

Soluble Steroids I

Sugar Derivatives

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Glucamine, glucosamine, and N-methylglucamine derivatives of cholesterol, testosterone, 9- α -fluorohydrocortisone, triamcinolone acetonide, and hexestrol have been synthesized in an attempt to provide compounds with increased aqueous solubility. The acylable hydroxy group of the steroid was converted to the chloroformate and then condensed with the appropriate amino sugar. In general, the derivatives which have been prepared possess 8 to 13 times the aqueous solubility of the parent compounds. The N-methylglucamine and glucosamine derivatives of triamcinolone acetonide, when applied topically, failed to show appreciable pharmacological activity.

THERE HAVE been two general methods for the preparation of water-soluble steroidal compounds. One method is by means of physical factors, that is, solubilizing agents which have been used to increase the solubility of the steroid. The second method for the preparation of water-soluble steroidal compounds has been by modification of structure. Of the many modifications that have been reported, the preparation of poly-hydroxy derivatives have been mentioned in only a few cases. Water-soluble compounds, useful as sedatives showing no hormonal activity, have been prepared by the formation of glycosides of 21-hydroxysteroids and of hemiglutarates and hemiphthalates (1, 2). A patent granted to the Upjohn Co. (3) describes physiologically active water-soluble glycoside derivatives of corticoid hormones. One of the compounds prepared was the N-methylglucamine salt of hydrocortisone-21-hemi- β -methylglutarate.

Nakagawa and Mori (4) prepared methoxy poly-(oxyethylene)-propionic acid and obtained water-soluble esters with various steroids.

Plungian (5) reported the preparation of a stable, nontoxic complex of rutin and N-methylglucamine (3:1), which retained the therapeutic properties of rutin. This complex was soluble in water to the extent of 20% and had a pH suitable for oral or parenteral preparations.

These various findings suggested then that a sugar moiety attached to a steroid nucleus might give compounds with increased water solubility. The poly-hydroxy chain would be so attached

to the steroid nucleus that it would be readily hydrolyzed in the body, a condition which would allow the free steroid to exert its full pharmacological effect. It is also possible that such derivatives should have some effect upon the absorption and distribution of the drug in the body. Thus, the present investigation is intended to make available for testing various steroids containing sugar moieties, such as glucamine, N-methylglucamine, and glucosamine.

DISCUSSION

Several methods have been reported for the preparation of amine derivatives of steroids. Pierce and co-workers (6) prepared a series of steroidal amines by direct replacement of halogen or tosylate groups with an amine group.

Heyl and Herr (7) prepared a series of C₃-(N-pyrrolidyl)-enamines (α,β -unsaturated amines) from steroidal C₃-ketones by azeotropic distillation with pyrrolidine. The enamines were readily hydrolyzable to regenerate the carbonyl function. Using this method, a model synthesis for application to steroids was attempted with cyclohexanone. Cyclohexanone was refluxed with N-methylglucamine in benzene with constant water separation. The compound prepared, N-methyl-N-(1-cyclohexenyl)-glucamine, was completely water soluble. However, when Δ^4 -cholestenone-3 was chosen as a representative steroid, the enamine was not obtained. Several modifications were also attempted without success. The reactants were refluxed in solvents other than benzene, dehydrating agents were added, the steroid was changed to testosterone, and the sugar was changed to 2,3,4,5,6-pentaacetyl-N-methyl glucamine. The application of the Leuckart reductive amination process (8) to Δ^4 -cholestenone-3 and the direct reaction of cholesteryl chloride with a sugar amine also were unsuccessful.

The report of Verdino and Schadendorf (9) that amines could be condensed with cholesterol chloroformate to give carbamates, and the finding of Miescher and Scholz (10) that carbonates of 17-estradiol had increased physiological action, suggested a second method for the attachment of amino sugars to steroids.

