New Compounds

Some Aminoacyl Derivatives of Amino Sugar Nucleosides

HERBERT A. FRIEDMAN

Department of Pharmacology, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania 19104

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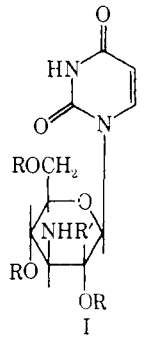
It was recently reported[1] that amino acids could be condensed with amino sugar nucleosides to give the corresponding aminoacyl derivatives. In the quest for new potential nucleoside antibiotics the L-Lys and the L-Glu-γ-Me ester derivatives of 1-(3-amino-3-deoxy-β-D-glucopyranosyl)uracil were prepared. Their syntheses are given below.



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a, R = Ac; R′ = H
b, R = Ac; R′ = Cbo-L-Glu-γ-Me ester
c, R = OH; R′ = Cbo-L-Glu-γ-Me ester
d, R = OH; R′ = L-Glu-γ-Me ester
e, R = OH, Ac, Ac; R′ = di-Cbo-L-Lys
f, R = OH, Ac, Ac; R′ = L-Lys

Cbo = $C_6H_5CH_2OCO$

Experimental Section[2]

1-(3-*N*-Carbobenzoxy-L-glutamylamido-γ-methyl Ester 3-Deoxy-2′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)uracil (Ib).—1-(3-Amino-3-deoxytri-*O*-acetyl-β-D-glucopyranosyl)uracil·HCl[3] (Ia·HCl) (1.2 g, 2.9 mmoles) was added to 7 ml of dry $CHCl_3$. Soln took place upon the addition of 0.81 ml (5.8 mmoles) of Et_3N. A second soln was prepd containing *N*-Cbo-L-Glu-γ-Me ester[4] (856 mg, 2.9 mmoles), Et_3N (0.41 ml, 2.9 mmoles), and $CHCl_3$ (8 ml). Both solns were cooled to 0° in an ice bath. Methyl chloroformate (0.22 ml, 2.9 mmoles) was added to the second soln, and the mixture was stirred for 20 min at 0°. The soln contg the nucleoside was added to the mixed anhydride, and the mixture was stirred for an additional 15 min at 0° followed by overnight stirring at room temp. The soln was extd with 0.2 *N* HCl, followed by a satd soln of $NaHCO_3$ and finally with H_2O contg a few crystals of NaCl (to discourage emulsion formation). The $CHCl_3$ layer was dried ($MgSO_4$) and evapd *in vacuo*. Trituration of the residue with cyclohexane–$CHCl_3$ (10:1) yielded partially cryst material (450 mg, 23%). It had an indefinite melting point beginning at 105°. Silica gel tlc ($CHCl_3$–MeOH, 5:1) indicated one spot with a slight trace of impurity. *Anal.* ($C_{30}H_{36}N_4O_{14}$) C, H, N.

1-(3-*N*-Carbobenzoxy-L-glutamylamido-γ-methyl Ester 3-Deoxy-β-D-glucopyranosyl)uracil (Ic).—Compound Ib (450 mg) was added to 15 ml of anhyd MeOH. Following the addition of 7 mg of anhyd LiOH the soln, protected from moisture, was allowed to stir for 26 hr at room temp. Li ion was removed by the addition of a small amt of Dowex 50 (H^+) resin and stirring the slurry for 1 hr. Silica gel tlc ($CHCl_3$–MeOH, 5:1) indicated one major component along with a trace of impurity. The compd had an indefinite melting point, yield 320 mg (85% based on Ib). *Anal.* ($C_{24}H_{30}N_4O_{11}\cdot H_2O$) C, H, N. The H_2O presumably came from the resin.

