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Derivatives of β-Phenylethylamines and β-Phenylethylmethylamines

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In continuation of previous work on the correlation of physiological action with chemical structure, three additional series of β-phenylethylamine derivatives have been prepared and are here described. The series are (a) β-phenylethylureas, (b) β-phenylethylmethylureas, and (c) 1-β-phenylethyl-5,5-diethylbarbituric acids. The β-phenylethylamines and β-phenylethylmethylamines used as starting materials have been previously described. The pharmacological testing will be reported in another place.

The reaction used for preparing the ureas was the Wöhler reaction, the intramolecular transformation of the amine cyanate into the urea.

$$RCH_2CH_2NH_2\cdot HCNO \longrightarrow RCH_2CH_2NHCONH_2$$
$$RCH_2CH_2NHCH_3\cdot HCNO \longrightarrow RCH_2CH_2NCH_3CONH_2$$

The diethylbarbituric acids were prepared by the usual method, the condensation of the urea with the diethylmalonic ester in the presence of sodium ethylate.

$$RCH_2CH_2NHCONH_2 + (C_2H_5)_2C(COOC_2H_5)_2 \longrightarrow RCH_2CH_2{-}N(CO{-}C(C_2H_5)_2{-}CO{-}NH{-}CO)$$

The 3,5- and the 2,6-dimethoxy compounds were not prepared, owing to the inaccessibility of the starting materials.

Experimental

β-Phenylethylureas and β-Phenylethylmethylureas.—One mole of amine was dissolved in one mole of dilute sulfuric acid (7%), and an aqueous solution (20%) of one mole potassium cyanate added, all in the cold. The resulting clear solution was then evaporated to dryness on the steam-bath (about four hours required) and the residue repeatedly extracted with hot absolute alcohol. On concentrating the extract and adding a little water, the urea usually crystallized out on standing in the cold. The product was filtered off and recrystallized until pure. The reaction went well in all cases, and the yields, allowing for losses in recrystallization, were all very good.

The ureas are all white. The β-phenylethylureas all

TABLE I

β-PHENYLETHYLUREAS

No.	Substituent in amine and urea	Appearance	Solvent recryst.	M. p., °C. corr.	Formula of urea	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	Unsubst.	Overgrown rect. plates	Water	115	$C_9H_{12}ON_2$	65.81	7.37	65.83	7.24
2	2-Methoxy	Jagged striated leaves	Aq. alc.	98	$C_{10}H_{14}O_2N_2$	61.82	7.27	62.02	7.27
3	3-Methoxy	Stout jagged needle-prisms	Aq. alc.	104	$C_{10}H_{14}O_2N_2$	61.82	7.27	61.66	7.24
4	4-Methoxy	Small stout prisms	Aq. alc.	133	$C_{10}H_{14}O_2N_2$	61.82	7.27	62.12	7.36
5	2,3-Dimethoxy	Felted needles	Alcohol	135	$C_{11}H_{16}O_3N_2$	58.89	7.19	59.00	7.15
6	3,4-Dimethoxy	Small flat prisms	Alcohol	162	$C_{11}H_{16}O_3N_2$	58.89	7.19	58.81	7.10
7	2,4-Dimethoxy	Small thick hexagons	Aq. alc.	169	$C_{11}H_{16}O_3N_2$	58.89	7.19	59.07	7.13
8	2,5-Dimethoxy	Small feathery tufts	Aq. alc.	131	$C_{11}H_{16}O_3N_2$	58.89	7.19	58.76	7.27

TABLE II

β-PHENYLETHYLMETHYLUREAS

No.	Substituent in amine and urea	Appearance	Solvent recryst.	M. p., °C. corr.	Formula of urea	Analyses, % Calcd. C	Calcd. H	Found C	Found H
9	Unsubst.	Thin rect. plates	Aq. alc.	143	$C_{10}H_{14}ON_2$	67.37	7.92	67.26	7.89
10	2-Methoxy	Felted small needles	Alc.–ether	82	$C_{11}H_{16}O_2N_2$	63.42	7.75	63.63	7.71
11	3-Methoxy	Slender plates	Aq. alc.	102	$C_{11}H_{16}O_2N_2$	63.42	7.75	63.71	7.94
12	4-Methoxy	Thin rect. plates	Aq. alc.	158	$C_{11}H_{16}O_2N_2$	63.42	7.75	63.35	7.64
13	2,3-Dimethoxy	Small stout prisms	Ethyl acet.–ether	69	$C_{12}H_{18}O_3N_2$	60.47	7.62	60.40	7.84
14	3,4-Dimethoxy	Stout flat prisms	Alc.–ether, alc., bz.	129	$C_{12}H_{18}O_3N_2$	60.47	7.62	60.59	7.59
15	2,4-Dimethoxy	Tiny felted needles	Eth. acet., aq. alc., bz.–ether	94	$C_{12}H_{18}O_3N_2$	60.47	7.62	60.41	7.63
16	2,5-Dimethoxy	Long small striated prisms	Alc.–ether	91	$C_{12}H_{18}O_3N_2$	60.47	7.62	60.45	7.70

No. 2 requires very little solvent for recrystallization. With No. 7 the urea forms rapidly and is filtered off in place of evaporation. Nos. 10 and 13 were very difficult to crystallize until a seeding crystal was obtained.