Cholesterol was converted to 5-cholesten-3 β -yl-chloroformate by the method of Wieland, Honold

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and Pascual-Vila (11) in quantitative yields. The chloroformate was then refluxed with N-methylglucamine in a dioxane-water mixture. The reaction was completed in 1 hour and the product, 3 β -(5-cholesten-N-methyl-N-1-(1-desoxyglucosyl)carbamate) was isolated. Carbon-hydrogen analysis on recrystallized samples of this compound repeatedly resulted in low results, and it was only after the compound had been dried 2 hours at 105–110° that a satisfactory analysis was obtained. A water analysis showed the presence of 1 mole of water per mole of compound in the sample dried at 56° *in vacuo*.

5-Cholesten-3 β -yl-chloroformate was also coupled with glucosamine, but only gave a gummy product with glucamine.

The product obtained after the treatment of 9 α -fluorohydrocortisone with phosgene contained only one chloroformyl group. Thus, it was desirable to determine the position of condensation since hydroxyl groups are present at positions 11, 17, and 21. Steric considerations make it practically impossible for reaction to occur with the 11 β -hydroxyl group. The two strong methyl:hydroxyl

repulsions and one hydroxyl:hydrogen interaction place the molecule under considerable strain. Since these factors would not be relieved by chloroformyl formation, the 11 β -hydroxyl group is practically unacylatable. In addition, an equatorial hydroxyl group is acylated more readily than an axial group at the same position and, in this case, the hydroxyl groups at the 11 and 17 positions are axial. Final evidence that the 21 position is involved was obtained when phosgene was introduced into a tetrahydrofuran solution of 9 α -fluorohydrocortisone-21-acetate and no chloroformate was obtained. Only the parent substance, the acetate, was isolated.

Triamcinolone acetonide also gave only a mono-chloroformate. However, with this compound as well as with the 9 α -fluorohydrocortisone all three sugar derivatives were obtained. The general reaction for the preparation of the sugar derivatives is summarized by the following equation and the analytical data are given in Table I.

An attempt was also made to prepare the sugar derivatives of diethylstilbestrol as it is a representative of that class of steroids and steroid-like materials which contain a phenolic hydroxyl group. The method of Crosby and Niemann (12) for the preparation of chloroformates of phenol with diethylstilbestrol gave, on one attempt, a product with the properties of a chloroformate. However, a carbon-hydrogen analysis did not agree with the calculated values for the chloroformate. Successive trials, and even modifications in the procedure as suggested by Dirschel (13) were of no avail in the preparation of the chloroformate of diethylstilbestrol.

When hexestrol, however was dissolved in aqueous sodium hydroxide and a cooled solution of phosgene in benzene was added, a good yield of 3,4-bis-(*p*-chloroformylphenyl)-*n*-hexane was obtained. Sugar derivatives of hexestrol chloroformate were then prepared in the usual manner. The hydroscopic nature of the chloroformate and sugar derivatives of hexestrol presented difficulty in obtaining analytically pure samples.