1-(3-*N*-L-Glutamylamido-γ-methyl Ester 3-Deoxy-β-D-glucopyranosyl)uracil (Id).—Compd Ic was prepd without the isolation of Ib and was dissolved in 80% aq MeOH. The soln pH was maintained at *ca.* 1 by adding HCl during hydrogenolysis (10% Pd–C). The product, a tan-colored compd, was isolated by filtration of the catalyst and evapn of the supernatant soln. Recrystn from *n*-PrOH gave a compd in a yield of 280 mg (19% based on Ia). The melting point was of no value as shrinking began at *ca.* 60° and continued slowly with rising temp. Silica gel tlc (*t*-BuOH–MEK–H_2O–NH_4OH 4:3:2:1) indicated minor impurities similar to those found prior to purification. *Anal.* ($C_{15}H_{22}N_4O_9\cdot HCl\cdot C_3H_7OH\cdot H_2O$) C, N; H: calcd, 6.43; found, 5.63.

1-(3-*N*,*N*′-Dicarbobenzoxy-L-lysylamido-3-deoxydi-*O*-acetyl-β-D-glucopyranosyl)uracil (Ie).—The prodedure followed was similar to that for Ib and Ic except that *N*,*N*′-di-Cbo-L-Lys[5] was used. During the deacetylation reaction with LiOH a ppt developed which was filtered and washed well with Et_2O; yield 18% (based on Ia), mp 110–125°. Silica gel tlc ($CHCl_3$–MeOH, 5:1) indicated a pure compd. *Anal.* ($C_{36}H_{43}N_5O_{13}\cdot CH_3OH$) C, H; N: calcd, 8.92; found 8.43. The results indicate that only one acetate group was removed during the deacetylation reaction, the resultant diacetoxy compd being insol. Prolonged reaction times with increased amts of LiOH did not change the results according to tlc. The position of deacetylation remains uncertain.

1-(3-L-Lysylamido-3-deoxydi-*O*-acetyl-β-D-glucopyranosyl)uracil Dihydrochloride (If).—The procedure followed was similar to that for Id except that EtOH was used for trituration; white solid, yield 67% (based on Ie); mp 196–203°. *Anal.* ($C_{18}H_{31}N_5O_9\cdot 2HCl\cdot 0.5H_2O$) C, H; N: calcd, 12.89; found, 12.30.

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(5) National Biochemicals Corp., Cleveland, Ohio

Heterocyclic *N*-Carboxamides as Anticonvulsants

GIANFRANCO PALA,* ARTURO DONETTI, ANTONIO MANTEGANI, AND AMEDEO OMODEI SALÉ

Research Laboratories of Istituto De Angeli, Milan, Italy

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In view of the potent anticonvulsant activity of carbamazepine,[1] three new heterocyclic *N*-carboxamides were synthesized. Anticonvulsant tests have shown that only 1-carbamyl-2,3-diphenylaziridine (**4**) is active, even though its potency was found to be distinctly inferior to that of carbamazepine.

(1) H. A. Friedman, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, **32**, 3775 (1967).

(2) Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorr. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(3) K. A. Watanabe, and J. J. Fox, *Chem. Pharm. Bull.*, **12**, 975 (1964); K. A. Watanabe, J. Beranek, H. A. Friedman, and J. J. Fox, *J. Org. Chem.*, **30**, 2735 (1965).

(4) Mann Research Laboratories, New York, N.Y.

* To whom correspondence should be addressed.

(1) W. Theobald and H. A. Kunz, *Arzneim.-Forsch.*, **13**, 122 (1963).

Experimental Section[2]

5,6-Dihydro-7*H*,12*H*-6-carbamyldibenz[*c*,*f*]azocine (1).—A soln of KCNO (3.57 g, 0.044 mole) in H_2O (55 ml) was added to a soln of 5,6-dihydro-7*H*,12*H*-dibenz[*c*,*f*]azocine·HCl[3] (10.8 g, 0.044 mole) in H_2O (6500 ml). After 15 days stirring at room temp, the reaction mixture afforded, when concd, a solid which was recrystd from EtOH to give 1 (6.6 g, 59.4%) as colorless crystals, mp 237–239°. *Anal.* ($C_{16}H_{16}N_2O$) C, H, N.

