gave the starting material (98 mg) and the less polar fraction gave a monotosylate (IVb) (66 mg), mp 203—205°. Mass Spectrum *m/e*: 598 (M^+) ($C_{37}H_{54}D_2O_4S$). IR ν_{max} cm^{-1}: 3600, 3400, 2200, 1360, 1170. NMR τ: 2.22, 2.70 (4H, A_2B_2q, J=8 Hz, aromatic protons), 4.91 (1H, t, J=3 Hz, olefinic H), 6.10, 6.48 (2H, ABq, J=9 Hz, C<u>H</u>$_2$-OTs), 6.80 (1H, q, J=6, 9 Hz, C<u>H</u>-OH), 7.56 (3H, s, aryl-CH_3), 8.90—9.44 (6×CH_3).

***β*-Amyrin-23,23-d_2 (Va)**——A mixture of the monotosylate (IVb) (66 mg), NaI (90 mg), and abs. acetone (3 ml) was heated in a sealed tube at 160° for 37 hr. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with dil. Na_2CO_3, dried ($MgSO_4$), and evaporated. Purification of the residue by preparative TLC afforded an iodide (IVc) (47 mg). IR ν_{max} cm^{-1}: 3600, 3400, 2260. NMR τ: 4.75 (1H, t, J=3 Hz, olefinic H), 6.64, 6.99 (2H, ABq., J=10 Hz, C<u>H</u>$_2$I), 6.80 (1H, q, J=6, 9 Hz, C<u>H</u>-OH), 8.84—9.21 (6×CH_3).

The above iodide (IVc) (47 mg) was then hydrogenated over W-2 Raney nickel (1.2 g) in EtOH (5 ml) at room temperature and atmospheric pressure, until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue (35 mg) was separated by preparative TLC (Merck Kieselgel GF_{254} impregnated with silver nitrate) and then recrystallized from CH_2Cl_2–MeOH to afford colorless needles (Va) (28 mg), mp 198—200°. $[\alpha]_D^{22}$ +88° (c=0.96, $CHCl_3$). Mass Spectrum *m/e*: 428 (M^+) ($C_{30}H_{46}D_2O$). IR ν_{max} cm^{-1}: 3600, 3450, 2200. NMR τ: 4.81 (1H, t, J=3.5 Hz, olefinic H), 6.79 (1H, q, J=6, 9 Hz, C<u>H</u>-OH), 8.86—9.21 (7×CH_3).

***β*-Amyrin Acetate-23,23-d_2 (Vb)**——A solution of Va (28 mg) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was left stand overnight at room temperature. Working up of the mixture in the usual manner afforded a crystalline product (30 mg), which was recrystallized from CH_2Cl_2–MeOH to give β-amyrin acetate-23,23-d_2 (Vb) (18 mg) as colorless needles, mp 243—244°. $[\alpha]_D^{20}$ +70° (c=1.02, $CHCl_3$). Mass Spectrum *m/e*: 470 (M^+) ($C_{32}H_{48}D_2O_2$). IR ν_{max} cm^{-1}: 1720, 2200, 1250. NMR τ: 4.81 (1H, t, J=3 Hz, olefinic H), 5.49 (1H, q, J=6, 9 Hz, C<u>H</u>-OAc), 7.95 (3H, s, Ac), 8.86—9.16 (7×CH_3).

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Studies on Peptides. XXXV.[1,2] Some *p*-Methoxybenzyloxycarbonyl-Amino Acid Derivatives

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Recently we published a new procedure for the preparation of Z(OMe)-amino acids utilizing *p*-methoxybenzyl mixed carbonates.[4] From the practical standpoint, *p*-methoxybenzyl-8-quinolyl carbonate has a superior property to the others. We now have modified the procedure for the preparation of this carbonate, with which we have been able to produce a number of Z(OMe)-amino acids, including some new derivatives in fairly good yield, except for histidine derivatives. For the preparation of the latter derivatives, the classical azide procedure[5] is preferable because of the easiness with which it renders to purification. In this report, we wish to record physical data of these new derivatives.

For the detection of Z(OMe)-derivatives, spraying with 10% $SbCl_5$ in chloroform,[6] besides $Ce(SO_4)_2$,[4] is convenient, since it gives specific red-purple color for these derivatives on thin-layer plate.

1) Part XXXIV: H. Yajima and K. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 682 (1973).
2) Amino acids and their derivatives mentioned here are of the L-configuration. Abbreviation: Z(OMe)=*p*-methoxybenzyloxycarbonyl.
3) Location: *Sakyo-ku, Kyoto.*
4) H. Yajima, F. Tamura and Y. Kiso, *Chem. Pharm. Bull.* (Tokyo), **18**, 2574 (1970).
5) F. Weygand and K. Hunger, *Chem. Ber.*, **95**, 1 (1962).
6) K.G. Krebs, D. Heusser and H. Wimmer "Thin-Layer Chromatography," ed. by E. Stahl, Springer-Verlag, Berlin, 1969, p. 858.