Absorption Data.—The ultraviolet spectra of the

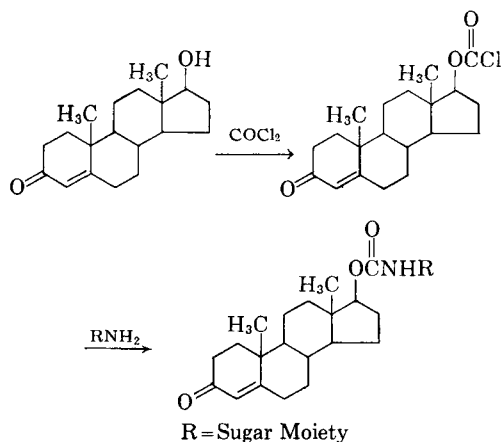


TABLE I.—CHLOROFORMATE AND SUGAR DERIVATIVES OF SELECTED STEROIDS

Compound	M.p., °C. ^a	Yield, %	Formula	Analyses, % ^b			
				Carbon		Hydrogen	
				Calcd.	Found	Calcd.	Found
Cholesterol-NMG ^c	131–133	90	C ₃₅ H ₆₁ NO ₇	69.15	68.38	10.12	9.79
			C ₃₅ H ₆₁ NO ₇ ·H ₂ O	67.16	66.98	10.15	10.14
Cholesterol-GLS ^c	155–158	63	C ₃₄ H ₅₇ NO ₇	69.00	68.70	9.71	9.53
			C ₃₄ H ₅₇ NO ₇ ·H ₂ O	67.01	67.07	9.75	9.66
Testosterone-CF ^c	110–111	95	C ₂₀ H ₂₇ ClO ₃	68.46	68.72	7.75	7.76
Testosterone-NMG	183–185	95	C ₂₇ H ₄₃ NO ₈	63.63	63.27	8.50	8.68
Testosterone-GLS	185–190 ^d	89	C ₂₆ H ₃₈ NO ₈	63.24	63.09	7.75	8.18
			C ₂₆ H ₃₈ NO ₈ ·H ₂ O	61.04	61.98	7.88	8.14
9 α -Fluorohydrocortisone-CF	159–162	95	C ₂₂ H ₂₈ ClFO ₆	59.66	59.66	6.37	6.96
9 α -Fluorohydrocortisone-NMG ^e	120 ^f	52	C ₂₉ H ₄₄ FNO ₁₁ ·H ₂ O	56.21	55.71	7.48	7.45
9 α -Fluorohydrocortisone-GLS ^e	176–178	68	C ₂₈ H ₄₀ FNO ₁₁ ·H ₂ O	55.73	55.35	7.01	6.62
9 α -Fluorohydrocortisone-GLC ^{e,g}	105–110	54	C ₂₈ H ₄₂ FNO ₁₁ ·H ₂ O	55.53	55.93	7.32	6.97
Triamcinolone acetonide-CF	165–167	90	C ₂₅ H ₃₀ ClFO ₇	60.44	60.17	6.08	5.73
Triamcinolone acetonide-NMG ^e	152 ^g	38	C ₃₂ H ₄₆ FNO ₁₂ ·H ₂ O	57.05	57.22	7.18	6.34
Triamcinolone acetonide-GLS ^e	250–255 ^d	98	C ₃₁ H ₄₂ FNO ₁₂ ·H ₂ O	56.61	56.59	6.74	6.74
Triamcinolone acetonide-GLC ^e	150 ^d	83	C ₃₁ H ₄₄ FNO ₁₂ ·H ₂ O	56.44	55.58	7.03	6.94
Hexestrol-CF	115–117	66	C ₂₀ H ₂₆ Cl ₂ O ₄	60.77	62.81	5.10	5.40
Hexestrol-NMG	80–82	28	C ₃₄ H ₅₂ N ₂ O ₁₄	57.29	59.55	7.35	7.11
Hexestrol-GLS	188–190	15	C ₃₂ H ₄₄ N ₂ O ₁₄	56.46	56.21	6.52	6.65

^a Melting points are not corrected. ^b Analyses by Weiler and Strauss, Oxford, England, and by Carol K. Fitz, Needham Heights, Mass. ^c NMG is N-methylglucamine, GLS is glucosamine, GLC is glucamine, and CF is chloroformate. ^d With decomposition. ^e These compounds possess a molecule of water which is not driven off at 105–110°. ^f Softened only. ^g With previous softening.

sugar derivatives which have been described parallel those of the parent compounds, and no new maxima are exhibited.

Several significant changes appear, however, in the infrared spectra of the derivatives in the range from 2.5 to 6.5 μ . The 2.8 or 2.9 band, which is attributed to the hydroxyl group, is not found in the spectrum of the chloroformates but is present in the sugar derivatives of cholesterol, testosterone, and hexestrol.