5,7,12,13-Tetrahydro-6-carbamyldibenz[*c*,*g*]azonine (2).—Compound **2** was obtained similarly in 73.2% yield from 5,7,12,13-tetrahydro-6*H*-dibenz[*c*,*g*]azonine·HCl[4] (12 g, 0.046 mole) and KCNO (3.75 g, 0.046 mole) in H_2O (2000 ml). Colorless crystals from 95% EtOH, mp 194–196°. *Anal.* ($C_{17}H_{18}N_2O$) C, H, N.

1-Cyano-2,3-diphenylaziridine (3).—A soln of BrCN (20.36 g, 0.19 mole) in Et_2O (80 ml) was dropped at 0–5° for 20 min into a soln of *cis*-2,3-diphenylaziridine[5] (31.2 g, 0.16 mole) and Et_3N (19.4 g, 0.19 mole) in Et_2O (400 ml). The mixture was stirred for 4 hr at room temp and then filtered, the cake was repeatedly washed with Et_2O, and the combined filtrates were evapd to dryness. The residue was taken up with hexane and filtered to give **3** (33 g, 94%) as a colorless solid, mp 116–117°. *Anal.* ($C_{15}H_{12}N_2$) C, H, N.

1-Carbamyl-2,3-diphenylaziridine (4).—A mixture of **3** (41.3 g, 0.187 mole), NaOH (75 g), H_2O (130 ml), and dioxane (950 ml) was stirred for 7 days at room temp and then for 24 hr at 50°. The resulting cloudy soln was evapd to dryness under reduced pressure, and the residue was taken up with H_2O and little Et_2O and then recrystd from C_6H_6 to give **4** (11.2 g, 25%) as colorless crystals, mp 158–160°. *Anal.* ($C_{15}H_{14}N_2O$) C, H, N.

(2) Melting points are corrected and were taken on a Büchi capillary melting point apparatus. All compounds were analyzed for C, H, N and anal. results were within ±0.4% of the theoretical values.

(3) G. Pala, A. Mantegani, and E. Zugna, *Tetrahedron*, **26**, 1275 (1970).

(4) G. Pala, E. Crescenzi, and G. Bietti, *ibid.*, in press.

(5) A. Weissberger and H. Bach, *Chem. Ber.*, **64B**, 1095 (1931).

Some Derivatives of 7-Oxabicyclo[2.2.1]heptane-*exo*-*cis*-2,3-dicarboxylic Acid

Samuel J. Dominianni* and Ronald L. Young

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

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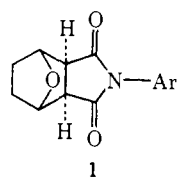
Recently some 7-oxabicyclo[2.2.1]heptane-2,3-dicarboximides (**1**) with anticonvulsant activity were described.[1] Some aryloxyethyl esters **2** were also reported[2] as plant growth regulators. We record herein the preparation of additional examples of **1** and of some mono esters **3**, all of which proved to be highly toxic CNS depressants (Table I).



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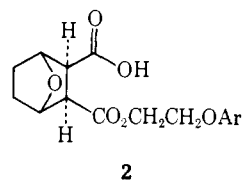
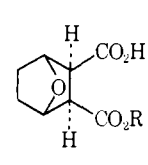


2



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Experimental Section

***N*-Fluoroarylimides. 1.**—A mixture of equimolar amts of 7-oxabicyclo[2.2.1]heptane-*exo*-*cis*-2,3-dicarboxylic anhydride and the appropriate fluoroaniline was heated without solvent at 150° for 1–2 hr. The cooled residue was then recrystd from EtOH.

Monoesters. 3.—A mixture of anhydride and the appropriate alcohol was heated at 125° for 1–2 hr. The cooled residue was extd with aq Na_2CO_3 and the aq extracts were acidified with HCl. The ppt was collected, washed with H_2O, dried, and recrystd from an appropriate solvent, usually C_6H_6–Skelly B.

The *i*-Pr deriv **3a** was prepared by refluxing the anhydride in *i*-PrOH containing pyridine.

