TABLE II.—CHEMICAL STABILITY OF FORMULATIONS[a]

Formula G	Initial Assay	60°C. 1 wk.	45°C. 1 wk.	45°C. 4 wk.	45°C. 8 wk.	45°C. 10 wk.	45°C. 12 wk.
Acetylsalicylic acid	319	271	314	297	273	267	252
Salicylic acid	7.0	76	10.5	18.7	58.0	77.0	82.0
Pyrilamine resin adsorbate (expressed as pyrilamine maleate)	12.7	...	12.7	...	11.8	...	11.0
Sodium ascorbate (expressed as ascorbic acid)	24.6	...	23.4	...	13.8	...	1.2
Formula H							
Acetylsalicylic acid	317	317	308	304	321	322	310
Salicylic acid	7.4	16	10.3	7.9	9.2	8.7	9.4
Pyrilamine resin adsorbate (expressed as pyrilamine maleate)	12.8	...	12.7	...	12.2	...	12.2
Sodium ascorbate (expressed as ascorbic acid)	25.6	...	23.8	...	24.8	...	24.7
Formula I							
Acetylsalicylic acid	324	298	316	305	317	314	314
Salicylic acid	7.6	16	9.6	8.7	7.6	8.6	8.8
Pyrilamine resin adsorbate (expressed as pyrilamine maleate)	12.7	...	12.6	...	12.7	...	12.4
Sodium ascorbate (expressed as ascorbic acid)	25.1	...	23.4	...	24.2	...	23.8

[a] Assay results reported as milligrams per tablet.

and sample handling techniques. The heat treatment of tablets prior to packaging has been shown to enhance further the stability of such products when stored at elevated temperatures.

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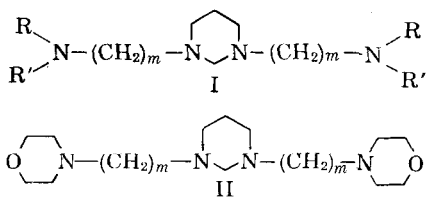
Hexahydropyrimidines I. Preparation of 2-Substituted-1,3-bis(*p*-dimethylaminobenzyl)-hexahydropyrimidines

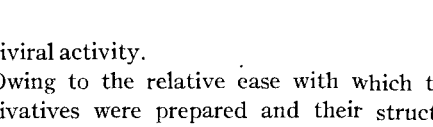
By JOHN H. BILLMAN and LINNEAUS C. DORMAN†

A number of 2-substituted-1,3-bis(*p*-dimethylaminobenzyl)hexahydropyrimidines have been prepared by allowing various aldehydes to react with 1,3-bis(*p*-dimethylamino)propane. The latter diamine was prepared by the catalytic reduction of the di-Schiff base 1,3-bis(*p*-dimethylaminobenzylideneamino)propane. It was felt that *these compounds might possess antifungal, antibiotic, and antiviral activity.*

ALTHOUGH the synthesis of hexahydropyrimidines from 1,3-diamines and carbonyl compounds has been described for some time by a number of workers (1–7), a review of the literature reveals that relatively few hexahydropyrimidines have been prepared and examined for medicinal activity. Two particularly interesting publications by Van Hook and Craig report that 1,3-bis(dialkylaminoalkyl)- (I) (8) and 1,3-bis(heterocyclicaminoalkyl)hexahydropyrimidines (II)(9) possess antifungal, antibacterial and



I



II

antiviral activity.

Owing to the relative ease with which these derivatives were prepared and their structural significance, it was of interest to determine if hexahydropyrimidines substituted in the 1-,2-, and 3-positions might also display similar, if not superior, pharmacological activity to the 1,3-di-

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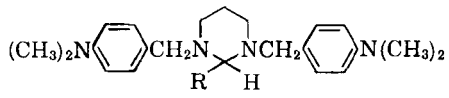
TABLE I.—2-SUBSTITUTED-1,3-BIS-(*p*-DIMETHYLAMINOBENZYL)HEXAHYDROPYRIMIDINES