The carbonyl band of the chloroformyl radical exhibits a maximum between 5.60 and 5.62 μ for all of the steroids. The carbonyl band for the substituted carbamates exhibits a maximum between 5.84 and 5.90 μ . The glucosamine and glucamine derivatives also show a new band between 6.44 and 6.58 μ which is attributed to the amide II band of secondary amides or secondary carbamates. Thus, this band furnishes evidence that the sugar derivatives are carbamates and not carbonates. The characteristic maxima of all compounds are found in Table II.

Although a pure chloroformate of diethylstilbestrol was not obtained, spectral evidence was obtained for the formation of such a compound.

Solubility Studies.—Since the primary objective of this project was an attempt to prepare a series of steroidal derivatives which would have an increased solubility in water over the parent steroids, a solubility study was undertaken. Approximately 25 mg. of product was accurately weighed and placed in a 50-ml. Erlenmeyer flask which contained exactly 25 ml. of distilled water. The flask was stoppered and placed on a mechanical shaker for 24 hours at 25°. At the end of this time the contents of the flask were filtered by means of a tared sintered-glass funnel. The insoluble material which collected on the funnel was dried to constant weight in a desiccator over anhydrous calcium chloride. The funnel and the contents were then accurately weighed and the amount of product which dissolved was determined by difference. The results of this study are summarized in Table III.

It will be noted that the increase in solubility of the various sugar derivatives of the steroids follows a pattern when steroids substituted at the same position are compared. However, when a 3-hydroxy steroid is compared with a 21-hydroxy steroid, the solubilizing effect of a particular sugar moiety does not follow a pattern as would be expected. No explanation for these results is available at this time.

Preliminary Hydrolysis Study.—It was desirable to obtain information regarding the rate of hydrolysis of the sugar derivatives in order to predict their stability characteristics.

Using the N-methylglucamine derivative of cholesterol it was noted that no measureable hydrolysis occurred after 7 hours in either U.S.P. XVI simulated gastric or intestinal fluid at 37°. However, after 4 hours in solutions of 1 N sodium hydroxide and 1 N hydrochloric acid, 13% of the sugar derivative in the alkaline solution had hydrolyzed, while no hydrolysis was noted in the acid solution.

Hydrolysis was detected in the aqueous solutions by extracting them with ether and isolating the cholesterol which was released.

Preliminary Pharmacological Results.—At the present time, two of the compounds (N-methyl-

glucamine and glucosamine derivatives of triamcinolone) have been tested at the Squibb Institute for Medical Research. The steroids were assayed in adrenalectomized male rats. In liver glycogen studies the N-methylglucamine derivative was approximately 10 times as active as cortisone acetate, while the glucosamine derivative was only 2.5 times as active. In antigranuloma (pellet) and thymolytic tests, the sugar derivatives were about 0.1 as active as the parent compound. It appears from these tests that the sugar moiety stabilizes the carbamate linkage to hydrolysis with the resultant loss in activity.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

N-Methyl-N-1-(1-cyclohexenyl)glucamine.—Cyclohexanone (National Aniline), 10.0 Gm. (0.1 mole), was dissolved in 50 ml. of dried benzene. N-Methylglucamine (Aldrich Chemical Co.), 19.52 Gm. (0.1 mole), was added to the benzene solution and the resulting mixture was refluxed for 5 hours with constant water separation by means of a Bidwell-Sterling moisture trap. The insoluble material was then filtered, dried, and recrystallized from a benzene-methanol mixture. A quantitative yield of white needles which melted at 93–95° was obtained.

Anal.—Calcd. for $C_{13}H_{25}NO_5$: C, 56.7; H, 9.1. Found: C, 56.4; H, 7.9.

2,3,4,5,6-Pentaacetyl-N-methylglucamine Hydrochloride.—N-Methylglucamine hydrochloride, 15 Gm. (0.064 mole), was placed in 75 ml. of acetic anhydride, and five drops of concentrated sulfuric acid was slowly added to the mixture. The mixture was heated 2 hours on a steam bath, cooled, and refrigerated overnight. The product was precipitated from solution by the addition of several volumes of ether and was collected on a filter. The white amorphous product was washed several times with ether and stored under anhydrous conditions in a refrigerator. The product weighed 22.8 Gm. (80%) and melted at 90–92° with previous softening.

