hydro-1-[2-(*N*-ethyl-*N*-hydroxy)aminoethyl]-2*H*-1,4-benzodiazepin-2-one (7). A mixture of 30 g of **3a** in 150 ml of toluene was heated to reflux for 15 min. The solvent was evaporated under reduced pressure and the residue was chromatographed over 600 g of silica gel. Elution with a 1:1 mixture of EtOAc and CH_2Cl_2 yielded 12.5 g (57.5%) of the vinyl derivative **6a**, which crystallized from hexane–Et_2O: mp 89–90°; nmr ($CDCl_3$) δ 3.94 (d, 1) and 4.89 (d, 1) (AB system, J = 11 Hz, C_3-H), 4.7 (m, 2, $=CH_2$), 6.8–8.0 ppm (m, 8, –CH= and arom H). *Anal.* ($C_{17}H_{12}ClFN_2O$) C, H, N.

The second more polar product was eluted with EtOAc. Crystallization of the combined clean fractions from Et_2O yielded 4 g (15.5%) of the hydroxylamine **7** with mp 132–133°: nmr ($CDCl_3$) δ 0.83 (t, 3, J = 7 Hz, CH_3), 2.52 (q, 2, J = 7 Hz, $-CH_2CH_3$), 2.66 [m, 2, $-N(OH)CH_2-$], 3.76 (d, 1) and 4.83 (d, 1) (AB system, J = 10.5 Hz, C_3-H), *ca.* 3.7 (m, 1) and *ca.* 4.67 (m, 1) (ABX_2 system, $-NCH_2CH_2-$), 5.5 (br s, 1, OH), 6.8–7.8 ppm (m, 7, arom H). *Anal.* ($C_{19}H_{19}ClFN_3O_2$) C, H, N.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-1-vinyl-2*H*-1,4-benzodiazepin-2-one (6b). A mixture of 8 g of **3b** and 150 ml of toluene was heated to reflux for 15 min. The solvent was evaporated under reduced pressure and the residue was crystallized from ether to yield 6 g (92%) of product with mp 106–108°. The analytical sample was purified by chromatography over silica gel using 10% EtOAc in CH_2Cl_2 and was crystallized from hexane: mp 114–115°; nmr ($CDCl_3$) δ 3.83 (d, 1) and 4.86 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.73 (m, 2, $=CH_2$), 7.0–7.8 ppm (m, 8, –CH=, arom H). *Anal.* ($C_{17}H_{12}Cl_2N_2O$) C, H, N.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-vinyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (5). A mixture of 10 g of **4** and 100 ml of toluene was heated to reflux for 15 min. The residue obtained after evaporation was chromatographed over 200 g of silica gel. Compound **5** was eluted with EtOAc and was crystallized from CH_2Cl_2–Et_2O: mp 183–184°; yield 4 g (50%). *Anal.* ($C_{17}H_{13}ClFN_2O_2$) C, H, N.

6-Chloro-1-(2-dimethylaminoethyl)-4-phenylquinazolin-2(1*H*)-one (9) and 6-Chloro-2-(2-dimethylaminoethoxy)-4-phenylquinazoline (10). Potassium *tert*-butoxide, 13 g (0.115 mol), was added to a solution of 25.6 g (0.1 mol) of 6-chloro-4-phenylquinazolin-2(1*H*)-one[5] in 150 ml of DMF. After stirring in an ice bath for 1 hr, a solution of 2-dimethylaminoethyl chloride, liberated from 21 g (0.145 mol) of hydrochloride, in 50 ml of C_6H_6 was added. The reaction mixture was stirred and refluxed for 2 hr, diluted with H_2O, and extracted with C_6H_6. The extracts were washed with H_2O, dried, and evaporated. Crystallization of the residue from CH_2Cl_2–petroleum ether and recrystallization from the same solvents yielded 10 g (30.5%) of compound **9** with mp 165–166°. *Anal.* ($C_{18}H_{18}ClN_3O$) C, H, N. Fractional crystallization of the mother liquor yielded 8 g (24.5%) of the known 6-chloro-2-(2-dimethylaminoethoxy)-4-phenylquinazoline[6] with mp 98–100°.

6-Chloro-1-(2-dimethylaminoethyl)-4-phenylquinazolin-2(1*H*)-one *N*-ω-Oxide Hydrate (11). A solution of 9.8 g (0.03 mol) of **9** and 5.5 g (0.032 mol) of *m*-chloroperbenzoic acid in 200 ml of CH_2Cl_2 was stirred at room temperature for 20 min. The reaction mixture was worked up as described in previous examples, and the product was crystallized from CH_2Cl_2–Et_2O to yield 8 g (75%) of *N*-oxide hydrate with mp 170–171° dec: nmr ($CDCl_3$) δ 3.33 [s, 6, $N(CH_3)_2$], 3.68 [t, 2, J = 6.5 Hz, $-N(\rightarrow O)CH_2-$], 3.03 (t, 2, J = 6.5 Hz, NCH_2-), 7.5–8.5 ppm (m, 8, arom H). *Anal.* ($C_{18}H_{18}ClN_3O_2$) C, H, N, H_2O.

