filtrate on acidification to a *p*H of 2.0 gave 46 g. (83.2%) of crude 1-(γ-carboxypropyl)-3-(ε-carboxypentyl)-thiourea (m.p. 96–100°).

The thiourea (10 g., 0.036 mole) was oxidized in the usual manner with sodium hypochlorite to give 7.5 g. (79.6%) of crude urea derivative (m.p. 120–155°). This crude material was subjected to triangular crystallization starting with 60 cc. of acetone–water. The least soluble material (1.45 g., m.p. 154–158°) was obtained after two crystallizations. This was crystallized again to give 1.24 g. of 1,3-di-(ε-carboxypentyl)-urea (m.p. 161–162°). The most soluble material (2.25 g., m.p. 125–130°) was dissolved in 50 cc. of 10% methanolic hydrogen chloride and methylated at room temperature overnight. The methanol was evaporated *in vacuo* at room temperature. The residue was dissolved in chloroform and the extract was washed with 5% sodium bicarbonate solution and water. The dried solution on evaporation gave a crystalline residue which, after one crystallization from benzene, yielded 1.98 g. (80%) of diester, m.p. 87–88°. It gave a depression in melting point on admixture with 1,3-di-(γ-carbomethoxypropyl)-urea (m.p. 112–113°) or 1,3-di-(ε-carbomethoxypentyl)-urea (m.p. 101–102°). The dimethyl ester melting at 88–89° was shown on analysis to be 1-(γ-carbomethoxypropyl)-3-(ε-carbomethoxypentyl)-urea.

Anal. Calcd. for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72. Found: C, 54.27; H, 8.53; N, 9.54.

A mixture of 1-(γ-carbomethoxypropyl)-3-(ε-carbomethoxypentyl)-urea and sodium hydroxide (507 mg.) in water (10 cc.) was refluxed for 30 minutes. The solution on cooling and acidification to *p*H 2.0 gave 782 mg. (86.6%) of 1-γ-carboxypropyl)-3-(ε-carboxypentyl)-urea (m.p. 127–131°). Two crystallizations from water raised the melting point to 135–136°.

Anal. Calcd. for $C_{11}H_{20}N_2O_5$: C, 50.76; H, 7.74; N, 10.77. Found: C, 50.74; H, 7.85; N, 10.94.

1,3-Di-(ω-carbethoxytetradecyl)-thiourea.—1,3-Di-(ω-carboxytetradecyl)-thiourea (0.95 g., 0.017 mole) was suspended in absolute ethanol (80 cc.) containing 1.5% hydrogen chloride and the mixture was shaken for 8 hours at room temperature. After the reaction mixture had remained standing overnight at room temperature, a small amount of insoluble material was removed by filtration. The filtrate was diluted with water (100 cc.) and the white precipitate was recovered by filtration, yield 0.90 g. (86%). The melting point was raised from 74–76° to 75–76° by crystallizing from ethanol.

1,3-Di-(ω-carbethoxytetradecyl)-urea and 1,3-Di-(ω-carbethoxydecyl)-urea.—Both 1,3-di-(ω-carbethoxytetradecyl)-thiourea and 1,3-di-(ω-carbethoxydecyl)-thiourea were converted into the corresponding urea derivatives by a process similar to that described by Kjaer, *et al.*[6] Since both compounds were prepared by the same method only the preparation of 1,3-di-(ω-carbethoxytetradecyl)-urea is given in detail.

1,3-Di-(carbethoxytetradecyl)-thiourea (305 mg., 0.00048 mole) was dissolved in hot ethanol (5 cc.) and a solution of silver nitrate (190 mg., 0.0011 mole) in 83% ethanol was added. A precipitate of silver sulfide formed immediately. The mixture was refluxed for 20 minutes after which it was filtered hot. The filtrate was diluted with several volumes of water and the precipitate was collected on a sintered glass filter, yield 255 mg. (86%). The melting point (100–102°) of the crude product was raised to a constant value of 102–103° by two crystallizations from ethanol. The purified yield was 212 mg. (71%).

1,3-Di-(ω-carboxytetradecyl)-urea.—An attempt to saponify the diethyl ester of 1,3-di-(ω-carboxytetradecyl)-urea by refluxing for 4 hours with a large excess of aqueous potassium hydroxide solution failed. The hydrolysis was accomplished successfully by dissolving the diethyl ester (520 mg., 0.0009 mole) in methyl Cellosolve (100 cc.) containing 2.5 cc. of 1.037 *N* potassium hydroxide solution and refluxing for three hours. The solution was concentrated to 20 cc., acidified with hydrochloric acid and then diluted with water (60 cc.). The precipitate (m.p. 130–133°) was removed from the cooled reaction mixture by filtration, yield 490 mg. (97%). Three crystallizations from ethanol (71.5 cc./g.) raised the melting point to 137–138°.

