specific rotational values of these halogen derivatives shows that these straight chain biose derivatives behave the same as the branched chain biose derivatives investigated in the previous article, as agreement with the regular relationship observed for the corresponding derivatives of the monose sugars is obtained only by excluding the values for the fluoro derivatives.

Besides the pure α-halogen derivatives of gentiobiose, impure β-chloro and iodo compounds were obtained.

The Walden inversion from β-octa-acetylgentiobiose to α-chloro- and iodo-hepta-acetyl gentiobiose by the action of hydrochloric and hydriodic acids proceeds at least in *two* definite steps, β-chloro- or iodo-hepta-acetylgentiobiose being intermediately formed.

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ACYL ISO-UREAS

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The chemistry of methyl- and ethyl-*iso*-ureas (oxygen ethers of urea) and their acyl derivatives has been studied mainly by Stieglitz and his collaborators,[1,2,3] and by Wheeler and Johnson.[4]

More recently E. A. Werner[5] has made important contributions to this field of study.

In an investigation of the pharmacological properties of acyl *iso*-ureas, it was observed by one of us[6] that carbethoxy-ethyl-*iso*-urea was mildly depressing to the central nervous system and caused a large and rapid fall of body temperature. Later it was shown that dicarbethoxy-ethyl-*iso*-urea possessed similar properties but in greater degree[7] while carbo-*n*-butoxy-ethyl-*iso*-urea had only slight physiological action.[8]

In view of these results, the preparation of a greater variety of acyl *iso*-ureas was undertaken. Since only methyl- and ethyl-*iso*-ureas and their derivatives have been prepared up to the present, a study of the possibility of obtaining propyl-, butyl-, phenyl-, benzyl- and phenylethyl-*iso*-ureas was commenced, preliminary results of which are reported in this

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[1] Dains, THIS JOURNAL, **21**, 136 (1899).

[2] Bruce, *ibid.*, **26**, 419 (1904).

[3] McKee, *Am. Chem. J.*, **26**, 209 (1901).

[4] Wheeler and Johnson, *ibid.*, **24**, 189 (1900).

[5] Werner, *J. Chem. Soc.*, **105**, 923 (1914); "The Chemistry of Urea," Longmans, London and New York, **1923**.

[6] Basterfield, *J. Pharmacol.*, **20**, 451 (1923).

[7] Basterfield and Paynter, THIS JOURNAL, **48**, 2176 (1926).

[8] Basterfield, Woods and Wright, *ibid.*, **48**, 2371 (1926).

paper. A considerable number of new acyl derivatives of methyl- and ethyl-*iso*-ureas are also described.

The *iso*-urea hydrochlorides were prepared by the method of Stieglitz and Bruce[2] which consists in the addition of anhydrous alcohols to cyanamide in the presence of dry hydrogen chloride. The acyl derivatives were obtained by treating the *iso*-urea hydrochlorides in ether suspension with the required amount of acyl halide, the whole being shaken with concentrated aqueous potassium or sodium hydroxide. Details of purification are given in the experimental part of the paper.

The addition of *n*-propyl and *n*-butyl alcohols to cyanamide was found to take place much less readily than that of methyl and ethyl alcohols. The hydrochlorides of *n*-propyl and *n*-butyl-*iso*-ureas were obtained but could not be satisfactorily purified. A fairly pure sample of *n*-propyl-*iso*-urea was obtained as an oil and acyl derivatives of both *iso*-ureas were prepared in pure condition. Work on benzyl- and phenylethyl-*iso*-ureas is in progress.

Experimental Part

I. Derivatives of Methyl-*iso*-urea

Data on yields, melting points and analyses are given in Table I.

Phenylacetylmethyl-*iso*-urea, $C_6H_5CH_2CONHC(OCH_3)NH$.—This was obtained as an oil which was decomposed somewhat by distillation under reduced pressure. The oil was dissolved in anhydrous ether and the solution treated with dry hydrogen chloride. The precipitated hydrochloride was analyzed for chlorine by titration with a standard solution of silver nitrate.

Chloro-acetylmethyl-*iso*-urea, $CH_2ClCONHC(OCH_3)NH$.—This was obtained as an oil which was converted into the hydrochloride and analyzed for displaceable chlorine. The salt was purified by recrystallization from ethyl alcohol.

Carbo-*n*-propoxymethyl-*iso*-urea, $C_3H_7OCONHC(OCH_3)NH$.—This compound, prepared from methyl-*iso*-urea and *n*-propyl chlorocarbonate, was obtained as an oil which rapidly solidified in a desiccator. It was recrystallized from ligroin.