Table I

Compd	R or Ar	Formula[a]	Mp,[b] °C	Approx[c] LD, mg/kg
1a	*o*-FC_6H_4	$C_{14}H_{12}FNO_3$	135–137	1000
1b	*m*-FC_6H_4	$C_{14}H_{12}FNO_3$	136–138	300
1c	*p*-FC_6H_4	$C_{14}H_{12}FNO_3$	168–169	300
3a	$(CH_3)_2CH$	$C_{11}H_{16}O_5$	127–129	300
3b	*o*-$CH_3OC_6H_4CH_2$	$C_{16}H_{18}O_6$	98–100	30
3c	*m*-$CH_3OC_6H_4CH_2$	$C_{16}H_{18}O_6$	127–128	30
3d	*p*-$CH_3OC_6H_4CH_2$	$C_{16}H_{18}O_6$	110–112	10
3e	$C_6H_5CH_2$	$C_{15}H_{16}O_5$	122–124	30
3f	*m*-$ClC_6H_4CH_2$	$C_{15}H_{15}ClO_5$	143–145	30
3g	*p*-$ClC_6H_4CH_2$	$C_{15}H_{15}ClO_5$	158–160	30
3h	*p*-$FC_6H_4CH_2$	$C_{15}H_{15}FO_5$	135–136	10
3i	3,4-$(OCH_2O)C_6H_3CH_2$	$C_{16}H_{16}O_7$	145–147	10

[a] All new compounds described gave elemental analyses for C and H within ±0.4% of the calculated values. Ir and nmr spectra were also in agreement with the assigned structures; in particular, the nmr spectra confirmed the assignment of exo-cis stereochemistry.[1] [b] Uncorr; recorded on a Mel-Temp apparatus. [c] Dose at which fatalities occurred; compds were administered ip to mice.

* To whom correspondence should be addressed.

(1) E. R. Bockstahler, L. C. Weaver, and D. L. Wright, *J. Med. Chem.*, **11**, 603 (1968).

(2) V. A. Kraft and N. N. Mel'nikov, *Biol. Aktivn. Soedin.*, 255 (1965); *Chem. Abstr.*, **64**, 673*g* (1966).

Potential Antidiabetics. 7. N^1-(β-Hydroxybenzylmethyl)-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones and N^1-(β-Hydroxybenzylmethyl)-3-methyl-4-arylazo-5-methyl- or -phenylpyrazoles

H. G. Garg and Chandra Prakash

Department of Chemistry, University of Roorkee, Roorkee, India

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A few pyrazoles and related compounds appear to give promising results in antidiabetic tests[1,2] and, therefore, further combinations seem worthwhile studying. This paper describes the synthesis of N^1-(β-hydroxybenzylmethyl)-3-methyl-4-arylhydrazono-2-pyrazolin-5-ones and N^1-(β-hydroxybenzylmethyl)-3-methyl-4-arylazo-5-methyl- or -phenylpyrazoles and also includes the hypoglycemic activity of 3-methyl-4-arylazo-5-phenylisoxazoles.[2]

Biological Results.—On oral administration at various doses (25–100 mg/kg) in fasted guinea pigs for 18 hr prior to and during testing, 4-phenylazo-, 4-(2-nitrophenylazo)-, 4-(3-nitrophenylazo)-, 4-(2-methylphenylazo)-, 4-(2-methoxyphenylazo)-, 4-(3-methoxyphenylazo)-, 4-(4-ethoxyphenylazo)-, 4-(2,5-dichlorophenylazo)-, and 4-(2,6-dichlorophenylazo)-3-methyl-5-phenylisoxazoles essentially displayed no hypoglycemic activity as compared with chloropropamide. After a predetermined time of peak effect the blood was ana-

(1) H. G. Garg, D.Sc. Thesis, Agra University, India (1969).

(2) H. G. Garg and P. P. Singh, *J. Med. Chem.*, **13**, 1250 (1970), and ref cited therein.