1,3-Di-(α-methyl-γ-carboxypropyl)-thiourea.—5-Methyl-2-pyrrolidone (12.8 g., 0.129 mole) was converted into the sodium salt of γ-aminovaleric acid which was condensed with carbon disulfide under the conditions described above for the preparation of 1,3-di-(ω-carboxyalkyl)-thioureas. However, the solution on acidification remained clear. It was concentrated *in vacuo* to 100 cc. and then placed in the refrigerator overnight. A crystalline precipitate (m.p. 148–150°) was obtained, yield 5 g.

The filtrate on concentration *in vacuo* gave an oil which was recovered by extraction with chloroform and ethyl acetate. Evaporation of the combined extracts gave an amorphous residue. This residue in water (50 cc.) was heated for 30 minutes with excess alkali. The solution was decolorized with Norite, cooled in ice and acidified with 10% hydrochloric acid solution. Removal of most of the solvent *in vacuo* gave 3.7 g. of crystals melting at 148–150°. The total yield was 8.7 g. (52%).

1,3-Di-(α-methyl-γ-carboxypropyl)-thiourea (2.2 g.) was dissolved in 40% aqueous methanol (75 cc.) at room temperature. This solution was filtered and then concentrated to half volume *in vacuo*. On cooling overnight in the refrigerator white platelets separated from the solution, yield 1.7 g. The melting point (155–156°) was not altered by repeated crystallizations.

1-(γ-Carboxypropylthiocarbamyl)-2-pyrrolidone.—A mixture of 1,3-di-(γ-carboxypropyl)-thiourea (2 g., 0.008 mole) and *p*-toluenesulfonic acid monohydrate (0.2 g.) was heated at 180–195° *in vacuo* (30 mm.) for approximately 10 minutes. After the melt cooled, it was crystallized from water (5 cc.), yield 1.09 g. (58.8%). The melting point was raised from 127–128° to 128.5–129.5° by one crystallization from acetone–water solution.

Anal. Calcd. for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.17; S, 13.92; neut. equiv., 230. Found: C, 46.51; H, 6.25; N, 12.21; S, 13.63; neut. equiv., 227.

1-(γ-Carboxypropylcarbamyl)-2-pyrrolidone.—A mixture of 1,3-di-(γ-carboxypropyl)-urea (1.0 g., 0.004 mole) and *p*-toluenesulfonic acid monohydrate (0.1 g.) was heated *in vacuo* (10 mm.) until frothing ceased. The cooled melt was dissolved in water (4 cc.). On cooling, 0.49 g. (53.2%) of crystalline product (m.p. 116.5–117.5°) was obtained. The melting point was not raised by further crystallization.

Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08; neut. equiv., 214.22. Found: C, 50.51; H, 6.51; N, 12.80; neut. equiv., 214.

VILLE LASALLE, QUEBEC, CANADA

COMMUNICATIONS TO THE EDITOR

17,20;20,21-BISMETHYLENEDIOXY STEROIDS

Sir:

The sensitivity of the dihydroxyacetone side chain of adrenocortical hormones to reagents such as lithium aluminum hydride, bromine, Grignard reagents, and strong acids and base is well known. Two methods have been generally used for protection of the side chain: (1) formation of the C_{20} dioxolane,[1] which renders the side chain inert to essentially all the above reagents except acid; (2)

(1) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953), and subsequent papers by Bernstein and co-workers summarize most of the syntheses utilizing 20-dioxolanes.

use of the $\Delta^{17,20}$-21-hydroxy group[2] as a precursor for the dihydroxyacetone chain. The latter method has been particularly useful for the synthesis of alkyl homologs of cortisone and hydrocortisone because of its applicability to base-catalyzed alkylations. Both of these methods have intrinsic limitations for some applications, however.

A new type of protecting group has been found and consists of two formaldehyde units bridging C_{17}, C_{20} and C_{21}. It results from acid-catalyzed condensation of a 17α,21-dihydroxy-20-ketopregnane with formaldehyde in the presence of a strong acid. Once formed the bismethylenedioxy function can be removed by fairly vigorous treatment with acids.