An attempt to prepare the hydrochloride yielded only *n*-propyl-allophanic ester; m. p. 167°. The salt is evidently unstable and loses methyl chloride even at room temperature. The allophanic ester was further identified by analysis.

Anal. Calcd. for $C_5H_{10}N_2O_3$: N, 19.17. Found: 19.02.

Carbo-*n*-butoxymethyl-*iso*-urea, $C_4H_9OCONHC(OCH_3)NH$.

Carbo-*iso*-amoxymethyl-*iso*-urea, $C_5H_{11}OCONHC(OCH_3)NH$.—This was obtained

Table I

Derivatives of Methyl-*iso*-urea

				Analyses, %			
Derivative	Formula	Yield, %	M. p., °C.		Calcd.	Found	
Phenylacetyl	$C_{10}H_{22}N_2O_2$	85	207 (dec.)[a]	Cl	15.51[a]	15.61	15.62
Chloro-acetyl	$C_4H_7N_2O_2Cl$	Poor	183[a]	Cl	18.95[a]	18.80	18.70
Carbo-*n*-propoxy	$C_6H_{12}N_2O_3$	..	36–37	N	17.50	17.52	17.56
Carbo-*n*-butoxy	$C_7H_{14}N_2O_3$	67	32	N	16.09	16.06	15.96
Carbo-*iso*-amoxy	$C_8H_{16}N_2O_3$	94	93	N	14.88	14.71	

[a] M. p. of hydrochloride and percentages of displaceable chlorine.

as an oil which did not solidify readily. It was taken up in ligroin and cooled in a freezing mixture. Crystals were obtained in small quantity. Treatment with dry hydrogen chloride in ether gave *iso*-amyl allophanic ester, m. p. 162°.

TABLE II

DERIVATIVES OF ETHYL-*iso*-UREA

Derivative	Formula	Yield, %	M. p., °C.	Analyses, % Calcd.		Found	
Phenylacetyl	$C_{11}H_{14}N_2O_2$	90	(b. p. 160, 20 mm.)	N	13.59	13.68	13.78
p-Nitrobenzoyl	$C_{10}H_{11}N_3O_4$	90	125	N	17.73	17.76	17.60
α-Bromopropionyl	$C_6H_{11}N_2O_2Br$	100	141	N	12.58	12.76	12.68
Chloro-acetyl	$C_5H_9N_2O_2Cl$	V. poor[a]	140[a]	N	14.04[a]	13.94	
				Cl	17.76[a]	17.85	17.90
Carbo-*n*-propoxy	$C_7H_{14}N_2O_3$	−100[b]	. . .	N	16.09	16.17	16.12
Carbo-*iso*-amoxy	$C_9H_{18}N_2O_3$	−100[b]	−10	N	13.86	13.96	13.94
Benzenesulfonyl	$C_9H_{12}N_2O_3S$	92	86	N	12.28	12.24	12.20
			101	N	12.28	12.28	

[a] Yield and m. p. of and percentages of N and Cl for hydrochloride.

[b] Almost quantitative yield.

II. Derivatives of Ethyl-*iso*-urea.

See Table II for further data on these derivatives.

Phenylacetylethyl-*iso*-urea, $C_6H_5CH_2CONHC(OC_2H_5)NH$.—This compound was an oil which was purified by distillation under reduced pressure.

***p*-Nitrobenzoylethyl-*iso*-urea, $NO_2C_6H_4CONHC(OC_2H_5)NH$.**—Slightly yellow crystals from ether.

α-Bromopropionylethyl-*iso*-urea, $CH_3CHBrCONHC(OC_2H_5)NH$.—This was obtained as an oil which was decomposed by distillation under reduced pressure. After standing for several months, the oil had deposited a quantity of white crystals. The solid was insoluble in ether but was soluble in warm alcohol. It was at first thought that the substance might be 2-ethoxy-4-methylhydantoin but analysis showed the required nitrogen content for α-bromopropionylethyl-*iso*-urea. The insolubility in ether, however, suggests that the solid is a polymer, the original oil being the unpolymerized compound.

Chloro-acetylethyl-*iso*-urea, $CH_2ClCONHC(OC_2H_5)NH$.—The base, a viscid oil, was converted into the hydrochloride.

Carbo-*n*-propoxy-ethyl-*iso*-urea, $C_3H_7OCONHC(OC_2H_5)NH$.—The clear oil first obtained solidified in a freezing mixture. Analysis showed it to be quite pure.

