of XV was converted to the diacetate (XII) which was recovered as 8.42 g. (104%) of a syrup; $\lambda_{max(\mu)}^{film}$ 5.68 (acetate C=O), 5.78 (benzoate C=O), 7.27, 8.39, 8.49 (—OSO_2—), 7.84 (benzoate C—O—C), 8.07, 8.21 (acetate C—O—C), 12.24 (*p*-disubstituted benzene), 14.00 (C_6H_5C=O).

*2-O-Acetyl-5-O-benzoyl-3-O-(p-tolylsulfonyl)-*D*-xylofuranosyl chloride* (XIb). The above diacetate (XII), 8.42 g., was converted to the chloride (XIb) by the procedure described for the preparation of XIa. A white, solid residue remained which showed none of the 8.07 μ absorption attributed to the C—O—C of the 1-*O*-acetate. The residue was directly coupled with chloromercuri-6-benzamidopurine using the procedure described for the coupling of XIa.[2] The solid product from the coupling and deblocking procedure, after regeneration of the picrate, weighed 0.43 g. and contained the anhydronucleoside (VIII), adenine, and some other purine-containing materials, as shown by paper chromatography in solvents A and B. If the residue had been pure VIII, the yield would have been 10.5% based on the isopropylidene compound (XV).

*9-[3'-Deoxy-3'-(ethylthio)-β-*D*-xylfuranosyl]adenine* (IX).[2] The conversion of 353 g. (0.79 mole) of diacetate (X) to the chloro sugar (XIa) was carried out as described previously.[2] Coupling of the chloro sugar (XIa) with 560 g. (0.785 mole) of 66.7% chloromercuri-6-benzamidopurine mixed with Celite was run for 2.25 hr.; it was found necessary to extract the filter cake with five 900-ml. portions of boiling chloroform to remove all the product. The crude, blocked nucleoside (345 g.) was converted to the anhydronucleoside (VIII) by dissolving it in 1600 ml. of methanol, cooling the solution to 10°, and adding a cold (10°) solution of 35 g. (0.65 mole) of sodium methoxide in 500 ml. of methanol. The resulting, stoppered solution, after standing at room temperature 14–15 hr., was adjusted to *p*H 7.4 with glacial acetic acid, then evaporated *in vacuo* at 55°, leaving 311 g. of crude VIII. A solution of the residue in 600 ml. of methanol was heated under reflux for 20 hr. with a methanolic sodium ethyl mercaptide solution (prepared from 227 g. (4.2 moles) of sodium methoxide, 340 ml. (4.6 moles) of ethanethiol, and 900 ml. of methanol) with exclusion of moisture. The solution was cooled to room temperature and adjusted to *p*H 8 with glacial acetic acid while cooling the mixture with an ice bath and maintaining the temperature below 45°. After evaporating the solution *in vacuo* at 50°, the residue was dissolved in 1500 ml. of water and continuously extracted with chloroform for 3.5 days to give 54.2 g. of crude IX. Recrystallization was effected by dissolving the material in 1500 ml. of 95% ethanol, evaporating the solution to 700 ml., and chilling to give 43.8 g. of a first crop, m.p. 183–185° (prior melting and resolidification 130–160°), whose infrared spectrum and paper chromatographic behavior were in excellent agreement with the previous analytical sample,[2] and a second crop of 3.1 g., m.p. 180° (with prior melting and resolidification 130–150°). The total product, 46.9 g., constituted a 19% over-all yield from the diacetate (X).

The main changes in the procedure from that of reference 2 are: (1) thorough extraction of the Celite residues from the initial coupling reaction with chloroform, (2) shorter reaction time in the deblocking to form VIII (3) neutralization of the reaction mixture from the reaction of VIII with sodium ethyl mercaptide before evaporation.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and his staff for the paper chromatography.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XLIV. Some Derivatives of Uracil-5- and -6-carboxylic Acid

LEONARD O. ROSS, LEON GOODMAN, AND B. R. BAKER

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The reaction of the butyl esters of uracil-5- and 6-carboxylic acid with hydrazine, butylamine, and with 2-aminoethanol gave the expected amides. The hydrazide of uracil-6-carboxylic acid was converted with nitrous acid to uracil-6-carboxazide.

In a continuation of interest in derivatives of uracil as potential anticancer agents,[2,3] attention was focused on some transformations of uracil-5-carboxylic acid and orotic acid (uracil-6-carboxylic acid). The latter compound is a key intermediate in the *de novo* synthesis of pyrimidine ribonucleotides and deoxyribonucleotides[4] and, as such, represents an interesting area for the synthesis of possible antimetabolites.

The principal objective in these studies was to prepare a number of new amides from the uracil-5- and 6-carboxylic acids. One of the common routes to amides, *via* an acid chloride, was not feasible because of the unavailability of the acid chlorides of the two uracil acids. A few attempts in this work to prepare these acid chlorides were unsuccessful, probably because of the insolubility of the acids; no mention of the two acid chlorides appears in the literature. Accordingly, the preparation of the amides *via* the esters of uracil-5-carboxylic acid and orotic acid was investigated.

