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A STUDY OF SOME UREA DERIVATIVES IN THE ALKANOLAMINE SERIES

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The monoalkyl derivatives of urea have long been known to possess hypnotic properties. While the relative effects of alkyl groups on hypnotic activity have been studied,[1] few attempts have been made to study the effects produced by the presence of substituted alkyl groups.

With this fact in mind it was decided to prepare and study some hydroxyalkyl-substituted ureas. It was to be expected that the presence of the hydroxyl group would produce a decrease in hypnotic activity as well as lower the toxicity. One of the necessary qualifications a hypnotic must have is a safe margin between the effective dose and the toxic dose, and since the presence of the hydroxyl group affects both, it was hoped that such a combination might be obtained in this way.

The starting materials for these compounds were the alkanolamines except in one case where 6-aminothymol was used. These amino compounds when treated with nitrourea yielded the corresponding hydroxyalkyl ureas.

In addition to the simple substituted ureas certain of their derivatives appeared to be of interest. The *p*-aminobenzoyl and cinnamoyl derivatives were prepared. Since many of the esters of *p*-aminobenzoic acid and cinnamic acid have local anesthetic properties, it was thought that the corresponding carbamidoalkyl esters of these two acids might have similar properties.

Two of the hydroxyalkylureas, β-hydroxyethylurea[2] and *unsym.*-di-β-hydroxyethylurea[3] had been previously prepared. The remaining hydroxyalkylureas as well as the derivatives of all of the hydroxyalkylureas represent new compounds.

EXPERIMENTAL

Preparation of the hydroxyalkylureas.—A slight excess of nitrourea[4] was added in small portions to a concentrated aqueous solution of the alkanolamine, and the

[1] DE BEER, BUCK, AND HJORT, *J. Pharmacol.*, **52**, 216, (1934).

[2] FRANCHIMONT, *Rec. trav. chim.*, **13**, 488, (1894).

[3] PRELOG, DRIZA, AND HANOUSEK, *Collection Czechoslov. Chem. Communications*, **3**, 578, (1931).

[4] DAVIS AND BLANCHARD, *J. Am. Chem. Soc.*, **51**, 1790, (1929).

solution was allowed to stand for several hours. When the reaction was completed, as evidenced by the cessation of gas evolution, the water was removed by slow evaporation on the steam bath. The crude products were purified by recrystallization from water, alcohol or dioxane. The yields obtained by this method were uniformly good, ranging from 85 to 95 per cent. Equally good yields were obtained by carrying out the reaction in 50 to 95 per cent. alcohol solution. During the course of this work Buck and Ferry[5] reported the use of alcohol as a solvent in the nitrourea method for the preparation of substituted ureas from amines.

Preparation of α-naphthylhydroxyalkylureas.—Slightly less than the theoretical amount of α-naphthyl isocyanate was added in small portions to a cold ether or dioxane suspension of alkanolamine, and the mixture was allowed to stand with occasional stirring until the odor of isocyanate was no longer noticeable. The product was filtered, washed with ether, and recrystallized from dioxane or alcohol. The yields were practically quantitative.

That the isocyanate reacted with the amino group rather than the hydroxyl group was readily established. These reactions were quite vigorous, and considerable heat was evolved. When α-naphthyl isocyanate was added to a primary alcohol, such as ethyl alcohol or ethylene chlorohydrin, a vigorous reaction did not take place. With a primary amine such as ethylamine, however, a rapid and fairly vigorous reaction resulted. From the qualitative standpoint it was not difficult to show that urethane formation was slow compared to urea formation. Finally, if the isocyanate had reacted with the hydroxyl group, the resulting product would form a hydrochloride, as it would contain a free primary amino group. This was not the case. When the isocyanate was added slowly and with stirring to the alkanolamine the resulting product was entirely the urea derivative, and no hydrochloride was obtained.

Acylation.—The hydroxyalkylurea (0.1 mole) was suspended in 200–300 cc. of dry benzene, and slightly less than the theoretical quantity (0.1 mole) of acyl chloride was added. The mixture was refluxed on the steam bath until hydrogen chloride evolution ceased. The product was separated from the benzene by decantation, and washed several times with dry benzene to remove traces of unreacted acyl chloride. Purification was accomplished by recrystallization from alcohol or dioxane. The yields of acylated product varied from 50 to 65 per cent.