Refs. to amines—Nos. 2, 3, 5, 7, 8, 10, 11, 13, 15, 16, Buck, THIS JOURNAL, **54**, 3661 (1932); Nos. 6, 14, *ibid.*, **52**, 4119 (1930); No. 4, *ibid.*, **53**, 2192 (1931); Nos. 9, 12, the N-methylation was carried out substantially as *ibid.*, **54**, 3661 (1932); No. 1, this was prepared by the action of NaOCl on phenylpropionamide.

show very similar solubilities. They are fairly to readily soluble in water, readily soluble in alcohol, sparingly soluble in ether, very soluble in chloroform, moderately to readily soluble in benzene, and soluble in cold dilute hydrochloric acid (1:3). The β-phenylethylmethylureas show similar solubility phenomena, but in general they are considerably more soluble than the β-phenylethylureas. Details of the compounds are given in Tables I and II.

1-β-Phenylethyl-5,5-diethylbarbituric Acids.—Three atoms of metallic sodium was dissolved in the minimum amount of absolute alcohol. To this solution was added one mole of diethylmalonic ester and then one mole of the β-phenylethylurea. The whole was then refluxed on the steam-bath for the necessary time, allowing some of the alcohol to evaporate toward the end of the period. In general, the product was obtained by pouring the reaction mixture into water, and making slightly acid with acetic acid. After standing, the oily or crystalline mass was collected and recrystallized until pure. Very careful treatment and long standing at 0° are sometimes necessary in order to obtain the initial crystals.

The rather drastic methods often reported in the literature proved to be unnecessary with the present compounds. The reaction, in every case, gave the desired product, and the yield of crude material was usually good, although sometimes considerably diminished during purification. Aqueous alcohol was used as the final solvent for recrystallization in all cases.

The barbituric acids, when once obtained crystalline, are readily recrystallized from aqueous alcohol, from which solvent they separate as white or colorless crystals. The solubilities are of the same order for all the compounds. They are all soluble in 10% sodium hydroxide solution, very sparingly soluble in hot water, readily soluble in alcohol, moderately to readily soluble in benzene, very soluble in chloroform, and moderately to readily soluble in ether. Details of the compounds are given in Table III.

TABLE III

1-β-PHENYLETHYL-5,5-DIETHYLBARBITURIC ACIDS

No. compd. No. urea used	Substituent in amine and product	Appearance	M. p., °C. corr.	Hours reflux	Formula of product	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	Unsubst.	Glitt. prism needles	147	4	$C_{16}H_{20}O_3N_2$	66.63	6.99	66.51	7.00
2	2-Methoxy	Glitt. stout prisms	60	7	$C_{17}H_{22}O_4N_2$	64.12	6.97	63.98	7.27
3	3-Methoxy	Glitt. prism needles	96	4.5	$C_{17}H_{22}O_4N_2$	64.12	6.97	64.41	6.87
4	4-Methoxy	Small glitt. prisms	173	2.5	$C_{17}H_{22}O_4N_2$	64.12	6.97	64.11	7.02
5	2,3-Dimethoxy	Felted small needles	122	4.5	$C_{18}H_{24}O_5N_2$	62.03	6.95	62.12	6.96
6	3,4-Dimethoxy	Irreg. flat prisms	87	4	$C_{18}H_{24}O_5N_2$	62.03	6.95	62.35	7.09
7	2,4-Dimethoxy	Felted tiny prisms	92	7.5	$C_{18}H_{24}O_5N_2$	62.03	6.95	62.21	7.01
8	2,5-Dimethoxy	Tiny glitt. prisms	92	1.5	$C_{18}H_{24}O_5N_2$	62.03	6.95	61.82	6.95

Compounds 2, 6 and 8 were very difficult to crystallize until seeding crystals were obtained. Compound 2 only crystallized from a very cold, clear solution. Compound 7 had always to be freed from some of the unchanged urea.

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Summary

Three series of β-phenylethylamine derivatives, β-phenylethylureas, β-phenylethylmethylureas, and 1-β-phenylethyl-5,5-diethylbarbituric acids have been prepared with a view to examining their physiological action. Their preparation and properties are described.

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