ml. of absolute ethanol, at 44 lb. pressure of hydrogen. The theoretical drop in pressure, 1.4 lb., occurred within 15 minutes. The alcohol solution was filtered and diluted with 200 ml. of anhydrous ether, and stored in a refrigerator. The brown crystals which formed were recrystallized from ethanol–ether mixture to yield 1.3 g. (72%) of tan crystals, melting at 159.5–161° (cor.). Further recrystallizations did not lighten the color or improve the melting point.

Anal. Calcd. for $C_{12}H_{21}O_2N_2SCl$: N, 9.57. Found: N, 9.59.

The free base was quite unstable to heat, and could not be purified.

BLOOMINGTON, INDIANA RECEIVED JANUARY 24, 1951

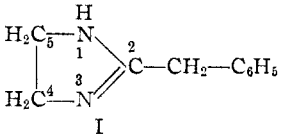
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

2,5,5-Trialkyl-1,4,5,6-tetrahydropyrimidines

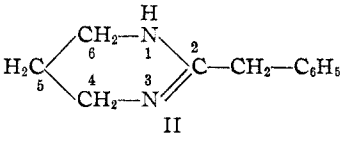
BY GLENN S. SKINNER AND PAUL R. WUNZ[1]

The synthesis of these tetrahydropyrimidine derivatives was undertaken in order to compare them with similar imidazolines which have shown sympathomimetic action. The presence of two alkyl groups at position 5 was desired for the further purpose of simulating physiologically active barbiturates. The radical at position 2 was varied in a homologous manner. Pharmacological screening tests indicate that they are not effective.

Some of the sympathomimetic amines such as epinephrine, ephedrine, benzedrine and propadrine contain the characteristic structure of β-phenylethylamine. 2-Alkylimidazolines[2] also show sympathomimetic action, the most effective being 2-benzylimidazoline (I) which likewise contains the β-phenylethylamine skeleton. The similar 2-benzyl-1,4,5,6-tetrahydropyrimidine (II) has not been reported. Although some other 2-alkyl-1,4,5,6-tetrahydropyrimidines have been described, the parent compound has not. Neither have any derivatives with two alkyl groups at position 5 been reported. The fact that two alkyl groups are located at position 5 in the physiologically active barbituric acids seemed to afford additional reason for making compounds of this type.



I



II

A number of methods of preparing the simpler 2-alkyl-1,4,5,6-tetrahydropyrimidines have been reported but the most generally satisfactory method appeared to be that used by Aspinall[3] in which an ester and trimethylenediamine are heated in a sealed tube with lime. We have modified the method to avoid the use of lime and the sealed tube.

Because the 2,2-dialkyl-1,3-propanediamines are of the neopentyl type and not available, their synthesis provided the difficult part of the problem. The needed 2,2-dialkyl-1,3-propanediols[4] were obtained in yields of 48–77%. The yields of dibromides were not above 37% and the yield of diphthalimido compound was almost nil if the alkyls are ethyl radicals. The method of Komppa and Sevon[5] is therefore impractical. The dibenzenesulfonates were obtained in practical yields but the route through the phthalimido compounds failed.

In our hands the best route to the needed 2,2-dialkyl-1,3-propanediamines[6a,b] involved the condensation of the corresponding ketones with nitromethane to give the 2,2-dialkyl-1,3-dinitropropanes which were reduced to the diamines with the aid of Raney nickel. These then gave the desired tetrahydropyrimidines (Table I). The compounds derived from 1,3-diaminobutane were mixtures as expected.

The pharmacological screening tests were made by Eli Lilly and Co. The determinations of the pressor value by vein in anesthetized cats indicate that the tetrahydropyrimidines produce a slight fall in blood pressure. Therefore, no attempt was made to separate the mixture of isomers derived from 1,3-diaminobutane. The 1,3-propanediamides (Table II) in rats by mouth gave no hypnotic action.

Experimental

2,2-Dialkyl-1,3-propanedibenzenesulfonates.—These compounds were made from the diol and benzenesulfonyl chloride in pyridine.[7] By treating the residue from the filtrate with more benzenesulfonyl chloride and pyridine the yield of the diethyl compound was increased from 69 to 86%.

Alkyls		Diol, mole	Chloride, mole	Pyridine, moles	Yield, %	M.p., °C.	Sulfur, % Calcd.	Found
CH_3–	CH_3–	0.050	0.105	0.20	62	65.5	17.58	17.63
C_2H_5–	C_2H_5–	.30	.70	1.20	69	55.5	15.53	15.47
C_2H_5–	*n*-C_4H_9–	.30	.90	1.20	81	67–68	14.55	14.86

2,2-Dialkylphthalimidopropanes.—In a typical experiment a mixture of 19.2 g. (0.050 mole) of 2,2-dimethyl-1,3-propanedibenzenesulfonate, 27.8 g. (0.15 mole) of potassium phthalimide and 100 cc. of kerosene was stirred for six hours at 210–215° and then heated at this temperature for 14 hours longer. The solid product was filtered, washed with petroleum ether, digested with dilute alkali to remove phthalimide, washed with water and ether. By recrystallization from a 1:1 mixture of alcohol and chloroform 4.7 g. (26%) of 2,2-dimethylphthalimidopropane (235–237°) was obtained. The yield from the dibromide was 11%. Neither the disulfonate nor the dibromide of the diethyl compound gave the desired phthalimido derivative.

(1) du Pont Fellow, 1949. Augsburg College, Minneapolis, Minnesota.