The acylation of the hydroxyalkylureas proceeded smoothly in most cases, but difficulties were encountered in determining the position of acylation. These compounds contain two groups, amide and alcohol, either or both of which might be acylated. The acylated compounds were studied qualitatively for evidence which might indicate the direction of acylation. β-Hydroxyethylurea, β-hydroxy-*n*-propylurea and di-(β-hydroxyethyl)urea after being dried over phosphorus pentoxide gave marked tests with sodium in dry benzene or toluene. The dried *p*-nitrobenzoyl and *p*-aminobenzoyl derivatives, however, did not give tests under the same conditions, which would indicate that the free hydroxyl group was no longer present. Another reaction which gave confirmatory evidence for the above statement was that of ammonolysis. When the *p*-nitrobenzoyl derivatives of β-hydroxyethylurea and β-hydroxy-*n*-propylurea were treated with a solution of ammonia in dry alcohol at 100° in a pressure flask, *p*-nitrobenzamide was readily obtained. This reaction indicated the presence of an ester linkage.

Reduction of nitro compounds.—Reduction was carried out at room temperature

[5] Buck and Ferry, *ibid.*, **58**, 854, (1936).

with the nitro compound in alcoholic solution or suspension, and freshly prepared palladium black as the catalyst. The apparatus and procedure, otherwise, were essentially those of Shaefer.[6] When the reaction was complete, as indicated by the fact that the volume of hydrogen in the buret became constant, the catalyst was filtered from the alcoholic solution containing the amino compound. In some cases, heating was necessary to effect complete solution of the reduction product before filtration. The product was recovered from the filtrate by evaporation of the alcoholic solution and dilution with water. In some cases treatment with animal charcoal was necessary to obtain a colorless product. The yields, as shown by comparison of the theoretical and experimental volumes of hydrogen absorbed, were quantitative.

The preparation of hydrochlorides of these amino compounds was attempted, but the results were not uniformly successful. Dry hydrogen chloride was passed over a cold saturated alcoholic solution of the amine until no more hydrogen chloride was absorbed. The hydrochlorides were less soluble than the parent compounds, and precipitated as colorless crystals under these conditions. In general the products so obtained were not stable, could not be purified by recrystallization, and were highly hygroscopic.

Analysis.—The macro Kjeldahl method was used for the analytical determination of nitrogen in the compounds not previously prepared. Ten cc. of 10 per cent. copper sulfate solution was used as the digestion catalyst. The distillate was absorbed in 4 per cent. boric acid solution and titrated to a methyl red endpoint.[7] The analytical results reported under the individual compounds are average results based on determinations which checked within the accepted limit of error.

Molecular weights.—The Rast method of molecular weight estimation was used. With a few of the compounds, decomposition or chemical reaction occurred, rendering the method impractical.

β-Hydroxyethylurea.—This urea was previously prepared by the action of potassium cyanate on ethanolamine hydrochloride.[2] It was obtained by the nitrourea method in yields of 85 to 90 per cent. The crystalline mass was purified by recrystallization from alcohol, and finally from a large volume of dioxane. The crystals so obtained were needles which melted at 94–5° (corr.)

β-p-*Nitrobenzoxyethylurea.*—The yields of this compound varied from 50 to 55 per cent. It was purified by recrystallization from alcohol and obtained in the form of colorless needles which melted at 183–183.4° (corr.). Mol. wt.: calc'd, 253; found, 249.

That a *p*-nitrobenzoate and not a *p*-nitrobenzoylurea was formed in this reaction was further indicated in the following reactions. β-Hydroxyethylurea was suspended in dry xylene, and heated with the theoretical amount of sodium. When this reaction was complete, slightly less than the theoretical amount of *p*-nitrobenzoyl chloride was added, and refluxing was continued for several hours. The sodium chloride formed during the reaction was filtered out, and the xylene was evaporated. The resulting product after recrystallization from alcohol had the same melting point as the product prepared without the use of sodium. A mixture melting point completed the proof of the identity of the two products. While this did not give absolute proof of structure, it confirmed the qualitative evidence given earlier that benzoylation occurred on the hydroxyl group.

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[6] SHAEFER, *Ind. Eng. Chem., Anal. Ed.*, **2**, 115, (1930).

[7] MEEKER AND WAGNER, *ibid.*, **5**, 396, (1933).

