$[\alpha]^{30}D$ −3.5° (*c* 2, acetic acid) [lit.[6] mp 112–113°, $[\alpha]^{22}D$ −3.7° (*c* 2, acetic acid)].

A solution of 1.5 g of this ester in 7.5 ml of glacial acetic acid was treated with 7.5 ml of 4 *N* HBr–acetic acid and the mixture was kept at room temperature for 1 hr. Excess HBr and acetic acid were removed *in vacuo* at 20° and the residue, after washing with dry ether, was dissolved in water, treated with triethylamine to pH 8, and extracted with ethyl acetate, and the extract was worked up to give 0.8 g of L-alanyl-D-glutamic acid dibenzyl ester as an oil (R_f (A) 0.82) which was used for condensation without any further purification.

2-(1-O-Benzyl-2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-D-glucopyranosyl)acetyl-L-alanine Benzyl Ester (III).—To a stirred suspension of 100 mg of N-ethyl-5-phenylisoxazolium 3′-sulfonate (Woodward's reagent K)[7] in 10 ml of dry acetonitrile at 0°, a solution of 200 mg of I and 0.6 ml of triethylamine in 20 ml of acetonitrile was added. The mixture was stirred at 0° until a clear solution was obtained (40 min). A cold solution of benzyl alaninate (obtained by treating 155 mg of the *p*-toluenesulfonic acid salt of benzyl alaninate in 15 ml of acetonitrile with 0.05 ml of triethylamine) was added, and the mixture was stirred for an additional 1 hr at 0° and kept overnight at room temperature. The solvent was removed *in vacuo* and the residue was washed with 0.5% $NaHCO_3$ solution. The precipitate was extracted with ethyl acetate, the extract was washed successively with 0.5% Na_2CO_3, 5% citric acid, water, and saturated NaCl solution. The organic phase was dried ($MgSO_4$) and evaporated, and the residue was washed with ether and crystallized from ethyl acetate–petroleum ether or ethanol, mp 172–173°.

2-Acetamido-3-O-carboxymethyl-2-deoxy-D-glucose.—Unexpected difficulty was experienced in the hydrogenolytic splitting of the blocking groups and an aqueous medium seemed to be favorable for this step. In view of the insolubility of the blocked compounds in water removal of the blocking groups had to be carried out either stepwise, *i.e.*, first acid cleavage to remove the benzylidene group followed by hydrogenation in aqueous methanol, or in one step by carrying out the hydrogenation in a vigorously stirred mixture of ethyl acetate and water.

Method A. Stepwise Removal of Blocking Groups.—A solution of 340 mg of I in a mixture of 12 ml of glacial acetic acid and 8 ml of water was shaken in a closed flask for 2.5 hr at room temperature. The solvents were removed *in vacuo* at 60–70°, the residue was evaporated to dryness after adding water to remove the last traces of acetic acid, dissolved in glass-distilled water, and filtered. A part of the aqueous solution was lyophilized to give presumably benzyl 2-acetamido-3-O-carboxymethyl-2-deoxy-α-D-glucoside, mp 155–157° (from ethyl acetate); yield 70%.

Anal. Calcd for $C_{17}H_{23}NO_8$: C, 55.29; H, 6.23; N, 3.97. Found: C, 54.98; H, 6.20; N, 3.70.

The above aqueous solution was then hydrogenated using 10% Pd–C for 5–6 hr at ordinary temperature and pressure, the catalyst was filtered, and the aqueous phase was lyophilized to give the desired compound as a colorless hygroscopic powder.

In the case of compounds containing a benzyl ester as well, the compounds were first hydrogenated in methanol and subsequently in water.

Method B. One-Step Removal of Protecting Groups.—Compound I (300 mg) was dissolved in excess moist ethyl acetate (approx 200 ml), by warming if necessary, and 50 ml of distilled water and 0.3 g of 10% Pd–C were added. The mixture was vigorously stirred and hydrogenated at ordinary temperature and pressure until no more hydrogen was absorbed (5–6 hr). The catalyst was filtered and the aqueous phase was extracted twice with ethyl acetate. The aqueous extract was now stirred for 30 min with 4 g of Dowex 50 (H^+ form), the resin was filtered, the filtrate was lyophilized, and the residue was crystallized from a mixture of methanol–ethyl acetate. The compound was identical in all respects with that obtained by method A.

2-(2-Acetamido-2-deoxy-3-O-D-glucopyranosyl)acetyl-L-alanine (X) was prepared from III according to method B described above for the hydrogenolysis.

Acknowledgment.—We wish to express our thanks to Dr. M. L. Dhar, Director, for his interest in this work and to Mr. J. Saran and his associates for microanalyses.

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Myelographic Agents III. Glycol Iodobenzoates[1]

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In continuation of our study of contrast agents for X-ray visualization of the spinal cord, we have prepared some reverse esters (Table I) analogous to the series previously reported.[2] We were able to realize our hope that this small molecular modification would permit rapid elimination from the spinal canal. After cisternal administration into cats and dogs, the esters enabled details of the spinal canal to be visualized and were eliminated from the animals in periods ranging from a few weeks to a few months.