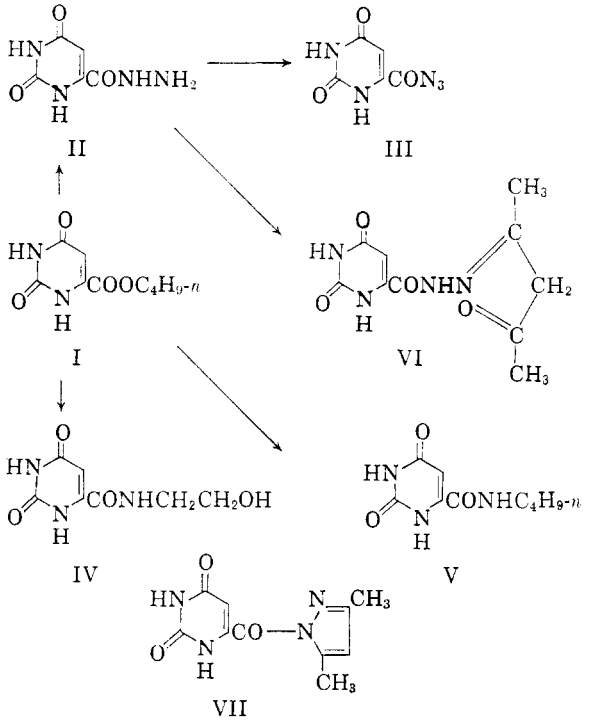
(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, *J. Org. Chem.*, in press.

(2) A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press, paper XXXVI of this series.

(3) W. A. Skinner, M. G. M. Schaelstraete, and B. R. Baker, *J. Org. Chem.*, **25**, 149 (1960), paper XXVIII of this series.

(4) J. N. Davidson, *The Biochemistry of the Nucleic Acids*, Methuen & Co., Ltd., London, 1957, p. 161.

The *n*-butyl ester (I) of orotic acid, chosen in order to enhance the solubility of the orotic acid derivative in organic solvents, was prepared in good yield by the reaction of the acid with *n*-butyl alcohol in the presence of concentrated sulfuric acid. A mixture of the ester (I) and excess *n*-butylamine in refluxing ethanol gave a fair yield of the *n*-butylamide (V) and the reaction of I with excess 2-aminoethanol in ethanolic solution, carried out in a sealed bomb at 100°, gave a good yield of the 2-hydroxyethylamide (IV).

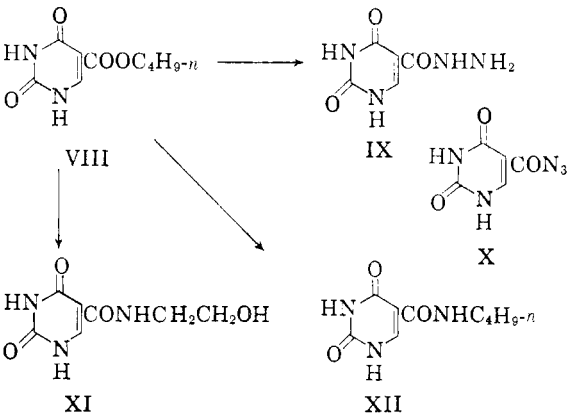


II III I VI IV V VII

The infrared spectra of the two crystalline amides IV and V, run in Nujol mulls, showed no similarities in the 2.9–7.0 μ region but the ultraviolet spectra of the two compounds were very similar and in general agreement with that of the *n*-butylester (I). It seems clear that the two amides show markedly different interactions in the crystal state but show structural similarity in solution. A number of attempts were made to convert IV to the interesting 2-chloroethylamide of orotic acid by the use of thionyl chloride. There was a definite introduction of chlorine into IV but no pure product could be isolated from the reaction.

The *n*-butyl ester (I) with hydrazine hydrate in methanol gave an excellent yield of the carboxyhydrazide (II). In turn, the hydrazide (II), in cold dilute hydrochloric acid with a slight excess of sodium nitrite, gave a fair yield of the carboxyazide (III) which was readily identified by the strong azide infrared absorption at 4.59 μ. The carboxyhydrazide (II) was allowed to react with 1,3-pentanedione in an effort to prepare the orotylpyrazole (VII). Acyl pyrazoles have been prepared similarly by Ried and Schleimer[5] and have been used as acylating agents. In the reaction of 1,3-pentanedione with II, however, the reaction seemed to stop at the simple hydrazone (VI) stage. The crystalline product had a correct analysis for VI (although this would not preclude a monohydrate of VII). When attempts were made to make a derivative of the free carbonyl group in VI with phenylhydrazine or *p*-nitrophenylhydrazine, the hydrazide (II) was regenerated, a strong indication that the pyrazole ring had not formed. In the experiments of Ried and Schleimer,[5] reaction of an amine with an acylpyrazole led to displacement at the carbonyl carbon to yield a amide and the free pyrazole; a similar course of reaction between VII and phenylhydrazine would have given the phenylhydrazide of orotic acid as the product rather than II, which was actually isolated and would be the expected product from VI by hydrolysis.