β-p-*Aminobenzoxyethylurea.*—This compound was prepared in almost quantitative yields by the method outlined. The crude product was purified by recrystallization from hot dilute alcohol solution from which it crystallized in colorless needles; m.p. 203° (corr.).

Anal. Calc'd for $C_{10}H_{13}N_3O_3$: N, 18.83. Found: N, 18.63.

sym.-*α-Naphthyl-β-hydroxyethylurea.*—The yield of the symmetrical urea was practically quantitative. It was recrystallized from dioxane; colorless needles, m.p. 186° (corr.).

Anal. Calc'd for $C_{13}H_{14}N_2O_2$: N, 12.17. Found: 11.98.

Mol. wt.: calc'd, 230; found, 224.

sym.-*α-Naphthyl-β*-p-*nitrobenzoxyethylurea.*—The yields varied between 55 and 65 per cent. The crude product was recrystallized from alcohol and obtained in the form of colorless needles; m.p. 191° (corr.), with decomposition.

sym.-*α-Naphthyl-β*-p-*aminobenzoxyethylurea.*—After the catalytic hydrogenation, the alcohol solution was partly evaporated, and the product was precipitated by dilution with water. On recrystallization from alcohol the urea was obtained in almost quantitative yield in the form of fine colorless needles; m.p. 193–193.5° (corr.), with decomposition.

Anal. Calc'd for $C_{20}H_{19}N_3O_3$: N, 12.03. Found: 11.85.

Mol. wt.: calc'd, 349; found, 357.

sym.-*Cinnamoyl-β-cinnamoxyethylurea.*—This product was obtained in yields of only 50 per cent. It was purified by recrystallization from alcohol, from which it precipitated in the form of colorless needles; m.p. 173.5–174° (corr.). The monocinnamoyl derivative was expected, but a dicinnamoyl compound was always obtained even when the conditions of acylation were varied. This was shown by nitrogen analysis, molecular weight determination and quantitative hydrogenation of the double bonds in which the sample absorbed a volume of hydrogen corresponding to two double bonds, within the experimental error introduced in reading the buret.

Anal. Calc'd for $C_{21}H_{20}N_2O_4$: N, 7.69. Found: 7.64.

Mol. wt.: calc'd, 364; found, 368.

β-Hydroxy-n-*propylurea.*—This urea was obtained in yields of 85 to 88 per cent. Recrystallization from alcohol and then from dioxane yielded colorless prisms; m.p. 119° (corr.).

Anal. Calc'd for $C_4H_{10}N_2O_2$: N, 23.73. Found: 23.84.

β-p-*Nitrobenzoxypropylurea and* sym.-p-*Nitrobenzoyl-β*-p-*nitrobenzoxypropylurea.*—The yields in this case varied from 60 to 65 per cent. On recrystallization from alcohol, colorless needles of uniform appearance formed. The melting points of several preparations varied from 182 to 186° (corr.). The variation in melting point indicated a mixture, but the product could not be further purified by fractional crystallization from alcohol or dioxane. That it was a mixture was established by the fact that reduction yielded two amino compounds.

β-p-*Aminobenzoxypropylurea and* sym.-p-*Aminobenzoyl-β*-p-*aminobenzoxypropylurea.*—The alcoholic solution containing the reduction product was diluted with one-fourth its volume of water and slowly evaporated on a steam bath until crystals separated on cooling to room temperature. After several recrystallizations from alcohol this product was obtained in colorless plates; m.p. 210–211° (corr.). The analysis and molecular weight of this compound corresponded to *sym.-p*-aminobenzoyl-*β-p*-aminobenzoxypropylurea.

Anal. Calc'd for $C_{19}H_{20}N_4O_4$: N, 15.73. Found: 15.57.

Mol. wt.: calc'd, 356; found, 376.

The filtrate from the less soluble compound was further diluted with water, heated with charcoal and filtered. It was then evaporated until on cooling colorless prisms separated; m.p. 149–150° (corr.). The analysis of this compound corresponded to β-*p*-aminobenzoxypropylurea.

Anal. Calc'd for $C_{11}H_{15}N_3O_3$: N, 17.72. Found: 17.64.

Mol. wt.: calc'd, 237; found, 249.

sym.-*α-Naphthyl-β-hydroxypropylurea.*—The yields of this urea were practically quantitative. Purification was accomplished by dissolving it in hot dioxane followed by dilution with one and one-half volumes of water. The product separated in colorless needles; m.p. 162° (corr.).

