[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Basically Substituted Aliphatic Derivatives of Urea

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Recently it became necessary to prepare certain urea derivatives, especially those containing basically-substituted aliphatic groups. Since various authors[1] have observed the formation of substituted ureas when primary or secondary amines are heated with urea, it was decided to follow this general procedure. The primary amine was mixed in the theoretical quantities with urea and heated from three to nine hours at a temperature above the melting point of urea, usually about 150°. During the reaction, the evolution of ammonia was observed. The symmetrically substituted ureas were isolated by distillation at reduced pressures.

The amines used in these reactions were δ-piperidinobutylamine, γ-piperidinopropylamine, γ-morpholinopropylamine, and γ-(β-diethylaminoethoxy)-propylamine. Data are found in the accompanying table.

When γ-(γ′-morpholinopropylamino)-propylamine reacted with urea, the waxy, white, solid product was obviously impure. Apparently both the primary and secondary amino groups in the starting material are capable of reacting with urea.

The reaction of morpholine and urea yielded N-carbamylmorpholine[2] as predicted by the theory of Davis and Underwood.[1b] In order to obtain the dimorpholino carbonyl, morpholine and diethyl carbonate were heated together in a sealed tube at 180°. This product gave a melting point depression of 17° with *n*-carbamylmorpholine.

We wish to thank Parke, Davis and Company for their help in this work.

Experimental

Following is the description of a typical experiment whereby the compounds in the accompanying table were synthesized.

N,N′-Di-(δ-piperidinobutyl)-urea.—A mixture of 16.9 g. (0.108 mole) of δ-piperidinobutylamine[3] and 3.18 g. (0.053 mole) of urea was heated with a little glass powder (to facilitate ammonia evolution) at a temperature of 155°. Gaseous ammonia was evolved after ten minutes of heating and was continuously evolved for another hour. After four hours the evolution had stopped and the reaction was considered complete. As the mixture cooled it became a waxy solid which was distilled from a small Claisen flask. The yield of symmetrical N,N′-di-(δ-piperidinobutyl)-urea was 11.3 g. (63%), b. p. 165–167° (3 mm.); m. p. picrate, 146–147°. Equivalent weight calcd.: 169.3. Found: 168.7, 168.9.

N-Carbamylmorpholine.[2]—A mixture of 7.76 g. (0.1293 mole) of urea and 43.73 g. (0.502 mole) of morpholine was placed in a flask equipped with a condenser and an inlet tube for nitrogen. During the reaction (sixteen hours at 145°) the evolved ammonia was absorbed in standard acid. This evolved ammonia amounted to 0.136 equivalent. The yield of the N-carbamylmorpholine was 96%; b. p. 174–183° (3 mm.), m. p. 109–110°. *Anal.* Calcd. for $C_5H_{10}N_2O_2$: N, 21.56. Found by the Kjeldahl method: N, 21.74. Knorr[2] records the melting point of this compound which he prepared from morpholine and potassium cyanate as 110–113°.

Dimorpholinocarbonyl.—A mixture of 20 g. (0.169 mole) of diethyl carbonate and 32.6 g. (0.375 mole) of morpholine was heated in a sealed tube for four hours at a temperature of 180°. The waxy, white solid was crystallized from ethanol; m. p. 95–97°. An attempt was made to distil the product at reduced pressure but the material sublimed Purification by sublimation gave 13 g. of a product melting at 101–103° sealed tube, yield 38%. *Anal.* Calcd. for $C_9H_{16}N_2O_3 \cdot H_2O$: C, 49.52; H, 8.32; N, 12.83. Found: C, 49.16; H, 8.26; N, 12.84.

N-Carbamylpiperidine.[4]—A mixture of 15.8 g. (0.186 mole) of piperidine and 5.5 g. (0.0916 mole) of urea was heated for six hours at a temperature of 120°. The product distilled at 155–170° (4–5 mm.); m. p. 97–98°, yield 7.6 g. or 65%. *Anal.* Calcd. for $C_6H_{12}N_2O$: N, 22.00.