Anal.—Calcd. for $C_{17}H_{27}NO_{10} \cdot HCl$: C, 46.20; H, 6.39. Found: C, 45.29; H, 6.17.

5-Cholesten-3 β -yl-chloroformate.—This compound was prepared according to the method of Wieland, Honold, and Pascual-Vila (11). A yield of 79% was obtained which melted at 121–122°. This melting point agrees with the reported value.

3 β -(5-Cholesteryl)-N-methyl-N-1-(1-desoxyglucosyl)carbamate.—To 9 Gm. (0.02 mole) of 5-cholesten-3 β -yl-chloroformate dissolved in 100 ml. of dioxane was added 8.0 Gm. (0.04 mole) of N-methylglucamine and sufficient water to obtain a clear solution. The mixture was refluxed for 1 hour and was then cooled and refrigerated. The product was collected on a filter and recrystallized from ethanol. A yield of 11.0 Gm. of white needles was obtained which melted at 131–133°.

Anal.—Calcd. for $C_{35}H_{61}NO_7 \cdot H_2O$: H_2O , 2.88. Found: H_2O , 2.70.

3 β -(5-Cholesteryl)-N-2-(2-desoxyglucosyl)carbamate.—5-Cholesten-3 β -yl-chloroformate, 4.5 Gm. (0.01 mole), was dissolved in 60 ml. of dioxane with slight warming. D(+) Glucosamine hydro-

TABLE II.—INFRARED ABSORPTION CHARACTERISTICS

Compound	Absorption Maxima, μ^a						
Cholesterol	2.80	...	...	...	...	...	...
Cholesterol-CF ^b	...	...	5.62	...	...	...	...
Cholesterol-NMG ^b	2.86	2.96	...	5.93	...	...	...
Cholesterol-GLS ^b	2.92	...	...	5.90	...	...	6.50
Testosterone	2.90	...	...	5.95	...	...	...
Testosterone-CF	...	...	5.60	5.95	...	...	...
Testosterone-NMG	3.00	...	5.90	5.95	...	...	...
Testosterone-GLS	2.85	...	...	5.95	...	...	6.58
9 α -Fluorohydrocortisone	2.70	2.90	...	5.80	6.01	6.15	...
9 α -Fluorohydrocortisone-CF	2.75	2.85	5.60	5.80	6.03	6.18	...
9 α -Fluorohydrocortisone-NMG	...	2.90	5.80	5.90	6.02	...	...
9 α -Fluorohydrocortisone-GLS	...	2.90	5.80	...	6.08	...	6.50
9 α -Fluorohydrocortisone-GLC ^b	...	2.88	5.80	5.98	...	...	6.50
Triamcinolone acetanide	2.90	...	...	5.86	6.02	6.19	...
Triamcinolone acetanide-CF	2.82	...	5.62	5.75	6.00	6.16	...
Triamcinolone acetanide-NMG	2.92	...	...	5.84	6.02	6.16	...
Triamcinolone acetanide-GLS	2.90	...	...	5.80	6.02	6.17	6.52
Triamcinolone acetanide-GLC	2.82	...	5.72	5.92	6.08	6.16	6.45
Diethylstilbestrol	2.85	...	...	...	...	6.23	...
Diethylstilbestrol-CF	...	...	5.58	...	...	6.23	...
Hexestrol	2.90	...	...	...	6.22	6.30	...
Hexestrol-CF	...	...	5.60	...	...	6.30	...
Hexestrol-NMG	2.88	...	...	5.93	6.23	6.30	...
Hexestrol-GLS	2.93	...	...	5.88	...	...	6.44