For example, 50 g. of cortisone in 2000 ml. of chloroform was stirred with 500 ml. of formalin (37% aqueous formaldehyde) and 500 ml. of concentrated hydrochloric acid for 48 hours to yield 39.5 g. of 17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione m.p. 242–250°. Similarly hydrocortisone, prednisone, prednisolone, 9α-fluorohydrocortisone (properties listed in Table I) and a number of other steroids have given bismethylenedioxy (BMD) derivatives.

TABLE I

PROPERTIES OF 17,20;20,21-BISMETHYLENEDIOXY STEROIDS

Steroid	Yield, %	M.p., °C.	$[\alpha]_D^{CHCl_3}$	C, H Calcd.	C, H Found
Cortisone BMD	70	258–261	+82	68.63 7.51	68.70 7.38
Hydrocortisone BMD	50	217–222	+26	68.29 7.97	68.01 7.97
Prednisone BMD	60	214–217	+57	68.98 7.05	68.60 7.11
Prednisolone BMD	60	270–274	−20	68.63 7.51	68.37 7.70
9α-Fluorohydrocortisone BMD	70	250–260 or 285–290	+30	65.38 7.39	65.74 6.89

In general, the BMD compounds are highly crystalline, high melting solids which are much less polar than the parent steroid as evidenced by solubility and chromatographic behavior. The molecular rotation change from the dihydroxyacetone to the bismethylenedioxy side chain is in a levorotatory direction (ΔM_D −390 to −490°). Although two stereoisomers at C_{20} are theoretically possible, one isomer has been isolated in all instances. The spiroketal grouping is quite stable to acid. For example, cortisone BMD survives 1.25 N hydrochloric acid in 50% methanol for 18 hours at 30°, or 1 N sulfuric acid in 90% methanol for 11 hours under reflux.

Removal of the bismethylenedioxy function to reform the dihydroxyacetone side chain is best accomplished with aqueous organic acids such as formic or acetic acid. Heating the BMD derivative in 60% formic acid at steam-bath temperature for ten to thirty minutes gives the parent steroid directly in 50–75% yield. Alternatively, 50% acetic acid at 100° for seven hours, followed by acetylation and chromatography, has given the corresponding 21-acetate in 50–60% yields.

These BMD derivatives have been subjected to a variety of reaction conditions without damage to the protected side chain: *e.g.*, alkylations, acylations, dioxolanations, brominations, oxidations, reductions, and acid catalyzed rearrangements. In all cases the spiroketal function remains essentially untouched. Details of these transformations will be the subject of future communications from these laboratories.

(2) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, THIS JOURNAL, **77**, 4436 (1955), and subsequent papers.

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RECEIVED FEBRUARY 13, 1958

DEMONSTRATION OF AN ATOM TRANSFER PROCESS BY ELECTRON SPIN RESONANCE[1]

Sir:

The electron spin resonance spectrum of a dilute solution of the sodium ketyl of benzophenone in 1,2-dimethoxyethane consists of more than eighty hyperfine components in a span of about 28 oersteds. While we have not yet made a complete analysis of the spectrum, we have determined by comparison with the spectra of the corresponding lithium and potassium ketyls that a splitting by the nuclear moment of Na^{23} (spin 3/2) occurs. The magnitude of this splitting is about 1 oersted or about 2.8 megacycles per second. The fact that it occurs indicates that each ketyl molecule retains its sodium atom for a time $\sim 3 \times 10^{-7}$ second or longer.

In the presence of benzophenone an exchange reaction occurs. The over-all reaction is $NaOC(C_6H_5)_2 + OC(C_6H_5)_2 = OC(C_6H_5)_2 + NaOC(C_6H_5)_2$. The question whether the reaction proceeds by transfer of sodium atoms or by separate and uncorrelated transfers of electrons and sodium ions may be answered by the electron spin resonance method. Should each unpaired electron interact with the nuclear magnetic moments of many sodium atoms as well as with the moments of many protons as the exchange reaction proceeds the resonance spectrum would collapse into a single line. On the other hand, if each electron carries its sodium nucleus with it during many exchanges (atom transfer), the spectrum would collapse into four lines, each line corresponding to one of the four possible orientations of the sodium nuclei.

In the presence of benzophenone at ~ 2 M we observe the latter possibility; the original spectrum of more than eighty lines has collapsed into four equally intense lines with separation 1.1 oersteds. Our observations are compatible with a second order rate constant for the exchange $K \geq 5 \times 10^7$ liter mole^{-1} sec.$^{-1}$. At a concentration of benzophenone ~ 2 M the mean life of each ketyl molecule $t_K \leq 10^{-8}$ second while the mean time of

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