(0.0403 mole), dissolved in 8 ml. of water. The reaction was stirred for 5.5 hr. at room temperature, allowed to stand overnight and then stirred for an additional 5 hr. with a current of air blowing over the surface of the liquid to remove methyl mercaptan and ammonia. The reaction mixture was filtered, the precipitate washed with absolute ethanol and all the filtrates combined and treated with picric acid. The reaction precipitate was dissolved in warm water (60°) and successive fractions of crystals collected by slow evaporation of the water. A total of 3.27 g. (51.8%) of material was recovered. After recrystallizing twice from water, the product, the dinitrate salt of compound IX, melted at 196–198° dec.

Anal. Calcd. for $C_7H_{20}O_8N_8$: C, 24.41; H, 5.86; N, 32.55. Found: C, 24.59; H, 5.98; N, 32.33.

The dipicrate was prepared from the nitrate salt and after crystallization from methanol melted at 257–259° dec.

Anal. Calcd. for $C_{19}H_{24}O_{16}N_{12}$: C, 33.74; H, 3.58; N, 24.85. Found: C, 33.81; H, 3.68; N, 24.85.

The picrates from the filtrate could not be separated. Conversion to the nitrate salts and extraction with acetone gave a small amount of the nitrate salt of the starting material, 2-methyl-2-thiopseudourea (XI).

Reaction of the Nitrate Salt of 2-Methyl-2-thiopseudourea with an Excess of 1,3-Diamino-2,2-bis-(hydroxymethyl)-propane.—To the diamine (2.951 g., 0.022 mole) dissolved in 2 ml. of water was added 3.719 g. (0.0275 mole) of the thiopseudourea salt in 2 ml. of water. The mixture was stirred for 5.5 hr., absolute ethanol added and the insoluble material removed and washed with absolute ethanol. This product was crystallized from water, and its properties indicated that it was the dinitrate salt of compound IX (13% yield).

The filtrate was heated with picric acid, and the picrates were collected and converted to the nitrate salts. Fractional crystallization from ethanol gave 1.43 g. (21.4%) of product X which melted at 128–129°.

Anal. Calcd. for $C_6H_{18}O_8N_6$: C, 23.84; H, 6.00; N, 27.80. Found: C, 24.50; H, 5.63; N, 27.49.

The dipicrate was prepared from the purified nitrate and after crystallization from methanol melted at 209.5–211.5° dec.

Anal. Calcd. for $C_{18}H_{12}O_{16}N_{10}$: C, 34.20; H, 3.51; N, 22.10. Found: C, 34.18; H, 3.42; N, 21.93.

It was found that 1-amino-2-guanidino-2,2-bis-(hydroxymethyl)-propane (X) could be cyclized to VI by the following procedure. The salt (0.365 g.) was converted to the free base with sodium ethoxide, dissolved in methanol and refluxed for 1.2 hr. The product was neutralized with dilute nitric acid and concentrated in a current of air. Absolute ethanol was then added and 0.163 g. of sodium nitrate removed. The filtrate was treated with picric acid and the picrate removed. After crystallization from water the product weighed 0.093 g. (20%) and melted at 179–180°. A mixed melting point with an authentic sample of the picrate of VI was not depressed.

2-Nitrimino-5,5-bis-(nitroxymethyl)-1,3-diazacyclohexane (VIII).—The nitrate salt of the imino compound VI (0.7 g., 0.0032 mole) was added to a nitration mixture consisting of 1.29 g. of 99% nitric acid and 2 ml. of 98% sulfuric acid at −15°. The mixture was kept below 10° for 12 minutes and then allowed to warm and stand at room temperature (21°) for 1.7 hr. It was then poured over 30 g. of crushed ice and the precipitate collected on a medium sintered-glass funnel. The product VIII (0.61 g., 65.9%) after crystallization from ethanol melted at 214–215° dec.

The nitrimino compound IV (0.465 g., 0.0023 mole) was added to 5 g. of 99% nitric acid at −10°. The solution was held at 10–15° for 30 minutes, poured over 30 g. of crushed ice, filtered and the precipitate washed with cold water. The product VIII (0.601 g., 89%) after crystallization from water melted at 214–215° dec.