Experimental Section[3]

o-Iodobenzoyl chloride and sodium *p*-iodobenzoate were prepared as previously described[2] from commercially available iodobenzoic acids. Aliphatic acid chlorides, ethylene chlorohydrin, and trimethylene chlorohydrin were commercial products used as obtained. Tetramethylene chlorohydrin (Matheson Coleman and Bell) was distilled before use, bp 82–84° (11 mm), $n^{25}D$ 1.4511.

2-Hydroxyethyl acetate (Eastman Kodak Co., practical) was stirred with ice-cold 25% aqueous K_2CO_3 and the mixture was extracted with chloroform. Washing with water, drying (Na_2SO_4), removal of solvent, and distillation gave 2-hydroxyethyl acetate satisfactory for our purposes, bp 98° (23 mm), $n^{25}D$ 1.4190.

Chloroalkyl Alkanoates.—The standard reaction between an acid chloride and an alcohol was used to prepare these compounds, with the exception of 3-chloropropyl 2-methoxyacetate.[4] The latter was prepared by the toluenesulfonic acid catalyzed reaction between methoxyacetic acid and trimethylene chlorohydrin.

The reaction of hexanoyl chloride with trimethylene chlorohydrin in hexane gave a 74% yield of 3-chloropropyl hexanoate, bp 134° (23 mm), $n^{25}D$ 1.4373.

Anal. Calcd for $C_9H_{17}ClO_2$: C, 56.10; H, 8.89; Cl, 18.40. Found: C, 56.42; H, 9.07; Cl, 18.78.

1-Chloro-2-propyl Valerate.—Commercial 1-chloro-2-propanol (Matheson Coleman and Bell) was fractionally distilled through a 15-cm Vigreux column to give a forerun, bp 49–51° (28 mm), which was discarded and a colorless fraction, bp 51° (28 mm), $n^{25}D$ 1.4355. Forty-seven grams (0.5 mole) of this alcohol was added dropwise to a stirred solution of 59 ml (0.5 mole) of butyryl chloride in hexane. After evolution of HCl had subsided, the mixture was heated under reflux for 2 hr, cooled, washed with 5% $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed and the oil was fractionally distilled through a 15-cm Vigreux column to give 54.8 g (80%) of the ester, bp 110° (30 mm), $n^{25}D$ 1.4290.

Anal. Calcd for $C_8H_{15}ClO_2$: C, 53.77; H, 8.46; Cl, 19.84. Found: C, 53.54; H, 8.56; Cl, 19.80.

Method A. 2-Acetoxyethyl *p*-Iodobenzoate (1).—To a solution of 62.0 g (0.250 mole) of *p*-iodobenzoic acid in 360 ml of dimethylformamide was added 35 ml (0.25 mole) of triethylamine, followed by 30.8 g (0.252 mole) of 2-chloroethyl acetate. The brown mixture was stirred 24 hr at 115°. After cooling and removal of $Et_3N \cdot HCl$ by filtration, the mixture was poured into water and the aqueous phase was extracted with $CHCl_3$. The combined organic extract was washed successively with cold 5% K_2CO_3, H_2O, cold 3% HCl, H_2O, and saturated NaCl. Drying over Drierite, decolorizing with charcoal, and removal of solvent gave an oil which amounted to 42.8 g (51%) of **1** after distillation. This product solidified after cooling in Dry Ice.

(1) Paper II: J. H. Ackerman, V. Akullian, C. Moore, and A. A. Larsen, *J. Med. Chem.*, **9**, 165 (1966).

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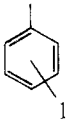
TABLE I

GLYCOL IODOBENZOATES

$COO(CH_2)_mOOC(CH_2)_nCH_3$



1

No.	Iodine position	m	n	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % I	Found, % C	Found, % H	Found, % I	$n^{25}D$
1	*p*	2	0	36.4–37.2	$C_{11}H_{11}IO_4$	39.54	3.32	37.99	39.34	3.38	38.29	
2	*o*	2	0	129–133 (0.005)	$C_{11}H_{11}IO_4$	39.54	3.32	37.99	39.75	3.09	37.83	1.5651
3	*p*	2	1	113 (0.02)	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.10	3.97	36.64	1.5594
4	*p*	2	3	120 (0.009)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.98	4.65	33.98	1.5470
5	*p*	2	4	154 (0.05)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	46.37	4.67	32.88	1.5414
6	*p*	2	5	143 (0.04)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.61	5.26	31.60	1.5368
7	*p*	3	0	44.0–45.0	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.65	3.98	36.76	
8	*p*	3	1	131 (0.02)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.42	4.36	35.52	1.5542
9	*p*	3	2	126 (0.007)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.92	4.84	34.63	1.5479
10	*p*	3	2[a]	154 (0.05)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.82	4.71	34.17	1.5450
11	*p*	3	3	129 (0.008)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	45.93	4.78	32.83	1.5420
12	*p*	3[b]	3	135 (0.009)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	46.21	4.78	32.04	1.4530
13	*p*	3	4	154 (0.05)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.43	5.21	31.73	1.5380
14	*p*	3	*c*	30.0–31.8	$C_{13}H_{15}IO_4$	41.28	4.00	33.56	41.45	4.13	33.37	
15	*p*	4	0	123 (0.02)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	42.93	4.37	35.68	1.5548
16	*p*	4	1	138 (0.04)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.51	4.38	34.39	1.5480
17	*p*	4	2	151 (0.04)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	45.89	4.97	32.69	1.5427
18	*p*	4	3	157 (0.009)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.52	5.33	31.57	1.5394
19	*p*	4	3[d]	142 (0.02)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.77	5.04	31.52	1.5362