^a All determinations were made on a Perkin-Elmer model 137 Infracord spectrophotometer. Samples were mounted as Nujol mulls. ^b CF is chloroformate, NMG is N-methylglucamine, GLS is glucosamine, and GLC is glucamine.

chloride (Nutritional Biochemicals Corp.), 4.31 Gm. (0.02 mole), was placed in 20 ml. of distilled water and 0.80 Gm. (0.02 mole) of sodium hydroxide was added. The neutralized aqueous solution of the sugar was then added to the dioxane solution, and the mixture was heated for 10 minutes on a hot plate. The mixture was then shaken for 1 hour and the precipitate which formed was collected on a filter, washed with acetone, and dried *in vacuo* at 56°. A yield of 3.75 Gm. was obtained, which melted at 155–158°.

Anal.—Calcd. for $C_{34}H_{57}NO_7 \cdot H_2O$: H_2O , 2.95. Found: H_2O , 3.26.

4 - Androsten - 3 - one - 17 β - yl - chloroformate.—To a solution of 5.0 Gm. (0.0175 mole) of testosterone (Matheson, Coleman, and Bell) dissolved in 100 ml. of benzene was added an excess of phosgene. The mixture was allowed to stand 1 hour, after which the solution was aerated for 2 hours. The

benzene was evaporated *in vacuo* and the residue recrystallized from Skelly B. A yield of 5.8 Gm. of yellow needles, which melted at 110–111°, was obtained. The melting point has previously been reported as 139–140° (14).

Anal.—Calcd. for $C_{20}H_{27}ClO_3$: C, 68.46; H, 7.75. Found: C, 68.72; H, 7.76.

17 β - (4 - Androsten - 3 - one) - N - methyl - N - 1-(1-desoxyglucosyl)carbamates.—In a manner similar to that described for the preparation of the N-methylglucamine derivative of cholesterol, using an acetone-water mixture as the solvent and a 3-hr. reflux time, there was obtained a white product. The product melted at 183–185° after recrystallization from aqueous methanol.

17 β - (4 - Androsten - 3 - one) - N - 2 - (2 - desoxyglucosyl)carbamate.—This was prepared by the procedure given for the condensation of glucosamine with cholesterol using an acetone-water solvent

TABLE III.—SOLUBILITY DATA

Compound	Solubility, ^a mg./100 ml.	Solubility Ratio ^b
Cholesterol	5.2	...
Cholesterol-NMG ^c	11.2	2.2
Cholesterol-GLS ^c	56.4	10.8
Testosterone	4.8	...
Testosterone-NMG	4.4	0.9
Testosterone-GLS	65.6	13.7
9 α -Fluorohydrocortisone	32.4	...
9 α -Fluorohydrocortisone-NMG	394.0	12.3
9 α -Fluorohydrocortisone-GLS	36.0	1.1
9 α -Fluorohydrocortisone-GLC ^c	269.6	8.3
Triamcinolone acetanide	26.4	...
Triamcinolone acetanide-NMG	319.6	12.1
Triamcinolone acetanide-GLS	37.6	1.4
Triamcinolone acetanide-GLC	354.0	13.4
Hexestrol	Insoluble ^d	...
Hexestrol-NMG	Soluble	++
Hexestrol-GLS	Slightly soluble	+

^a The solubilities of the compounds in water at 25° were determined by a gravimetric procedure following agitation for 24 hours. ^b Solubility of the derivative/solubility of the parent steroid. ^c NMG is N-methylglucamine, GLS is glucosamine, and GLC is glucamine. ^d Exact solubilities were not determined for hexestrol and its sugar derivatives due to the limited amount of material which was obtained in synthesis.

system. The product melted at 185–190°, with decomposition.

9 α - Fluoro - 11 β ,17 α - dihydroxy - 4 - pregnen - 3,20 - dione - 21 - chloroformate.—The 9 α - fluoro - hydrocortisone (E. R. Squibb and Co.) was treated with phosgene in tetrahydrofuran, as previously described, to give a waxy, light brown compound which melted at 159–162°.