Anal. Calcd. for $C_6H_{10}O_8N_6$: C, 24.49; H, 3.43; N, 28.57. Found: C, 24.56; H, 3.28; N, 28.63.

1,3-Bis-(nitroguanidino)-2,2-bis-(nitroxymethyl)-propane (VII).—The dinitrate salt of IX (1.008 g., 0.0029 mole) was nitrated by the procedure used to produce the nitrate salt of VI except that the holding time at room temperature was increased to 2.7 hr. The product VII (0.613 g., 53%) after crystallization from water melted at 158.5–160° dec.

The nitroguanidino compound III (0.39 g., 0.00129 mole) was nitrated in 4 ml. of 99% nitric acid using the same procedure as for the cyclic nitrimino compound IV. The product VII weighed 0.4393 g. (85.5%) and melted at 158–160° dec.

Anal. Calcd. for $C_7H_{14}O_{10}N_{10}$: C, 21.11; H, 3.54; N, 35.17. Found: C, 21.37; H, 3.66; N, 34.82.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

2,2-Disubstituted-1,3-propanediamines and Related Diurethans, Diureides and Hexahydropyrimidin-2-ones

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2,2-Disubstituted-1,3-propanediamines have been prepared and converted to diurethans, diureides and hexahydropyrimidin-2-ones. A practical synthesis of 5-alkyl-5-phenylhexahydropyrimidin-2-ones has been the major achievement. As a cyclization reagent diphenyl carbonate was superior to diethyl carbonate.

Since the replacement of carbonyl by methylene at position 2 in 5-ethyl-5-phenylbarbituric acid gave a compound[1] which still possessed anticonvulsant properties, it seemed of interest to prepare analogs with methylene groups at positions 4 and 6 in the ring. Our experimental work was practically complete when there appeared a paper[2] describing the preparation of one of these compounds (Table III) by reduction of the corresponding barbituric acid derivative.

Our syntheses depend upon the preparation of the 2,2-disubstituted-1,3-propanediamines. The method involving the condensation of ketones[3] with nitromethane generally gave poor yields when both radicals were larger than ethyl. In the case of propiophenone none of the intermediate dinitro compound was obtained.

The 2-alkyl-2-phenyl-1,3-propanediamines were therefore prepared from phenylcyanoacetamide[4] which was alkylated[5] and then reduced to the di-

(1) W. R. Boone, H. C. Carrington and C. H. Vasey, *C. A.*, **46**, 6162*a* (1952).

(2) F. J. Marshall, THIS JOURNAL, **78**, 3696 (1956).

(3) (a) H. B. Hass and J. F. Bourland, U. S. Patent 2,343,256 (1944); (b) M. S. Larrison and H. B. Hass, U. S. Patent, 2,383,603 (1945).

(4) J. C. Hessler, *Am. Chem. J.*, **32**, 120 (1904).

(5) T. J. Thompson, H. L. Bedell and G. M. Buffet, THIS JOURNAL, **47**, 875 (1925).

amine. The use of lithium aluminum hydride gave incomplete reduction, partial cleavage to 2-phenylbutylamine and a poor yield of the diamine when tested in the case of ethylphenylcyanoacetamide. The 2-phenylbutylamine was identical with that from 2-phenylbutyronitrile. Equimolar quantities of aluminum chloride[6] and the hydride afforded a good yield of the diamine and almost completely eliminated cleavage to the monoamine. The yields of VII, VIII, IX and X (Table I) all refer to this improved procedure.