(2) M. Hartmann and H. Isler, *Arch. exptl. Path. Pharmakol.*, **192**, 141 (1939).

(3) S. R. Aspinall, THIS JOURNAL, **62**, 2160 (1940).

(4) A. Franke, *Monatsh.*, **34**, 1893 (1913).

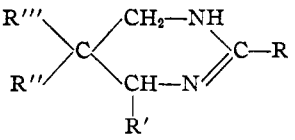
(5) G. Komppa and J. Sevon, *Ann. Acad. Sci. Fennicae*, **37A**, No. 7, 8 (1933).

(6) (a) H. B. Hass and J. F. Bourland, U. S. Patent 2,343,256 (1944); (b) H. B. Hass and M. S. Larrison, U. S. Patent 2,383,603 (1946).

(7) V. C. Sekera and C. S. Marvel, THIS JOURNAL, **55**, 345 (1933).

TABLE I

TETRAHYDROPYRIMIDINES

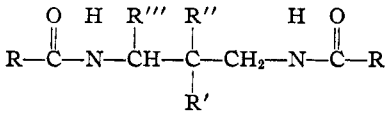


No.	R	R′	R″	R‴	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %
1	H–	H	H	H	88–89[a]	33.33	33.44	39
2	C_6H_5–	H	H	H	86–87.5[b]			68
3	$C_6H_5CH_2$–	H	H	H	113.5–115	16.09	15.89	58
4	$C_6H_5CH_2CH_2$–	H	H	H	107–109	14.89	14.69	72
5	C_6H_5–	CH_3	H	H	65–71[c]	16.09	15.89	40
6	$C_6H_5CH_2$–	CH_3	H	H	67–71[c]	14.89	14.75	82
7	C_6H_5–	H	CH_3	CH_3	125–126	14.89	14.68	51
8	$C_6H_5CH_2$–	H	CH_3	CH_3	95–96	13.86	13.70	73
9	$C_6H_5CH_2CH_2$–	H	CH_3	CH_3	95–96.5	12.96	12.76	60
10	C_6H_5–	H	CH_3	C_2H_5	107–109	13.86	13.81	70
11	$C_6H_5CH_2$–	H	CH_3	C_2H_5	78–80	12.96	12.86	76

[a] B.p. at 1 mm.; $n^{23.5}D$ 1.5143. [b] B.p. 152–156° (6 mm.); Aspinall gives m.p. 86–87°. [c] Mixtures of isomers.

TABLE II

1,3-PROPANEDIAMIDES



R	R′	R″	R‴	M.p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
C_6H_5–	H	H	H	146–147[a]		
C_6H_5–CH_2–	H	H	H	179–179.5	9.03	9.00
C_6H_5–CH_2–CH_2–	H	H	H	146–147	8.28	8.34
C_6H_5–	CH_3–	CH_3–	H	156–157[b]		
C_6H_5–CH_2–	CH_3–	CH_3–	H	143.5–145	8.28	8.19
C_6H_5–	H	H	CH_3–	164–166	9.46	9.51
C_6H_5–CH_2–	H	H	CH_3–	151–152.5	8.64	8.68
C_6H_5–CH_2–CH_2–	H	H	CH_3–	159–161	7.95	8.06
C_6H_5–	CH_3–	C_2H_5–	H	154–155	8.64	8.56

[a] H. Strache (*Ber.*, **21**, 2365 (1888)) gives m.p. 147–148°. [b] A. Lambert and A. Lowe (THIS JOURNAL, **69**, 1517 (1947)) give m.p. 152°.

2,2-Dialkyl-1,3-dinitropropanes.—2,2-Dimethyl-1,3-dinitropropane was prepared in yields of 27–53% using the procedure of Hass and Bourland.[6a] The 2-ethyl-2-methyl-1,3-dinitropropane was similarly obtained in 40–46% yields.

2,2-Dialkyl-1,3-propanediamines.—2,2-Dimethyl-1,3-dinitropropane (81 g.) in 250 cc. of absolute methanol and 15 g. of Raney nickel was subjected to the action of hydrogen at 50–75° and 1000 p.s.i. The yield of 2,2-dimethyl-1,3-propanediamine, b.p. 72–75° (45 mm.), was 54%. Similarly the yield of 2-ethyl-2-methyl-1,3-propanediamine, b.p. 69–75° (15 mm.), was 64%.

Tetrahydropyrimidines.—In a typical experiment 17.8 g. of ethyl β-phenylpropionate was added dropwise to 22.2 g. of trimethylenediamine at 100°. After 21 hours at this temperature the excess of diamine was distilled under a pressure of about 50 mm. The residue was heated for four hours at 175° under diminished pressure such that the higher boiling components were returned to the flask. The product was then distilled *in vacuo* (about 6 mm.) to separate 13.1 g. of the 2-β-phenylethyl-1,4,5,6-tetrahydropyrimidine (Table I) from 2.3 g. of the bis-phenylpropionamide (Table II).

The 2-alkyltetrahydropyrimidines distilled as colorless viscous liquids which solidified. They were purified by crystallization from ethyl acetate. The propanediamides were isolated from the residue by crystallization from ethyl alcohol. In the case of ethyl formate the ester and the diamine were mixed at 50° and then heated under reflux at 100°, and the cyclization step was done at 150° for three hours under diminished pressure (70–80 mm.). These tetrahydropyrimidines easily absorb carbon dioxide from the air.

NEWARK, DELAWARE RECEIVED DECEMBER 15, 1950