6-Chloro-4-phenyl-1-vinylquinazolin-2(1*H*)-one (12). A mixture of 6 g of **11** and 200 ml of toluene was refluxed for 1.5 hr. The solvent was removed under reduced pressure and the residue was crystallized from CH_2Cl_2–petroleum ether to yield 3.7 g (78%) of product with mp 186–187°. The analytical sample was recrystallized from Et_2O: nmr ($CDCl_3$) δ 5.8 (m, 2, $=CH_2$), 6.86 (q, 1, J_{AX} = 16 Hz, J_{BX} = 8 Hz, –CH=), 7.4–8.0 ppm (m, 8, arom H); ir ($CHCl_3$) 1670 cm^{-1} (CO). *Anal.* ($C_{16}H_{11}ClN_2O$) C, H, N.

Acknowledgment. The authors wish to thank the following members of our Physical Chemistry Department under the direction of Dr. R. Scott: Dr. F. Scheidl for the microanalyes, Mr. S. Traiman for the ir spectra, and Dr. V. Toome for the uv spectra. We thank Mr. C. Mason for technical assistance and we are obliged to Dr. L. O. Randall and Dr. W. Pool and their respective staff for the pharmacological data.

References

(1) R. Kalish, E. Broger, G. F. Field, T. Anton, T. V. Steppe, and L. H. Sternbach, *J. Heterocycl. Chem.*, in press.
(2) (a) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3929 (1949); (b) A. C. Cope, R. A. Pike, and C. F. Spencer, *ibid.*, **75**, 3212 (1953).
(3) L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, **8**, 815 (1965).
(4) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
(5) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **27**, 4424 (1962).
(6) Fujisawa Pharmaceutical Co., Ltd., Japanese Patent 13,750; *Chem. Abstr.*, **63**, 11585*g* (1965).
(7) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr in "Drugs Affecting the Central Nervous Systems," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, p 247.

α-(Ureidomethylene)lactones and Derived 5-(Hydroxyalkyl)uracils

George H. Denny* and Malcolm A. Ryder

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065. *Received May 28, 1974*

Antitumor activity has been observed for a number of α,β-unsaturated lactone derivatives.[1] Lactones bearing an α-(ureidomethylene) substituent are readily converted to 5-substituted uracils, a class of compounds that includes several important antitumor agents.[2]

We now wish to report the preparation and testing of the α-(ureidomethylene)lactones Ia–d and the derived 5-(hydroxyalkyl)uracils IIa–d. The compounds were prepared from the appropriate simple lactones *via* the sodio-α-(hydroxymethylene) derivatives, which were then combined with urea under acidic conditions to give compounds Ia–d. Isomerization with aqueous alkali, followed by acidification, gave the corresponding 5-substituted uracil derivatives IIa–d. The procedures were modifications of those previously described[3,4] for the preparation of 5-(2-hydroxyethyl)uracil.

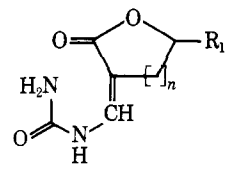
Spectral data (uv, ir, and nmr) were generally consistent with the proposed structures, with the exception that integration of the nmr spectrum of compound IIa did not show the presence of the aliphatic hydroxyl proton. As a structural probe the DMSO-d_6 solution of this compound was treated with trifluoroacetic anhydride. This resulted in the appearance of a new methine sextet centered at δ 4.85 ppm, in addition to the original sextet which was still visible in the spectrum at its original position (δ 3.78 ppm). This demonstrated that partial esterification had taken place causing a downfield shift of the methine protons adjacent to the ester function, thereby substantiating structure IIa. Molecular weight determination by mass spectrometry provided further confirmation in this instance.

The compounds were screened by the Drug Research and Development Branch, National Cancer Institute, against L1210 lymphoid leukemia in mice at dose levels between 100 and 400 mg/kg. Each compound was found to be inactive in this test system.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt using open capillary tubes and are uncorrected. Elemental analyses (C, H, and N) obtained for the compounds described in Tables I and II were within ±0.3% of the theoretical values. The ir spectra were obtained on a Perkin-Elmer Model 137 recording

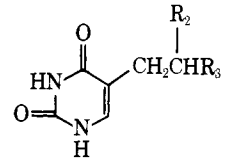
Table I. α-(Ureidomethylene)lactones



Compd	n	R_1	Formula	% yield[a]	Mp, °C	λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)
Ia	1	CH_3	$C_7H_{10}N_2O_3$	39	250–253	269 (25.1)
Ib	1	CH_2CH_3	$C_8H_{12}N_2O_3$	42	215–217	269 (25.8)
Ic	1	$CH_2CH_2CH_3$	$C_9H_{14}N_2O_3$	26	222–224	269 (25.3)
Id	2	H	$C_7H_{10}N_2O_3$	17	241–243	273 (21.0)

[a]Based on sodio-α-(hydroxymethylene) derivative.