TABLE I

2,2-DISUBSTITUTED-1,3-PROPANEDIAMINES, $RR'C(CH_2NH_2)_2$

	R	R'	B.p. °C.	Mm.	n^tD	t, °C.	d^t_4	t, °C.	Nitrogen, % Calcd.	Found	Yield, %
II	CH_3	i-C_4H_9	90–92	13	1.4626	20	0.8664	27	19.4	18.9	51
III	CH_3	n-C_5H_{11}	120–121.5	24	1.4621	20	.8573	30.2	17.7	17.9	39
IV	C_2H_5	C_2H_5	88–89	16	1.4651	25	.8851	22	21.5	21.9	77
V	C_2H_5	n-C_4H_9	123–125	31	1.4662	20.1	.8711	26.2	17.7	17.6	15
VI	i-C_4H_9	i-C_4H_9	130–132	20	1.4642	20	.8671	20	15.0	15.7	43
VII	CH_3	C_6H_5	108–109	0.75	1.5535	20	1.0247	20	17.06	16.94	80
VIII	C_2H_5	C_6H_5	113–114	0.65	1.5469	25	1.0132	25	15.72	15.71	74
IX	n-C_3H_7	C_6H_5	120.5–121	0.65	1.5412	20	0.9984	20	14.57	14.47	64
X	i-C_3H_7	C_6H_5	122.5–123	0.65	1.5487	20	1.0135	20	14.57	14.48	68

2,2-Dimethyl-1,3-propanediamine (I) when refluxed 4 days with 5 moles of diethyl carbonate until the theoretical amount of alcohol had distilled gave almost twice as many moles of diurethan XI as the hexahydropyrimidin-2-one XX (Table II). The identical diurethan prepared from ethyl chloroformate, when heated at 240–245°, gave diethyl carbonate and XX. In contrast to the action of diethyl carbonate on the diamine, diphenyl carbonate gave good yields of the hexahydropyrimidin-2-one (Table III) in 8 hr. XI was also converted to the diamine I by acid hydrolysis. The diureide XVI was thermally decomposed to the hexahydropyrimidin-2-one XXVIII. Finally, the hexahydropyrimidin-2-one XX was hydrolyzed to I by refluxing with sulfuric acid.

TABLE II

DIURETHANS AND DIUREIDES, $RR'C(CH_2NHCOZ)_2$

No.	Z	R	R'	M.p., °C.	Nitrogen, % Calcd.	Found	Yield, %
XI	OEt	CH_3	CH_3	62–64[a]	11.37	11.41[b]	87
XII	OEt	CH_3	C_6H_5	68–70	9.09	9.10	90
XIII	OEt	C_2H_5	C_6H_5	90–91	8.69	8.72	89
XIV	OEt	n-C_3H_7	C_6H_5	86–87	8.33	8.36	95
XV	OEt	i-C_3H_7	C_6H_5	99–100	8.33	8.36[c]	88
XVI	NH_2	CH_3	C_6H_5	204–205	22.39	22.30	84
XVII	NH_2	C_2H_5	C_6H_5	188–189	21.20	21.23	81
XVIII	NH_2	n-C_3H_7	C_6H_5	194–195	20.13	20.12	80
XIX	NH_2	i-C_3H_7	C_6H_5	112–113	18.91[d]	18.93	85

[a] B.p. 138–141° (0.65 mm.). [b] Calcd. for $C_{11}H_{22}N_2O_4$: C, 53.6; H, 9.0. Found: C, 53.8; H, 9.1. [c] Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.3; H, 8.4. Found: C, 64.8; H, 8.3. [d] Calcd. as monohydrate for $C_{14}H_{24}N_4O_3$: C, 56.73; H, 8.16. Found: C, 56.91; H, 7.91.

Preliminary pharmacological tests[7] indicate that the diurethans and hexahydropyrimidin-2-ones possess hypnotic and anticonvulsant activity while the diureides have little or no activity.

Experimental

2,2-Dialkyl-1,3-dinitropropanes.—These compounds were prepared by condensation of nitromethane[3] with the corresponding ketone. 2,2-Diisobutyl-1,3-dinitropropane is new. Diisobutyl ketone (427 g.), diethylamine (880 g.), nitromethane (735 g.) and Drierite (200 g.), allowed to react one week at ice temperature, gave 86.5 g. (11.7%) of the desired product, b.p. 153° (3.4 mm.).

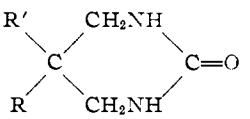
Anal. Calcd. for $C_{11}H_{22}O_4N_2$: N, 11.34. Found: N, 11.24.