Experimental

***p*-Methoxybenzyl-8-quinolyl Carbonate**——The solvent, tetrahydrofuran, used previously for the preparation of this reagent[4] was replaced by ether and AcOEt. By this minor modification, the procedure was simplified. The entire operation was performed under cooling with ice-NaCl. A solution of *p*-methoxybenzyl alcohol (74 ml, 0.6 moles) in dry ether (200 ml) was added with stirring to a solution of phosgen (60 g, 0.6 moles) in ether (100 ml) during a period of 30 min. After stirring was continued for 30 min, dry nitrogen gas was bubbled through the reaction mixture for 30 min and then 8-hydroxyquinoline (87 g, 0.6 moles) in AcOEt (600 ml) was added. To this solution, triethylamine (168 ml, 1.2 moles) in AcOEt (100 ml) was added dropwise over a period of 1 hr. The reaction was continued for an additional 1 hr with stirring. After addition of water, the organic phase was washed successively with 10% citric acid and NaCl-H_2O, dried over Na_2SO_4 and then evaporated. The resulting solid was recrystallized from EtOH; yield 156 g (85%), mp 92—94°. Identity of the product with the authentic sample was confirmed by comparison of their infrared (IR) spectra.

Z(OMe)-Amino Acids——The Z(OMe)-amino acids listed in Table I, except for histidine derivatives, were prepared according to the procedure of Z(OMe)-Ala-OH.[4] The product was recrystallized from appropriate solvents or converted to the corresponding dicyclohexylamine (DCHA) or cyclohexylamine (CHA) salts.

Table I. Z(OMe)-Amino Acid Derivatives

Z(OMe)-	Recryst. solvent	Yield (%)	mp (°C)	$[\alpha]_D^{19}$		Formula	Analysis (%) Calcd. (Found) C	H	N
Trp	AcOEt–pet. ether	64	115—117	− 9.9	c=1.2 MeOH	$C_{20}H_{20}O_5N_2$	65.21 (65.51)	5.47 (5.50)	7.61 (7.40)
Tyr DCHA	EtOH–ether	90	134—137	+25.2	c=1.0 MeOH	$C_{18}H_{19}O_6N \cdot C_{12}H_{23}N$	68.41 (68.56)	8.04 (8.25)	5.32 (5.07)
Arg(Tos)	ether–pet. ether	89	128—130	− 4.5	c=1.3 MeOH	$C_{22}H_{28}O_7N_4S$	53.64 (53.42)	5.73 (5.88)	11.78 (11.41)
Arg(Tos) CHA	MeOH–ether	66	130—134	+ 3.8	c=1.0 MeOH	$C_{22}H_{28}O_7N_4S \cdot C_6H_{13}N$	56.83 (56.58)	6.98 (6.87)	11.83 (11.85)
Lys(Z)[a]	AcOEt–pet. ether	76	80— 82	− 8.1	c=0.9 MeOH	$C_{23}H_{28}O_7N_2$	62.15 (62.40)	6.35 (6.59)	6.30 (6.02)
Lys(For)	AcOEt–ether	78	97— 99	− 6.4	c=1.2 MeOH	$C_{16}H_{22}O_6N_2$	56.79 (56.65)	6.55 (6.77)	8.28 (8.23)
Lys(Tos) DCHA	Aceton–ether	87	141—144	+ 5.2	c=0.8 MeOH	$C_{22}H_{28}O_7N_2S \cdot C_{12}H_{23}N \cdot H_2O$	61.51 (61.78)	8.05 (8.01)	6.33 (6.33)
His(Bzl)	MeOH	73	216—219	+13.4	c=1.1 DMF	$C_{22}H_{23}O_5N_3 \cdot H_2O$	61.81 (61.85)	5.90 (5.66)	9.83 (9.58)
His(Tos) DCHA	$CHCl_3$–AcOEt	77	165—166	+12.9	c=0.8 MeOH	$C_{22}H_{23}O_7N_3S \cdot C_{12}H_{23}N \cdot H_2O$	60.69 (60.98)	7.19 (7.14)	8.33 (8.50)
His–$NHNH_2$	EtOH	67	192—195	−24.7	c=0.9 0.1N HCl	$C_{15}H_{19}O_4N_5$	54.05 (54.20)	5.75 (5.80)	21.01 (21.04)

a) Lit. oil.[5] Tos=tosyl, Z=benzyloxycarbonyl, For=formyl, Bzl=benzyl, DMF=dimethylformamide

Z(OMe)-His(Bzl)-OH——This derivative was prepared by using *p*-methoxybenzyl azidoformate according to Weygand and Hunger.[5] Instead of MgO, two moles of triethylamine were employed during the acylation reaction of H-His(Bzl)-OH. After reaction, the solvent was neutralized with AcOH and the solvent was evaporated. Tritulration of the residue with chilled H_2O gave solids, which were further purified by recrystallization.