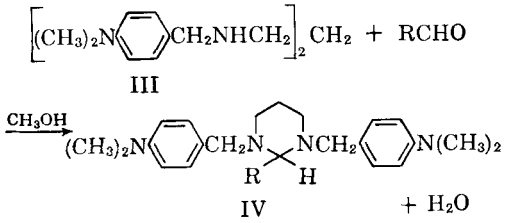


R	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
3,4-Dimethoxyphenyl[a]	54	118–119	$C_{30}H_{40}N_4O_2$	11.47	11.67
p-Dimethylaminophenyl[a]	53	149.5–151	$C_{30}H_{41}N_5$	14.85	14.95
p-Nitrophenyl[a]	38	132–133	$C_{28}H_{35}N_5O_2$	14.79	14.85
3,4-Methylenedioxyphenyl[a]	60	152–153.2	$C_{29}H_{36}N_4O_2$	11.85	11.85
p-Methoxyphenyl[b]	73	125.2–126.2	$C_{29}H_{38}N_4O$	12.22	12.18
m-Hydroxyphenyl[b]	56	139–140.5 d.	$C_{28}H_{36}N_4O$	12.60	12.68
o-Hydroxyphenyl[b]	79	143–144	$C_{28}H_{36}N_4O$	12.60	12.66
3-Thienyl[b]	61	151.2–152	$C_{26}H_{34}N_4S$	12.87	12.98
2-Propyl[b]	70	107.3–108.3	$C_{25}H_{38}N_4$	14.10	14.48
p-Acetamidophenyl[b]	52	179.5–181	$C_{30}H_{39}N_5O$	14.42	14.20

[a] Procedure (*B*). [b] Procedure (*A*).

substituted hexahydropyrimidines, (I) and (II).

To this end, a series of 2-substituted-1,3-bis(*p*-dimethylaminobenzyl)hexahydropyrimidines (IV) (Table I) were prepared by allowing the desired aldehydes to react with 1,3-bis(*p*-dimethylaminobenzylamino)propane according to the following equation. The reason for selecting the hexahydropyrimidines we did is that the N,N-dimethylaminobenzyl grouping resembles in a way



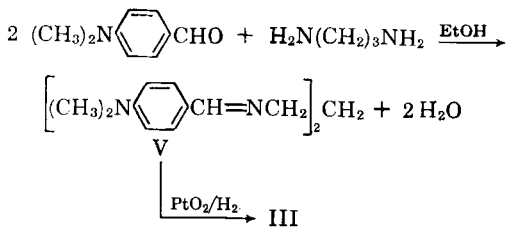
III

IV

the side-chains in the 1,3-bis(dialkylaminoalkyl)-hexahydropyrimidines (I) and 1,3-bis(heterocyclicaminoalkyl)hexahydropyrimidines (II). All three series of compounds have a tertiary-amino group at the end of the side-chains. In addition, the benzyl group should contribute to the solubility of the compounds to about the same extent as compounds of I and II with an average of five methylene groups in the side-chains.

Methanol was a convenient solvent for the ring closure reaction for producing the hexahydropyrimidines in yields of 33–78%. All of the compounds were solids and it was found that they could be hydrolyzed with dilute acid to regenerate the original reactants. In general the condensation reactions proceeded smoothly and rapidly at room temperature or on heating at moderate temperatures. However, difficulties were experienced with vanillin and furfural as these aldehydes failed to yield solid derivatives with 1,3-bis(*p*-dimethylaminobenzylamino)propane. Instead, dark viscous oils separated from their reaction mixtures and no pure products could be isolated.

The 1,3-bis(*p*-dimethylaminobenzylamino)propane (III) was prepared in two steps from trimethylenediamine and *p*-dimethylaminobenzaldehyde. In the initial step, the diamine was condensed with two moles of the aldehyde to produce the di-Schiff base, 1,3-bis(*p*-dimethylaminobenzylideneamino)propane (V). Reduction of the di-Schiff base with hydrogen over platinum oxide yielded the desired reagent.



V

III

The results to date indicate that none of the 2-substituted-1,3-bis(*p*-dimethylaminobenzyl)-hexahydropyrimidine derivatives possess antifungal or antibacterial activity. Other derivatives are now being prepared for testing.

EXPERIMENTAL[1]

Aldehydes.—Either reagent grades of aldehydes were used or they were purified by recrystallization from appropriate solvents. 3-Thiophenealdehyde was prepared by hydrolysis of its hexamethylenetetraammonium chloride salt (10) and used without further purification.

1,3 - Bis(*p*-dimethylaminobenzylideneamino)-

[1] Melting points were taken in open capillaries and are corrected. Microanalyses were performed by Miss J. Dickey of the Chemistry Department of Indiana University and/or by Midwest Microlab, Inc., Indianapolis, Ind.

propane (V).—To a refluxing solution of 64.3 Gm. (0.430 mole) of *p*-dimethylaminobenzaldehyde in 225 ml. of absolute ethanol was added a solution of 13.1 Gm. (0.177 mole) of trimethylenediamine in 30 ml. of absolute ethanol during a 30-min. period. The reaction mixture was refluxed an additional 30 minutes and the crystals which formed on cooling were collected and washed with ethanol; yield, 57.1 Gm. (96%), m.p. 144–145°. Recrystallization from absolute ethanol provided 45 Gm. (74%) of white crystals, m.p. 144.5° to 145°, $\lambda_{max.}^{KBr} = 6.05\mu$ (=C=N—).