Reduction of 2,2-Dialkyl-1,3-dinitropropanes to Diamines.—2,2-Diethyl-1,3-dinitropropane (0.20 mole) in 100 cc. of alcohol with 15 g. of Raney nickel[8] at an initial pressure of 1000 p.s.i. of hydrogen was allowed to react in a rocking bomb at 50–65° until there was no further drop in pressure (2 hr.). In addition to the desired product (20 g., 77%), diethylmalonamide (1.5 g., m.p. 219–219.5°) and low boiling cleavage products were formed.

The remaining dialkyldinitropropanes were reduced to II, III, V and VI, respectively, by iron and hydrochloric acid. The reduction procedure of Senkus[9] was followed except that alcohol was added to the reaction mixture to aid in the separation of the diamine from the voluminous precipitate of iron hydroxide. Thus the reaction mixture from 20.4 g. (0.100 mole) of 2-isobutyl-2-methyl-1,3-dinitropropane, 44.8 g. (0.800 mole) of iron turnings, 21 cc. of hydrochloric acid (sp. gr. 1.19), 100 cc. of water and 150 cc. of alcohol required 20 g. of sodium hydroxide to cause separation of the iron hydroxide so that the clear supernatant liquid could be decanted. The iron hydroxide was washed by decantation with small portions of alcohol. Sodium hydroxide was dissolved in the combined decantate and washings until two layers separated. The upper alcohol layer was removed and the lower aqueous layer was extracted with three 30-cc. portions of alcohol. The com-

TABLE III

5,5-DISUBSTITUTED HEXAHYDROPYRIMIDINE-2-ONES



No.	R	R'	M.p., °C.	Nitrogen, % Calcd.	Found	Yield, %
XX	CH_3	CH_3	255–257	21.9	21.8	89
XXI	CH_3	C_2H_5	221–222	19.7	19.4	87
XXII	CH_3	i-C_4H_9	191–192	16.5	16.7	77
XXIII	CH_3	n-C_5H_{11}	200–202	15.2	14.9	86
XXIV	C_2H_5	C_2H_5	224–225	17.9	17.5	88
XXV	C_2H_5	n-C_4H_9	147–148	15.2	15.0	63
XXVI	n-C_3H_7	n-C_3H_7	147–148	15.2	15.2	58
XXVII	i-C_4H_9	i-C_4H_9	157–158	13.2	13.3	59
XXVIII	CH_3	C_6H_5	217–219	14.73	14.77	78
XXIX	C_2H_5	C_6H_5	198–200[a]	13.72	13.74	82
XXX	n-C_3H_7	C_6H_5	171–173	12.83	12.82	55
XXXI	i-C_3H_7	C_6H_5	240–241	12.83	12.88	80

[a] This compound (m.p. 195–197°) has been made by the reduction of phenobarbital and was reported after our product had been prepared; ref. 2.

(6) R. F. Nystrom, THIS JOURNAL, **77**, 2544 (1955).

(7) By Merck, Sharp and Dohme, West Point, Pennsylvania.

(8) (a) L. W. Covert and H. Adkins, THIS JOURNAL, **54**, 4116 (1932); (b) M. Senkus, U. S. Patent 2,418,237 (1947).

(9) M. Senkus, *Ind. Eng. Chem.*, **40**, 506 (1948).

bined alcohol layer and extracts were dried over sodium sulfate. The alcohol was distilled and enough water was added to dissolve the residual sodium hydroxide. The supernatant liquid was removed and the water layer was extracted with four 20-cc. portions of ether. The combined liquid and extract were dried over sodium sulfate. II was obtained by distillation (Table I).

2-Alkyl-2-phenylcyanoacetamides.—Phenylcyanoacetamide was prepared by the action of aqua ammonia on phenylcyanoacetic ester[4] in yields of 75–80%. This was alkylated according to the method of Thompson, *et al.*[5] The methyl derivative does not appear to have been reported. In this case the temperature of the reaction mixture was lowered to 50° before the methyl iodide was added; yield 70%, m.p. 113–114°.