Anal. Calc'd for $C_{14}H_{16}N_2O_2$: N, 11.48. Found: 11.47.

Mol. wt.: calc'd, 244; found, 245.

sym.-*α-Naphthyl-β*-p-*nitrobenzoxypropylurea.*—The yields varied from 50 to 60 per cent. The product was obtained in colorless needles by recrystallization from a large volume of dioxane; m.p. 218–221° (corr.), with decomposition. Mol. wt.: calc'd, 393; found, 370.

sym.-*α-Naphthyl-β*-p-*aminobenzoxypropylurea.*—The catalytic hydrogenation of the corresponding nitro compound did not proceed smoothly. When approximately half of the theoretical volume of hydrogen had been absorbed, the mixture set to a gel. The apparatus was disconnected, and more alcohol was added, but the hydrogenation of the remainder of the material was extremely slow. The mixture was then heated to dissolve the reduction product, and was filtered while hot. The product separated as a gel from the filtrate. After filtration it dried slowly to a hard amorphous mass. The dried material was dissolved in a hot mixture of dry benzene and dry alcohol, from which it separated, on cooling, in the form of fine needles; m.p. 171° (corr.).

Anal. Calc'd for $C_{21}H_{21}N_3O_3$: N, 11.57. Found: 11.50.

sym.-*Cinnamoyl-β-cinnamoxypropylurea.*—Cinnamoylation of β-hydroxypropylurea yielded a diacyl derivative as in the case of hydroxyethylurea. The product was obtained in yields of 50 to 55 per cent. It was recrystallized from dioxane, from which it separated in the form of colorless prisms; m.p. 179–179.5° (corr.).

Anal. Calc'd for $C_{22}H_{22}N_2O_4$: N, 7.41. Found: 7.39.

Mol. wt.: calc'd, 378; found, 380.

unsym.-*Di-(β-hydroxyethyl)urea.*—This compound had been previously prepared by Prelog, Driza and Hanousek[3] by the potassium cyanate method. Their product was a heavy, viscous liquid which they identified by means of its dibenzoate; m.p. 108°.

By the action of nitrourea on a concentrated aqueous solution of diethanolamine, this same urea was prepared in quantitative yields.

unsym.-*Di-(β*-p-*nitrobenzoxyethyl)urea.*—Nitrobenzoylation of the above urea produced two products of different melting points, crystal structures and solubilities in dioxane. The yields varied from 55 to 65 per cent. The two products were separated by means of their different solubilities in dioxane and further purified by recrystallization from alcohol, in which the solubilities were not noticeably different. The least soluble form crystallized in needles, m.p. 140–140.5° (corr.), while the more soluble form was obtained in plates, m.p. 152–153° (corr.). These two forms were hydrogenated separately and yielded the same amino compound, as shown by the melting point, mixture melting point, and analysis.

unsym.-*Di-(β*-p-*aminobenzoxyethyl)urea.*—When either form of the corresponding

nitrobenzoate or a mixture of the two forms was catalytically hydrogenated, the theoretical quantity of hydrogen was absorbed. After the removal of the catalyst, the alcohol solution was diluted with three times its volume of water, boiled with charcoal, filtered hot and cooled. The amino compound separated in colorless prisms; m.p. 172.5–172.8° (corr.).

Anal. Calc'd for $C_{19}H_{23}N_4O_6$: N, 14.51. Found: 14.54.

Mol. wt.: calc'd, 386; found, 392.

α,α-Di-(β-hydroxyethyl)-α'-(α-naphthyl)urea.—This derivative, which was obtained in practically quantitative yields, was purified by adding water to its hot alcohol solution until precipitation started. On cooling colorless prisms were formed; m.p. 126–127° (corr.).

Anal. Calc'd for $C_{15}H_{19}N_2O_3$: N, 10.22. Found: 10.06.

Mol. wt.: calc'd, 274; found, 275.

Nitrobenzoylation of the above compound was attempted, but it did not proceed smoothly, yielding a mixture of at least three products which could not be separated satisfactorily.

1,3-Dicarbamidopropanol-2.—This diurea was prepared in 85 to 90 per cent. yields by the nitrourea method. It was very soluble in water, and crystallized only after most of the water had been removed on the steam bath. Recrystallized from a little water it was obtained in colorless prisms; m.p. 86–87° (corr.).