[a] $(CH_2)_nCH_3$ = isopropyl. [b] $(CH_2)_m$ = $-CH_2CH(CH_3)-$. [c] $(CH_2)_nCH_3$ = $-CH_2OCH_3$. [d] $(CH_2)_nCH_3$ = isobutyl.

Method B. 2-Acetoxyethyl *o*-Iodobenzoate (2).—To a stirred solution of 61.0 g (0.228 mole) *o*-iodobenzoyl chloride in 350 ml of dry pyridine at 60° was added 23.9 g (0.228 mole) of 2-hydroxyethyl acetate during 5 min. The mixture was stirred on a steam bath for 5 hr. After transferring to a beaker and cooling in a salt–ice bath, 880 ml of cold 6 *N* H_2SO_4 was added dropwise. After decanting the top layer, the black aqueous phase was extracted with ether. The combined organic phase was washed successively with cold H_2O, cold 5% K_2CO_3, and saturated NaCl and dried (Drierite). Acidification of the basic washes gave 24.8 g of *o*-iodobenzoic acid. After charcoaling and removal of solvent there remained a red oil which was distilled to give 28.8 g (38%) of **2**. Taking into account recovered *o*-iodobenzoic acid the yield of **2** was 67%. An aliquot was fractionally distilled to furnish an analytical sample.

Method C. 4-Propionoxybutyl *p*-Iodobenzoate (16).—Dimethylformamide (300 ml) which had been dried over silica gel was heated to 110° and 43.2 g (0.159 mole) of finely powdered sodium *p*-iodobenzoate was added rapidly with stirring. In one portion 28.0 g (0.170 mole) of 4-chlorobutyl propionate[5] was added and stirring at 105–115° continued for 20 hr. The cooled mixture was poured into ice water and the aqueous layer was decanted from the oil and extracted with hexane. The combined organic extracts were washed successively with cold water, cold 5% K_2CO_3, cold 2% HCl, 10% $NaHSO_3$, water, and saturated NaCl. After drying over Drierite and treatment with decolorizing charcoal, the solvent was removed at reduced pressure to give 55.5 g of colorless oil. Distillation gave 46.6 g (78%) of **16**. An aliquot of the distillate was fractionally distilled to furnish an analytical sample.

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Some Quinolines Containing a Cyclic Hydroxamic Acid Group

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1,2-Dihydro-1-hydroxy-2-oxoquinolines, quinolines containing a cyclic hydroxamic acid group, exhibit antibacterial activity,[2] and the nature of substituents at positions 3 and 4 of the quinoline ring appears to influence this activity.[2c] We have synthesized a series of 3-alkyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinolines by the route outlined in Scheme I.

Attempts to convert the 3-alkyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinolines into their fully aromatic counterparts have so far failed. Where aromatization was successful it was always accompanied by deoxygenation to yield a 3-alkylcarbostyril.

Experimental Section[3]

The compounds and methods are listed in Tables I and II.

Ethyl α-Alkyl-α-*o*-nitrobenzylmalonates. Method A.—*o*-Nitrobenzyl bromide (0.0525 mole) was added over 10 min at room temperature to a stirred solution of the appropriate α-alkylmalonate (0.05 mole) and sodium ethoxide (0.05 mole) in ethanol (30 ml). The mixture was stirred for 1 hr, the solvent was evaporated *in vacuo*, and the residue was triturated with

(1) Communications regarding this paper should be addressed to the Pharmacy Department, The University of Aston in Birmingham, Gosta Green, Birmingham 4, England.

(2) (a) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948); (b) K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, *J. Chem. Soc.*, 2091 (1949); (c) W. A. Loh and E. Shaw, *J. Am. Chem. Soc.*, **71**, 70 (1949); (d) R. T. Coutts, D. Noble, and D. G. Wibberley, *J. Pharm. Pharmacol.*, **16**, 773 (1964); (e) R. T. Coutts, W. N. Pilkethly, and D. G. Wibberley, *J. Pharm. Sci.*, **54**, 792 (1965).

(3) Microanalyses by Drs. G. Weiler and F. B. Strauss of the Microanalytical Laboratory, Oxford, England.