Table II. 5-(Hydroxyalkyl)uracils



Compd	R_2	R_3	Formula	% yield	Mp, °C	λ_{max} (MeOH), nm ($\epsilon \times 10^{-3}$)
IIa	OH	CH_3	$C_7H_{10}N_2O_3$	67	258–260	265 (7.7), 210 (12.0)
IIb	OH	CH_2CH_3	$C_8H_{12}N_2O_3$	51[a]	266–267	265 (7.6), 208 (9.3)
IIc	OH	$CH_2CH_2CH_3$	$C_9H_{14}N_2O_3$	76[a]	271–273	265 (7.8), 210 (9.4)
IId	H	CH_2OH	$C_7H_{10}N_2O_3$	79[a]	251–253	265 (7.7), 210 (9.4)

[a] Crystallization from H_2O not necessary as compound was pure following precipitation by acid.

spectrophotometer and the uv spectra by A. Kalowsky using a Cary Model 11 spectrophotometer. A Varian Associates A-60A instrument was used by Dr. A. W. Douglas and staff for recording nmr spectra (10% w/v volutions in DMSO-d_6). The authors are grateful to Mr. R. N. Boos and associates for microanalyses and to Mr. J. L. Smith for mass spectrometry.

General Procedures. α-Hydroxymethylene-γ-valerolactone Sodium Salt. A slurry was prepared under nitrogen from 54.0 g (1.0 mol) of sodium methoxide and 1 l. of dry ether. This was cooled to −5°, and to it was added dropwise with stirring over a 2-hr period a solution containing 78.5 g (1.3 mol) of methyl formate and 100 g (1.0 mol) of γ-valerolactone. The temperature was maintained between −5 and −3° and upon completion of addition the reaction mixture was stirred at room temperature for 16 hr. The product was collected by filtration, washed with ether, and dried at room temperature under vacuum to give 137 g (90%) of the hygroscopic product.

α-(Ureidomethylene)-γ-valerolactone (Ia).† To a cooled solution containing 102.2 g (1.68 mol) of urea in 675 ml of 3 *N* HCl was added in portions 130.4 g (0.81 mol) of α-hydroxymethylene-γ-valerolactone sodium salt, prepared as described above. Turbidity appeared approximately 30 min after the addition was completed. Stirring and cooling were continued for 16 hr and the gelatinous solid was collected by filtration. The damp cake was suspended in 1 l. of H_2O, filtered again, dissolved in 3.8 l. of hot H_2O (some remained undissolved), filtered while hot, and allowed to crystallize. The solid was collected by filtration, washed with two 250-ml portions of H_2O, and dried at 50° under vacuum using an arrangement in which a container of P_2O_5 was included in the vacuum system but located outside of the oven. This gave 56.9 g (39%) of pure Ia. The Beilstein test for halogen was negative. See Table I for physical data. The mother liquors yielded an additional 12.3 g of the product, giving a total yield of 69.2 g (47%).

5-(2-Hydroxy-2-methylethyl)uracil (IIa).‡ To a stirred solution of KOH (24.9 g) in methanol (625 ml) at room temperature was added all at once 51.0 g (0.3 mol) of α-(ureidomethylene)-γ-valerolactone. The resultant suspension was heated to reflux to give a clear solution, which became turbid again after 10 min at the reflux temperature. After a total of 4 hr under reflux the cooled reaction mixture gave a solid which was washed successively with cold methanol and with ether, dried, and dissolved in 100 ml of H_2O. The pH was next adjusted to 3 with 3 *N* HCl (41 ml required) to give the solid product. This material (39.6 g, mp 256–258°) gave a mixture melting point with starting material of 230–255°.

Most of the product (38.2 g) was purified by crystallization from hot H_2O (324 ml), the solution being allowed to cool spontaneously to room temperature over a 16-hr period. The product was washed successively with 30 ml of cold H_2O, 30 ml of cold ethanol, and five 100-ml portions of ether. Vacuum drying at room temperature over P_2O_5 gave 34.2 g (68%) of IIa. A sample for analysis was vacuum dried at 100°: ir (Nujol) 3500 cm^{-1} (OH); mass spectrum (70 eV) *m/e* 170 (M^+); $C_7H_{10}N_2O_3$ (170.2). See Table II for additional physical data.

Acknowledgment. This investigation was supported by Contract NIH-72-2002 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

References

(1) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(2) J. A. Montgomery, T. P. Johnston, and Y. F. Shealy in "Medicinal Chemistry," 3rd ed, A. Burger, Ed., Wiley, New York, N. Y., 1970, Chapter 28.
(3) J. D. Fissekis and F. Sweet, *J. Org. Chem.*, **38**, 264 (1973).
(4) K. A. Chkhikvadze, N. J. Koretskaya, N. S. Rodnyanskaya, and O. Yu. Magidson, *Khim. Geterotsikl. Soedin.*, **5**, 108 (1969).

†An alternative name for compound Ia is [(tetrahydro-5-methyl-2-oxofuran-3-ylidene)methyl]urea.

‡An alternative name for compound IIa is 5-(2-hydroxypropyl)-2,4(1*H*,3*H*)-pyrimidinedione.