Anal. Calcd. for $C_{10}H_{10}ON_2$: N, 16.08. Found: N, 15.82.

2-Alkyl-2-phenyl-1,3-propanediamines.—To a well-stirred mixture of 20.0 g. (0.528 mole) of lithium aluminum hydride and 150 cc. of absolute ether was added rapidly through the dropping funnel a solution of 70.5 g. (0.528 mole) of aluminum chloride[6] in 350 cc. of ether. Five minutes later a solution of 0.100 mole of the 2-alkyl-2-phenylcyanoacetamide in 150 cc. of absolute ether and 60 cc. of anhydrous tetrahydrous tetrahydrofuran was added dropwise to the stirred refluxing mixture. Refluxing was continued 18–24 hr. during which the color changed from light tan to dark gray.

The excess hydride was decomposed by the dropwise addition of 20 cc. of water to the cooled mixture. After careful addition of 700 cc. of 6 *N* hydrochloric acid and 500 cc. of water, the mixture was allowed to stand overnight. The ether layer was separated and the aqueous layer was extracted with four 100-cc. portions of ether. Potassium tartrate (380 g.) was dissolved in the aqueous layer and sodium hydroxide (scales) was carefully added until no solid remained. The alkaline solution was extracted with six 200-cc. portions of ether. The extract was dried over sodium sulfate and distilled (Table I). The amount of monoamine produced under these conditions was negligible in all cases.

Reduction to a Monoamine with $LiAlH_4$.—A mixture of 20 g. (0.528 mole) of the hydride and 300 cc. of dry ether (or tetrahydrofuran) was refluxed for 6 hr. To this was added dropwise a solution of 18.8 g. (0.100 mole) of 2-ethyl-2-phenylcyanoacetamide in 100 cc. of tetrahydrofuran. The mixture was refluxed 14 hr. and after cooling was decomposed with 20 cc. of water followed by 430 cc. of 9 *N* hydrochloric acid. Most of the solvent was distilled and the aqueous layer was extracted with ether. The aqueous layer was treated carefully with 300 g. of sodium hydroxide and then extracted with six 100-cc. portions of ether. The ether extract was dried over sodium sulfate and distilled: (1) b.p. 108–112° (20 mm.), 2.6 g. (18%); (2) b.p. 159–163° (20 mm.), 3.7 g. (21%). The combined products from three preparations were redistilled. Fraction 1: b.p. 109–109.5° (20 mm.)[10]; $n^{25}D$ 1.5162, d^{25} 0.9317. Calcd. for $C_{10}H_{15}N$: *MR*, 48.21; neut. equiv., 149. Found: *MR*, 48.39; neut. equiv., 151.

The hydrochloride was precipitated from a dry ether solution of the monoamine, m.p. 168–169° (lit.[10] 156°). An authentic sample of 2-phenylbutylamine (b.p. 108–110° (20 mm.), $n^{25}D$ 1.5163) prepared by reduction of 2-phenylbutyronitrile with $AlCl_3$ and $LiAlH_4$ (see above) gave a hydrochloride which, after crystallization from ligroin (b.p. 90°) containing enough alcohol to dissolve it at the boiling point, had m.p. and mixed m.p. 168–169°.

Anal. Calcd. for $C_{10}H_{16}NCl$: Cl, 19.09. Found: Cl, 19.10.

Redistilled fraction 2 had b.p. 162–164° (18 mm.). *Anal.* Calcd. for $C_{11}H_{14}(NH_2)_2$: neut. equiv., 89. Found: neut. equiv., 95.

Reaction of Diethyl Carbonate with 2,2-Dimethyl-1,3-propanediamine (I).—A mixture of 20.4 g. (0.200 mole) of I and 118 g. (1.00 mole) of diethyl carbonate was refluxed four days in a flask fitted with a small condenser (protected from air by Ascarite) and a small fractionating column. From time to time the alcohol from the reaction was distilled while the condenser was closed; yield of alcohol 17.7 g. (96%). The solid in the cooled residue was filtered with suction. One crystallization from alcohol gave XX, m.p. 255–257°, soluble in hot water and insoluble in ether. The filtrate was distilled to give 19.9 g. (41%) of the diurethan XI, b.p. 138–141° (0.6–0.7 mm.). The product crystallized on standing and was purified by crystallization from ligroin, m.p. 62–64°, identical with XI from the action of ethyl chloroformate on the diamine.