TABLE I

Name	Reaction Time, hr.	Reaction Temp., °C.	Yield, %	B. p., °C.	Press., mm.	Picrate m. p., °C.	Formula	Analyses Eq. weight Calcd.	Analyses Eq. weight Found
N,N′-Di-(δ-piperidinobutyl)-urea	4	155	63	165–167	3	146–147	$C_{19}H_{38}ON_4$	169.3	168.9
N,N′-Di-(γ-piperidinopropyl)-urea	6	150	68	163	2	186–187	$C_{17}H_{34}ON_4$	155.2	155.3
N,N′-Di-(γ-morpholinopropyl)-urea	8	155	85	163–166	4	205–207	$C_{15}H_{30}O_3N_4$	157.2	157.1
N,N′-Di-[γ-(β-diethylamino-ethoxy)-propyl]-urea	5	150	80	169–173	2	92– 94	$C_{19}H_{42}O_3N_4$	187.2	187.3
N,N′-Di-(α-Methyl-δ-diethyl-aminobutyl)-urea	6	155	56	160–170	7	Oil	$C_{19}H_{40}ON_4$	171.3	175.2
N-Carbamylmorpholine	6	125	96	174–183	3	109–110[a]	$C_5H_{10}O_2N_2$	21.56[b]	21.74[b]
Dimorpholinocarbonyl hydrate[c]	4	180	38		...	101–103[a]	$C_9H_{18}O_4N_2$	12.83[d]	12.84[d]
N-Carbamylpiperidine	6	120	65	155–170	4–5	97– 98[a]	$C_6H_{12}ON_2$	22.0[d]	21.86[d]

[a] Melting point of the free base. [b] Per cent. nitrogen determined by the Kjeldahl method. [c] Prepared from diethyl carbonate and morpholine. [d] Per cent. nitrogen determined by the Dumas method. Sublimes; melting point, sealed tube, 101–103°.

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[1] (a) Fleisher, *Ber.*, **9**, 995 (1876); (b) Davis and Underwood, THIS JOURNAL, **44**, 2595 (1922); (c) Davis and Blanchard, *ibid.*, **45**, 1816 (1923); (d) Girard, *Ber.*, **6**, 444 (1873); (e) Sonn, *ibid.*, **47**, 2437 (1914).

[2] Knorr, *Ann.*, **301**, 8 (1898).

[3] Whitmore, Mosher, Adams, Chapin, Taylor, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

[4] (a) Wallach and Lehmann, *Ann.*, **237**, 250 (1886); (b) Young and Clark, *J. Chem. Soc.*, **73**, 366 (1898).

Found by the Dumas method: N, 21.86. Curiously, the Kjeldahl method (two different operators) gave 14.30, 14.38, 14.27, 14.19; values which are quite close to the calculated 14.25 per cent. nitrogen in dipiperidino carbonyl. This latter compound cannot be formed if the accepted mechanism[1b] for the reaction is correct. Dipiperidinocarbonyl was therefore prepared from piperidine and phosgene and the melting point determined to be 45–46°. Reported by Kuhn,[5] 42–43°. From this it is apparent that the Kjeldahl method fails in this instance and that the mechanism of Davis and Underwood[1b] for the reaction is completely substantiated.

Summary

The formation of substituted ureas by heating a primary or secondary amine with urea has been applied to basically-substituted aliphatic amines. Five new compounds of this nature are described.

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[5] Kuhn, *Ber.*, **33**, 2900 (1900).

[CONTRIBUTION FROM DEPARTMENTS OF PHARMACOLOGY AND BIOLOGICAL CHEMISTRY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE]

β-D-Galactose-1-(barium phosphate)[1]

BY F. J. REITHEL

A new sugar phosphate ester has been synthesized which has properties indicating it to be the β isomer of D-galactose-1-(barium phosphate). The only synthesis of the β isomer of a hexose-1-phosphate which has appeared in the literature is that of Wolfrom, *et al.*[2]

Lipmann and Tuttle have published a method[3] for the synthesis of acetyl phosphate with "monosilver phosphate" as the phosphorylating agent and have suggested the use of this reagent for the synthesis of the Cori ester. It was found that α-bromo-D-glucose tetraacetate reacted with "monosilver phosphate" to form β-D-glucose-1-(barium phosphate), isolated as the barium salt.

β-D-Galactose-1-(barium phosphate) was synthesized both by the method of Wolfrom, *et al.*,[2] and by the use of "monosilver phosphate." The products obtained were very similar with respect to rotation and phosphorus content. Rotational changes during hydrolysis of the compound were in the right direction for the β isomer. It is concluded that the new compound is β-D-galactose-1-(barium phosphate) and that the method employing "monosilver phosphate" is generally applicable to the synthesis of the β isomer of hexose-1-phosphates.

