇ H ₁₅ N ₃ O ₃	13.59	13.55
C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	246-247	C ₂₃ H ₁₃ N ₃ O ₃	10.90	10.73
C ₆ H ₅	C ₆ H ₅	<i>p</i> -CH ₃ C ₆ H ₄	262.5-264	C ₂₄ H ₂₁ N ₃ O ₃	10.52	10.67
	-(CH ₂) ₁ -	H	202-203	C ₉ H ₁₀ N ₃ O ₃	19.90	19.71
	-(CH ₂) ₄ -	C ₆ H ₅	162.5-163	C ₁₃ H ₁₇ N ₃ O ₃	14.63	14.46
	-(CH ₂) ₅ -	H	208-209	C ₁₀ H ₁₂ N ₃ O ₃	18.66	18.38
	-(CH ₂) ₃ -	C ₆ H ₅	230-231	C ₁₄ H ₁₄ N ₃ O ₃	13.95	13.85
	-(CH ₂) ₂ -	<i>p</i> -CH ₃ C ₆ H ₄	259-260	C ₁₇ H ₂₁ N ₃ O ₃	13.33	13.32
		H	193-195 ^d	C ₁₁ H ₁₅ N ₃ O ₃	15.38	15.40
		C ₆ H ₅	224-225	C ₂₀ H ₁₉ N ₃ O ₃	12.03	11.92

^a Recrystallized from ethanol-acetone. ^b Recrystallized from aqueous acetic acid. ^c F. Sundberg (Table I, footnote *c*) reports m.p. 248-249°. ^d Recrystallized from acetone.

Experimental⁷

Ethyl 5,5-Disubstituted Hydantoin-3-acetates.—In a 500-ml. flask were placed 200 ml. of absolute ethanol and 2.3 g. (0.1 g.-atom) of sodium. After the sodium had dissolved, 0.1 mole of the 5,5-disubstituted hydantoin and 13.5 g. (0.11 mole) of ethyl chloroacetate were added. Alternately 18.4 g. (0.11 mole) of ethyl bromoacetate was used as the alkylating agent in several preparations. The mixture was refluxed for 24 hr., and the hot solution was filtered to remove the precipitated NaCl or NaBr. The volume of the solution was reduced to one-half or more by concentration *in vacuo*. Upon either cooling or the addition of ice, the product separated and was recrystallized.

5,5-Disubstituted Hydantoin-3-acetic Acids.—In a 500-ml. flask were placed 0.1 mole of the ethyl 5,5-disubstituted hydantoin-3-acetate and 200 ml. of absolute ethanol. To this solution was added 4 g. (0.1 mole) of NaOH dissolved in a minimum of water. The mixture was refluxed with stirring until saponification was completed, usually 1-4 hr. The sodium 5,5-disubstituted hydantoin-3-acetate began to precipitate out of solution shortly after refluxing was started. The sodium salt was filtered, washed with a small amount of absolute ethanol or petroleum ether, and dried. The salt was dissolved in a small amount of water, the solution was filtered, then acidified with dilute H₂SO₄. The acidified solution was thoroughly chilled, concentrated if necessary, and the 5,5-disubstituted hydantoin-3-acetic acid which crystallized out was purified by dissolution and reprecipitation from aqueous sodium bicarbonate, then recrystallized from aqueous ethanol.

Amide and Anilide Derivatives of 5,5-Disubstituted Hydantoin-3-acetic Acids.—A mixture of 0.1 mole of the 5,5-disubstituted hydantoin-3-acetic acid in benzene was refluxed with 47.6 g. (0.4 mole) of thionyl chloride for 1 hr. after solution had occurred.

One drop of pyridine was added as a catalyst. The excess thionyl chloride was removed by several flushes of benzene and concentration *in vacuo*. The substituted amides and anilides were prepared by carefully adding ammonium hydroxide or aniline to the chilled benzene solution of the acid chloride until the solution was basic to litmus. After refluxing for 3 hr., the benzene solvent was exchanged for acetone by flushing with acetone and concentrating *in vacuo*. Upon dilution with water the product was obtained and recrystallized from water, ethanol, or aqueous ethanol.

Acknowledgment.—The authors wish to thank the Board of Directors of the American Chemical Society and the Petroleum Research Fund Advisory Board for a grant-in-aid in support of this work. We wish also to thank James Renn, George VanDine, Ann Schwartz, Sally DeLong, Thelma Titus, Harriet Parker, Richard Neumann, Jules Brandes, John Reed, Dorothy King, and the Merck Sharp and Dohme Research Laboratories for their contributions to this study.

N,N-Diethyl-2,2-dimethylpropane-1,3-diamine

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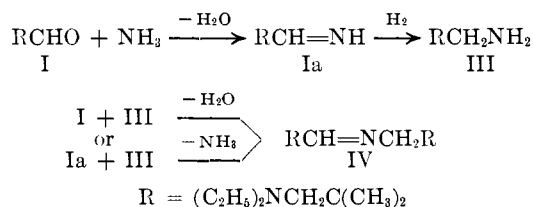
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Received September 24, 1964

A need in this laboratory for pure N,N-diethyl-2,2-dimethylpropane-1,3-diamine (III) as an intermediate in an antihypertensive program led to a comparison of two methods of preparation.

(7) Infrared spectrograms were obtained on the Perkin-Elmer 137B Infracord with sodium chloride plates and Nujol mull and on the Beckman IR4 with potassium bromide wafers. These spectrograms appear in the Sadler Standard Spectra Catalog, No. 22606-22650. Melting points were determined either in a liquid bath or in a Mel-Temp apparatus and are corrected. Nitrogen analyses are by the semimicro Kjeldahl method.

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.



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 anti-hypertensive 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.

Experimental²

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*_D²⁰ 1.4945. It weighed 43.9 g. (90.3% yield).

Anal. Calcd. for C₁₆H₂₈N₂: 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.),

(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.

*n*_D²⁰ 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 C₆H₂₄Cl₂N₂: 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*_D²⁰ 1.4420, and at 114° (47 mm.), *n*_D²⁰ 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*_D²⁰ 1.4513; $\lambda_{\text{max}}^{\text{min}}$ 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 C₁₈H₃₀N₂: 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-triazan-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*_D²⁰ 1.4507. It was redistilled at 119–125° (1 mm.), *n*_D²⁰ 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*_D²⁰ 1.4502, weighed 2.9 g. (53%). The infrared and n.m.r. spectra showed no unsaturation.

Anal. Calcd. for C₁₈H₄₁N₃: C, 72.17; H, 13.80; N, 14.02. Found: C, 71.96; H, 13.79; N, 14.13.

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

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Received September 10, 1964

Introduction of a hydroxyl group into position 14 of the morphine skeleton often leads to compounds with improved pharmacological properties. The observation² 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).