Anal.—Calcd. for $C_{21}H_{28}N_4$: N, 16.65. Found: N, 16.59.

1,3 - Bis(*p*-dimethylaminobenzylamino)propane (III).—A mixture of 23.0 Gm. (0.069 mole) of 1,3 - bis(*p*-dimethylaminobenzylideneamino)propane, 1 Gm. of platinum oxide and 150 ml. of absolute ethanol was reduced at room temperature in a low pressure Parr hydrogenator with an initial hydrogen pressure of 47 p.s.i. Approximately 35 minutes were required to complete the reduction. The catalyst was removed by filtration and the filtrate was treated with 100 ml. of absolute ethanol, then slowly, while stirring vigorously, with 34 ml. of concentrated hydrochloric acid. The precipitated hydrochloride salt was removed by filtration, washed with absolute ethanol, dried partially under suction and completely in a vacuum desiccator over sodium hydroxide. The yield of crude 1,3-bis(*p*-dimethylaminobenzylamino)propane tetrahydrochloride monohydrate was 33.6 Gm. (98%). An analytical sample was obtained by two recrystallizations of the crude material from a mixture of 10% hydrochloric acid and absolute ethanol, 1:10, (the hot amine salt dilute hydrochloric acid solution was filtered into the absolute ethanol); decompn. point, 240–242° (brass Maquenne block).

Anal.—Calcd. for $C_{21}H_{38}Cl_4N_4O$: N, 11.11; Cl, 28.12. Found: N, 11.03; Cl, 28.10.

The free tetramine was recovered from its aqueous salt solution by precipitation with 10% sodium hydroxide. It was collected on a filter, washed with water, partially dried (rubber dam), then quickly transferred to a vacuum desiccator where drying was completed over sodium hydroxide. The tetramine occasionally softened in the desiccator, but solidified again on repeated drying *in vacuo*. The tetramine liquifies in air, but remains in solid form when kept in a desiccator over solid alkali. An analytical sample of 1,3-bis(*p*-dimethylaminobenzylamino)propane was prepared from its purified hydrochloride salt with aqueous alkali and dried *in vacuo* over sodium hydroxide and Ascarite, m.p. 38–40° (sealed capillary).

Anal.—Calcd. for $C_{21}H_{34}N_4$: C, 74.07; H, 9.47; N, 16.46. Found: C, 73.72; H, 9.57; N, 16.45.

2 - Substituted - 1,3 - bis(*p*-dimethylaminobenzyl)hexahydropyrimidines (IV).—The 2-(2-propyl)- derivative was prepared by the following procedure (*A*). To a stirred solution of 5.0 Gm. (0.015 mole) of 1,3-bis(*p*-dimethylaminobenzylamino)propane in 15 ml. of methanol was added dropwise 1.1 Gm. (0.015 mole) of isobutyraldehyde during a 5-min. interval. The reaction mixture was refrigerated and the crystalline precipitate which formed was collected and washed with methanol, 5.4 Gm. (92%), m.p. 107–108°. Recrystallization from ethanol provided 4.1 Gm., m.p. 107.3° to 108.3°, for an overall yield of 70%.

Anal.—Calcd. for $C_{25}H_{38}N_4$: N, 14.19. Found: N, 14.48.

The 2-(3,4-dimethoxyphenyl)- derivative was prepared by the following procedure (*B*). To a solution of 9.3 Gm. (0.019 mole) of 1,3-bis(*p*-dimethylaminobenzylamino)propane tetrachloride monohydrate in 190 ml. of water was added dropwise, with stirring, 44 ml. of 10% sodium hydroxide. The precipitated tetramine (III) was collected on a filter, washed well with water, freed of most of the adhering water, then dissolved in 13 ml. of hot methanol. To this hot solution was added a hot solution of 3.1 Gm. (0.019 mole) of veratraldehyde in 6 ml. of methanol. The resulting solution was swirled, cooled to room temperature, then refrigerated. The precipitated derivative was collected and washed with methanol. The dried crude product, 6.3 Gm., was recrystallized from absolute ethanol providing 5.0 Gm. (54%) of white prisms, m.p. 118–119°.

Anal.—Calcd. for $C_{30}H_{40}N_4O_2$: N, 11.47. Found: N, 11.67.

SUMMARY

1. A series of ten 2-substituted-1,3-bis (*p*-dimethylaminobenzyl)hexahydropyrimidines has been prepared.

2. In general, these compounds failed to show any biological properties of significant interest.

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