Z(OMe)-His(Tos)-OH·DCHA Salt——To a solution of H-His-OH hydrochloride monohydrate (10.5 g) in H_2O (50 ml), triethylamine (28 ml) and *p*-methoxybenzyl azidoformate (20.7 g) in dioxane (50 ml) were added and the mixture was stirred at room temperature for 72 hr. Formation of two products was detected by thin-layer chromatography (*Rf* 0.46 and 0.29 in the solvent system of chloroform: MeOH: H_2O=40: 15: 5 v/v). The solvent was evaporated and the residue was dissolved in 1 N Na_2CO_3, which after washing with ether, was stirred at room temperature for 3 hr to cleave the N^{im}-Z(OMe) moiety partially formed by the above azidoformate. During this treatment, one spot, *Rf* 0.46, disappeared. According to Sakakibara and Fujii,[7] to this ice-chilled solution, *p*-toluene sulfonic chloride (19 g) in dioxane (70 ml) was added over a

7) S. Sakakibara and T. Fujii, *Bull. Chem. Soc. Japan*, **42**, 1466 (1969).

period of 1 hr, while the solution was maintained at pH 8 by addition of 1 N Na_2CO_3. After stirring for an additional 2 hr, the solution was washed with ether and then acidified with 10% citric acid. The resulting precipitate was extracted with AcOEt, which was washed with H_2O-NaCl, dried over Na_2SO_4 and then evaporated. The oily residue was converted to the corresponding DCHA salt in the usual manner; yield 25.0 g.

Z(OMe)-His-NHNH$_2$——*p*-Methoxybenzyl azidoformate (6.8 g) was added to a mixture of H-His-OMe hydrochloride (5.7 g) and triethylamine (4.1 ml) in chloroform (60 ml) and the solution was stirred at room temperature for 48 hr. The chloroform solution was washed with ether, dried over Na_2SO_4 and then evaporated. The residue was dissolved in EtOH and 90% hydrazine hydrate (5 ml) was added. The solid formed on standing overnight was recrystallized from EtOH; yield 6.7 g.

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Alkylated Pyrimidine Derivatives as Antiviral Agents. III.[1] Synthesis and Antiviral Effect of 5-Ethyluracil Nucleosides

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In the previous papers,[1,3] the authors have described that 5-ethyluracil (EU), 5-butyluracil (BU), 5-ethyluracil-1-β-D-ribofuranoside (EUR) and 5-butyluracil-1-β-D-ribofuranoside (BUR) exerted the inhibitory effect on Mahoney strain of poliomyelitis virus and type-1 strain of adeno virus and that the nucleosides of 5-alkyluracil were found to exert the effect more markedly than the free base on the viruses.

On the other hand, it has been reported that 5-ethyldeoxyuridine was the effective inhibitor for herpes simplex virus[4] and for vaccinia virus.[5]

On the basis of these findings, it is of interest to search for more effective antiviral agents by preparing additional 5-ethyluracil nucleoside analogues.

This paper is concerned with the synthesis and antiviral effect of 5-ethyluracil-1-β-D-galactopyranoside (EUGa) and 5-ethyluracil-1-β-D-xylopyranoside (EUXp).

According to the synthetic method of Fox,[6] EUGa and EUXp were prepared by the condensation of the mercury salt of 5-ethyluracil with corresponding tetra-O-acetyl-α-D-galactopyranosyl bromide[7] and tri-O-acetyl-α-D-xylopyranosyl bromide,[8] respectively. The deacetylation of the resulting 1-(tetra-O-acetyl-β-D-galactopyranosyl)-5-ethyluracil and 1-(tri-O-acetyl-β-D-xylopyranosyl)-5-ethyluracil with sodium methoxide gave the objective nucleosides EUGa and EUXp in 80—95% yield.

The antiviral effect of EUGa and EUXp were surveyed on the Mahoney strain of poliomyelitis virus, belonging to RNA virus and the type-1 of adeno virus, belonging to DNA virus in the Hep. No. 2 cells system.

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1) Part II: M. Muraoka, Y. Seto and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **18**, 269 (1970).
2) Location: *a) 2-8-1, Mejirodai, Bunkyo-ku, Tokyo; b) Shirogane Sanko-cho, Minato-ku, Tokyo.*
3) M. Muraoka, A. Takada and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **18**, 261 (1970).
4) K.K. Gauri and G. Malorny, *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.*, **257**, 21 (1967).
5) M. Swierkowski and D. Shugar, *J. Am. Med. Chem.*, **12**, 533 (1969).
6) J.J. Fox, N. Yung, J. Davoll and G.B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).
7) L.J. Haynes and A.R. Todd, *J. Chem. Soc.*, 1950, 303.
8) C.S. Hudson and J.M. Johnson, *J. Am. Chem. Soc.*, **37**, 2751 (1915).