21 - (9 α - Fluoro - 11 β ,17 α - dihydroxy - 4 - pregnen - 3,20 - dione) - N - methyl - N - 1 - (1 - desoxyglucosyl)carbamate.—This was prepared by the procedure given previously for N-methylglucamine derivatives. The light brown product softened at 120°.

21 - (9 α - Fluoro - 11 β ,17 α - dihydroxy - 4 - pregnen - 3,20 - dione) - N - 2 - (2 - desoxyglucosyl)carbamate.—This was prepared by the procedure given previously for glucosamine derivatives. The product melted at 176–178°.

21 - (9 α - Fluoro - 11 β ,17 α - dihydroxy - 4 - pregnen - 3,20 - dione) - N - 1 - (1 - desoxyglucosyl)carbamate.—The glucamine was prepared according to the method of Holly, *et al.* (15). The derivative was prepared by the procedure given previously for N-methylglucamine. The product after recrystallization from aqueous methanol, melted at 128–130°.

9 α - Fluoro - 11 β - hydroxy - 16 α ,17 α - isopropylidenedioxy - 1,4 - pregnadien - 3,20 - dione - 21 - chloroformate.—The triamcinolone acetonide (E. R. Squibb and Co.) was treated with phosgene in dioxane. The yellow waxy product, after recrystallization from aqueous acetone, melted at 165–167°.

21 - (9 α - Fluoro - 11 β - hydroxy - 16 α ,17 α - isopropylidenedioxy - 1,4 - pregnadien - 3,20 - dione) - N - methyl - N - 1 - (1 - desoxyglucosyl)carbamate.—This was prepared by the procedure given previously for N-methylglucamine derivatives. Purification of the product was accomplished by treating a warm acetone solution of the compound with charcoal. The yellow product, after drying for 2 hours at 110°, melted at 152° with previous softening.

21 - (9 α - Fluoro - 11 β - hydroxy - 16 α ,17 α - isopropylidenedioxy - 1,4 - pregnadien - 3,20 - dione) - N - 2 - (2 - desoxyglucosyl)carbamate.—This was prepared by the procedure given previously for glucosamine derivatives. Purification was accomplished in the same manner as described above. The product melted at 250–255°, with decomposition.

21 - (9 α - Fluoro - 11 β - hydroxy - 16 α ,17 α - isopropylidenedioxy - 1,4 - pregnadien - 3,20 - dione) - N - 1 - (1 - desoxyglucosyl)carbamate.—This was prepared according to the procedure given previously for N-methylglucamine derivatives. The product recrystallized from aqueous methanol melted at 150°, with decomposition.

3,4 - Bis - (p - chloroformylphenyl) - n - hexane.—Hexestrol, 0.54 Gm. (0.002 mole), (Nutritional Biochemicals Corp.) dissolved in 100 ml. of 2.5% aqueous sodium hydroxide was added, dropwise, to a cooled solution of 1.0 Gm. of phosgene in 75 ml. of benzene. The mixture was stirred for 3 hours at room temperature. The benzene layer was separated and was washed with two volumes of 2.5% aqueous sodium hydroxide and one volume of water. The benzene solution was dried and evaporated to give 0.52 Gm. of white crystals which melted at 115–117°.

3,4 - Bis - {p - [N - methyl - N - 1 - (1 - desoxyglucosyl)carbamoylphenyl]} - n - hexane.—This was prepared by the procedure given previously for N-methylglucamine derivatives. The syrupy residue which was obtained was dried *in vacuo* at 56°. The hygroscopic product melted at 80–82°.

3,4 - Bis - {p - [N - 2 - (2 - desoxyglucosyl)carbamoylphenyl]} - n - hexane.—This was prepared by the procedure given previously for glucosamine derivatives. Purification was effected in an acetone solution by treatment with charcoal. The product melted at 188–190°.

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