Carbo-*iso*-amoxy-ethyl-*iso*-urea, $C_5H_{11}OCONHC(OC_2H_5)NH$.—The oil first obtained was found to be quite pure.

Benzenesulfonylethyl-*iso*-urea, $C_6H_5SO_2NHC(OC_2H_5)NH$.—This compound was obtained as a solid, crystallizing from alcohol in large, rhombic prisms. The first sample melted at 86°. After standing for a few weeks the crystals were yellowish and moist. The substance was recrystallized, m. p. 76°. In the course of a few days the melting point had risen to 101°. Repeated recrystallizations gave fractions with different melting points, the highest being 110°. All fractions melted at 101° after standing for a few days. The material melting at 101° had exactly the same nitrogen content as the original substance. The phenomenon is probably due to di- or polymorphism.

III. *n*-Propyl-*iso*-urea, $NH_2C(OC_3H_7)NH$

Five g. of cyanamide was dissolved in 250 cc. of *n*-propyl alcohol and the calculated amount of dry hydrogen chloride passed into the solution cooled in ice. After standing for three days, the liquid gave no reaction for cyanamide. The alcohol was removed by distillation under reduced pressure. A viscous, semi-solid mass was left which became almost completely solid after prolonged standing in a vacuum desiccator. Recrystallization from alcohol even at low temperatures was unsuccessful. Concentrated alcoholic solutions poured into ether or ligroin at —20° gave only semi-solid products. The nearly solid mass obtained after long standing in a desiccator was very hygroscopic and became sirupy in a few minutes after exposure to the air.

From a sample of this impure hydrochloride, the free base was liberated by treatment with a large excess of powdered potassium hydroxide in ether suspension. The ether solution on evaporation yielded a slightly yellow oil of very obnoxious and penetrating odor. It was dried in a vacuum and analyzed without further purification.

Anal. Calcd. for $C_4H_{10}N_2O$: N, 27.27. Found: 27.27, 27.40.

Benzoyl-*n*-propyl-*iso*-urea, $C_6H_5CONHC(OC_3H_7)NH$.—The impure propyl-*iso*-urea hydrochloride from 5 g. of cyanamide was converted into the benzoyl derivative by the usual method. The product was an oil which was appreciably contaminated with propyl alcohol. It was taken up in ether and treated with dry hydrogen chloride. The precipitated hydrochloride was recrystallized from alcohol. It melted at 97° with evolution of *n*-propyl chloride. The yield was good but a portion was accidentally lost and the exact yield was not determined.

Anal. Calcd. for $C_{11}H_{14}N_2O_2.HCl$: Cl, 14.73. Found: 14.92, 14.85.

IV. *n*-Butyl-*iso*-urea Hydrochloride, $NH_2C(OC_4H_9)NH.HCl$

When hydrogen chloride was passed into a butyl alcohol solution of cyanamide (5 g. in 250 cc.) a fine, white, crystalline precipitate was rapidly formed. This was found to be the dihydrochloride of cyanamide, the latter acting in the di-imide form as a diacid base. To minimize the separation of this compound, 200–300 cc. more alcohol was used and an excess of hydrogen chloride carefully avoided. The reaction mixture stood for a month before the reaction for cyanamide had disappeared. The liquid had meanwhile assumed a reddish-brown color. When the alcohol had been removed by distillation in a vacuum, a red, semi-solid mass was obtained. Attempts to purify this were fruitless, but the presence of *n*-butyl-*iso*-urea was proved by the preparation from the impure product of the *p*-nitrobenzoyl derivative.

p-Nitrobenzoyl-*n*-butyl-*iso*-urea, $NO_2C_6H_4CONHC(OC_4H_9)NH$.—The impure butyl-*iso*-urea hydrochloride was suspended in ether and treated with the required quantity of *p*-nitrobenzoyl chloride in the presence of aqueous potassium hydroxide. The ether phase yielded on evaporation a pale yellow solid. Recrystallized from ether it melted at 118°.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: N, 15.84. Found: 15.76, 15.80.

Summary

1. A number of new acyl derivatives of methyl- and ethyl-*iso*-ureas have been prepared.

2. The addition of *n*-propyl and *n*-butyl alcohols to cyanamide has been studied and the impure hydrochlorides of *n*-propyl and *n*-butyl-*iso*-ureas have been obtained. *n*-Propyl-*iso*-urea has been obtained as an oil sufficiently pure for analysis, and its benzoyl derivative prepared and analyzed as the hydrochloride. *n*-Butyl-*iso*-urea has been characterized by the preparation and analysis of its *p*-nitrobenzoyl derivative.

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