Experimental

β-D-Galactose-1-(barium phosphate).—Monosilver phosphate, prepared from 1.05 g. of dry trisilver phosphate and 0.33 ml. 90% phosphoric acid, was suspended in 3 ml. of dry ether. To this suspension, kept at 5°, was slowly added 3.0 g. of pure dry α-bromo-D-galactose tetraacetate in absolute chloroform and the mixture allowed to react for ten minutes with good stirring. After centrifuging, the supernatant fluid was shaken with 10 ml. water at 0° and the mixture adjusted to *p*H 8 with normal sodium hydroxide. The chloroform layer was discarded and to the aqueous layer was added 2 g. of barium acetate in 10 ml. of water. The precipitate was centrifuged down and discarded. The aqueous solution was evaporated to dryness *in vacuo* at 30° and the residue taken up in 25 ml. of 98% alcohol. No attempt was made to crystallize this intermediate which is presumably the barium salt of D-galactose-1-phosphoric acid tetraacetate. It was deacetylated by pouring the above solution into alcohol containing sodium ethylate whereupon crude β-D-galactose-1-(barium phosphate) precipitated. The crude salt was purified by dissolving in water, adjusting to *p*H 8.5, and precipitating with 1.5 volumes 95% alcohol. After three such treatments there was obtained 270 mg. of a white amorphous solid which was completely soluble in water and which reduced alkaline copper solutions after mild acid hydrolysis. The specific rotation in water was $[\alpha]^{30}\text{D}$ +31.2° (*c*, 1.2).

Anal. Calcd. for $C_6H_{11}O_5PO_4Ba \cdot 3H_2O$: C, 16.05; H, 3.56; P, 6.90; Ba, 30.6. Found: C, 16.14, 16.16; H, 3.0, 3.2[4]; P, 6.88; Ba,[5] 30.6.

β-D-Galactose-1-(barium phosphate) was also synthesized by the method of Wolfrom, *et al.*[2] The phosphorylating agent, silver dibenzyl phosphate, was prepared from pure dibenzylphosphoric acid by adding an alcoholic solution of silver nitrate to an alcoholic solution of the acid. The pure silver salt thus obtained melted at 222° with decomposition.

Two grams of pure dry α-bromo-D-galactose tetraacetate, 2.8 g. pure silver diphenyl phosphate and 11 ml. of pure dry benzene were introduced into a flask equipped with a sealed stirrer and a condenser fitted with a calcium chloride tube. The mixture was heated slowly to 50° for thirty minutes, then at 65° for ninety minutes, vigorous stirring being maintained. After removal of the benzene, the sirup obtained was taken up in 4 ml. of absolute ether and allowed to stand overnight in the ice box. This procedure allowed any excess silver diphenyl phosphate to separate. To the filtered solution low boiling petroleum ether was added to incipient turbidity at 0°. After some days a mass of crystals appeared which were very difficult to separate from a small amount of adhering sirup. The impure crystalline mass, weighing 2.1 g., was taken up in 25 ml. of absolute ethanol and hydrogenated at room temperature and atmospheric pressure in the presence of 0.32 g. of palladous oxide catalyst.[6] The hexose phosphoric acid was made into the lead salt according to Wolfrom, *et al.*[2] After decomposing the lead salt with hydrogen sulfide, the filtered, aerated solution was made alkaline with barium hydroxide. The crude barium salt was obtained by adding 1.5 volumes 95% ethanol and was purified by alcohol precipitation as described above. Two hundred and fifty mg. of a white amorphous product was obtained which had a rotation in water of $[\alpha]^{30}\text{D}$ +34°.

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[1] This work was aided by a research grant from the Rockefeller Foundation. Original manuscript received October 16, 1944.

[2] Wolfrom, Smith, Pletcher and Brown, THIS JOURNAL, **64**, 23 (1942).

[3] Lipmann and Tuttle, *J. Biol. Chem.*, **153**, 571 (1944).

[4] The carbon and hydrogen analyses were kindly done by Dr. S. A. Thayer, St. Louis University School of Medicine.

[5] King, *Biochem. J.*, **26**, 586 (1932).

[6] Shriner and Adams, THIS JOURNAL, **46**, 1683 (1924).