The crystals could not be dried satisfactorily. The compound fused in the oven (with some decomposition) even at low temperatures and failed to give up its water completely over phosphorus pentoxide. Attempted molecular weight determinations were unsuccessful. The analysis indicated the probable presence of one molecule of water.

Anal. Calc'd for $C_5H_{12}N_4O_3$: N, 31.82.

$C_5H_{12}N_4O_3 \cdot H_2O$: N, 28.87. Found: 28.52.

1,3-Di-(α-naphthylureido)propanol-2.—Purification of this compound was difficult because of its relative insolubility in organic solvents. From a large volume of alcohol it separated as a gel which dried to a fine powder, definitely crystalline but of indeterminate structure; m.p. 171.5–172° (corr.).

Anal. Calc'd for $C_{25}H_{24}N_4O_3$: N, 13.08. Found: 13.12.

Mol. wt.: calc'd, 418; found, 388.

Acylation of this and the preceding urea was attempted without success. In each case a product of indefinite composition was produced.

6-Carbamidothymol.—This compound was prepared from 6-aminothymol hydrochloride,[8] by dissolving the latter in water, adding the theoretical amount of nitrourea and then slowly neutralizing with the calculated amount of sodium bicarbonate. The reaction product was washed with ether, dissolved in hot dilute alcohol, heated with animal charcoal and filtered. On cooling, the derivative crystallized in colorless silky needles; m.p. 179° (corr.).

Anal. Calc'd for $C_{11}H_{16}N_2O_2$: N, 13.46. Found: 13.55.

Mol. wt.: calc'd, 208; found, 187.

Pharmacological Results

A complete report cannot be made at this time, for the compounds have not been fully investigated. Four of the compounds of the ethanolamine series have

[8] KREMERS AND WAKEMAN, "Organic Syntheses," John Wiley and Sons, New York, **1932**, Coll. Vol., p. 498.

been studied for hypnotic action by the Merck Institute of Therapeutic Research. The hypnotic effects in the four cases examined were weak, and two of the compounds appeared to be rather toxic to white rats. The results are indicated below.

β-Hydroxyethylurea.—No effects were produced by doses of 0.1 to 4.0 grams per kilogram, given both subcutaneously and orally in water solution. This would indicate that the compound was not only much less efficient than ethylurea, but apparently weaker than urea itself.

β-p-*Aminobenzoxyethylurea.*—The only effect noticed upon subcutaneous injection of 1 gram per kilogram, in alcohol solution, was quietness; 0.5 gram per kilogram of the same solution administered orally caused a slight loss in the sense of balance of the rat. One gram per kilogram finally resulted in the death of the rat due to respiratory failure.

sym.-*α-Naphthyl-β-hydroxyethylurea.*—No symptomatic effect was produced by oral doses of 0.5 g./kg. or 2.0 g./kg. However, the rat receiving the latter dose died several hours later.

sym. -*α-Naphthyl-β*-p-*aminobenzoxyethylurea.*—No effects were produced by oral doses in glycerol of 0.2 g./kg. A dose of 2.0 g./kg., however, induced the appearance of drowsiness which lasted for some time.

SUMMARY

1. β-Hydroxyethylurea, β-hydroxy-*n*-propylurea, *unsym.*-di-(β-hydroxyethyl)urea, 1,3-dicarbamidopropanol-2 and 6-carbamidothymol were prepared by the action of nitrourea on the corresponding aminoalcohols.

2. *sym.*-α-Naphthyl-β-hydroxyethylurea, *sym.*-α-naphthyl-β-hydroxy-*n*-propylurea, α,α-di(β-hydroxyethyl)-α′-(α-naphthyl)urea, and 1,3-di-(α-naphthylureido)propanol-2 were prepared by the action of α-naphthyl isocyanate on the corresponding aminoalcohols.

3. The *p*-nitrobenzoyl and the *p*-aminobenzoyl derivatives of the following compounds were prepared: β-hydroxyethylurea, β-hydroxy-*n*-propylurea, *unsym.*-di-(β-hydroxyethyl)urea, *sym.*-α-naphthyl-β-hydroxyethylurea, and *sym.*-α-naphthyl-β-hydroxy-*n*-propylurea.

4. The cinnamoyl derivatives of the following compounds were prepared: β-hydroxyethylurea, and β-hydroxy-*n*-propylurea.

5. A preliminary pharmacological report has been included for four of the above compounds.