A mixture of 1.6 g. of XI, 6.6 g. of hydrochloric acid (37%) and 1.6 g. of glacial acetic acid was refluxed two days to yield 1.0 g. of the dihydrochloride[11] which had m.p. 256–257° (from alcohol). The m.p. of this salt varies greatly with the rate of heating. It was identical with an authentic sample prepared from the diamine.

Preparation of the Diurethans.—In a typical adaptation of a well known procedure,[12] 5.1 g. (0.050 mole) of I and 10.9 g. (0.100 mole) of ethyl chloroformate gave 10.7 g. (87%) of product which crystallized from ligroin to yield pure XI.

Conversion of the Diurethan to the Hexahydropyrimidin-2-one.—XI (2.5 g., 0.10 mole) was heated 1 hr. at 240–245° and 1 hr. at 265–275° during which 0.90 g. (76%) of diethyl carbonate (b.p. 124–126°) distilled. The cooled solid residue, after washing with ether, weighed 0.70 g. (55%). Crystallization from alcohol gave XX, m.p. 255–257°, identical with that obtained from the action of diethyl carbonate on I.

2-Alkyl-2-phenyl-1,3-propanediureides.—In a typical experiment 6.6 g. (0.040 mole) of VII was dissolved in 13 cc. of water and 6.6 cc. (0.080 mole) of hydrochloric acid (sp. gr. 1.19). To this solution was added rapidly with stirring a solution of 6.8 g. (0.084 mole) of potassium cyanate in 12 cc. of water. The mixture was heated on the steam-bath for 15 min. (5 for the isopropyl derivative) with occasional stirring. After standing at room temperature the mixture was cooled in ice. The crystalline XVI was filtered, crystallized from hot water and dried *in vacuo*.

Conversion of the Diureide to the Hexahydropyrimidin-2-one.—XVI (1.0 g.) was heated 30 min. at 210–215° and then 15 min. at 255–260°. The cooled material was dissolved in hot alcohol and filtered from a small amount of insoluble matter. The filtrate was evaporated to a small volume, mixed with two volumes of hot water and cooled. The crystals were recrystallized twice from 2:1 water-alcohol; yield of XXVIII, 0.32 g. (42%), m.p. 217–219°, identical with the product from the diamine (mixed m.p.).

Preparation of 5,5-Disubstituted Hexahydropyrimidin-2-ones.—In a typical case 13.5 g. (0.063 mole) of diphenyl carbonate was mixed portionwise with 9.8 g. (0.060 mole) of VII. The mixture was then heated in a bath at 160–170° for 8 hr. in an apparatus protected by a tube filled with Ascarite. After distillation of the phenol under diminished pressure, the cooled residue was triturated with ether. The crystalline material was filtered and crystallized from a 2:1 mixture of alcohol and water to give XXVIII (Table III).

Hydrolysis of 5,5-Dimethylhexylhydropyrimidin-2-one (XX).—XX (2.6 g., 0.020 mole) was refluxed in 20 cc. of sulfuric acid (40%) with the addition of 2.2-cc. portions of sulfuric acid (sp. gr. 1.84) at intervals until carbon dioxide was detected at the outlet. The resulting 60% solution was refluxed for 4 days. The deliquescent salt of the diamine was precipitated by 14 volumes of acetone. The solution of the salt in 40 cc. of water was treated with an excess of sodium hydroxide and extracted with six 10-cc. portions of ether. The organic base was identified as I by conversion to the diurethan XI (yield 53%, m.p. and mixed m.p. 62–64°).

NEWARK, DELAWARE

(10) Lit. 110° (13 mm.); P. Rampart and P. Amagat, *Ann. chim.*, **8**, 263 (1927).

(11) J. Rockett and F. C. Whitmore, THIS JOURNAL, **71**, 3249 (1949).

(12) W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 278.