In the uracil-5-carboxylic acid series, the *n*-butyl ester (VIII) was formed under similar conditions to those used in the preparation of I. There was somewhat more difficulty than in the orotic acid series in the conversion of VIII to the



VIII IX X XI XII

2-hydroxyethylamide (XI) and to the *n*-butylamide (XII), both preparations requiring the use of considerably higher temperatures in a sealed bomb. The 5-carboxyhydrazide (XI) was readily prepared in high yield from the ester (VII). Attempts to convert IX to the azide X gave very capricious results. In a few cases a strong azide band was present in the infrared spectrum of the product but in most of the attempts there was no evidence for the formation of X. Attempts to convert IX to a pyrazole by reaction with 1,3-pentanedione gave intractable products.

It was noteworthy in a comparison of ultraviolet spectra of the 5-substituted- and 6-substituted uracils that the 5-substituted derivative absorbed at a shorter wave length and with greater intensity at all three *p*H conditions employed than did the corresponding 6-substituted derivative.

(5) W. Reid and B. Schleimer, *Ann.*, **619**, 43 (1958).

This same relationship is true in a comparison of the ultraviolet spectra of uracil-5-carboxylic acid[6] and orotic acid.[7]

EXPERIMENTAL[8]

n-Butyl orotate (I). A suspension of 2.0 g. (12.8 mmoles) of orotic acid in a mixture of 200 ml. of *n*-butyl alcohol and 2.0 ml. of concd. sulfuric acid was heated under reflux for 6 hr. The solution was filtered to remove 0.30 g. of orotic acid and the filtrate was concentrated *in vacuo* to about 40 ml. and chilled. Water (50 ml.) was added to the chilled concentrate causing the precipitation of 1.90 g. (82% based on utilized orotic acid) of crystalline product, m.p. 178–180°. Recrystallization of the solid from 50 ml. of water gave 1.80 g. (78%) of the analytical sample, m.p. 182–184°; $\lambda^{KBr}_{max(\mu)}$ 3.23 (NH); 5.78 and 6.00 (uracil C=O); 5.87 (ester C=O); 6.14, 6.70 and 7.15 (pyrimidine ring); 7.93 (ester C—O—C); $\lambda^{pH\ 1}_{max(m\mu)}$ 286 (ϵ 5800); $\lambda^{pH\ 7}_{max(m\mu)}$ 280 (ϵ 7500); $\lambda^{pH\ 13}_{max(m\mu)}$ 284 (ϵ 7300). The product moved as a single spot on paper in solvent A with R_{Ad} 1.41.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.9; H, 5.70; N, 13.2. Found: C, 50.7; H, 5.72; N, 13.1.

Orotyl hydrazide (II). A stirred mixture of 5.0 g. (23.5 mmoles) of *n*-butyl orotate (I), 9.20 g. (0.185 mole) of hydrazine hydrate, and 50 ml. of reagent methanol was heated on the steam bath for 20 min. under gentle reflux, then chilled. The precipitated material (3.0 g., 75%) was removed by filtration and from the evaporated filtrate a second crop (0.80 g.) of the same material was recovered, giving a total crude yield of 95% of product which failed to melt at 300°. The material was recrystallized from 145 ml. of water with the aid of Norit to give 2.63 g. (66%) of product, m.p. >300°, $\lambda^{KBr}_{max(\mu)}$ 3.08 and 3.18 (NH and NH_2); 5.85–6.32 (uracil C=O, amide C=O, NH_2 and pyrimidine); 6.75 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 282 (ϵ 6000); $\lambda^{pH\ 7}_{max(m\mu)}$ 305 (broad, ϵ 5500); $\lambda^{pH\ 7}_{max(m\mu)}$ 295 (ϵ 8600). On paper chromatography in solvent C and D, the compound moved as a single spot with R_{Ad} 1.10 and 1.55, respectively.

Anal. Calcd. for $C_5H_6N_4O_3.H_2O$: C, 31.9; H, 4.28; N, 29.7. Found: C, 32.0; H, 4.36; N, 29.5.

Orotyl azide (III). A cold (7–10°) suspension of 1.0 g. (5.9 mmoles) of the hydrazide (II) in a mixture of 5.0 ml. of 6*M* hydrochloric acid in 100 ml. of water was vigorously stirred while a solution of 0.44 g. (6.4 mmoles) of sodium nitrite in 5 ml. of water was added dropwise over a 10-min. period. The suspension was stirred 10 min. more at 7–10° and was filtered. The solid residue was washed with three 20-ml. portions of cold water and was dried to give 0.60 g. (56%) of product; this compound gave no definite melting point, but gradually decomposed, with the decomposition most noticeable at 180–190°; $\lambda^{KBr}_{max(\mu)}$ 2.90 and 3.15 (NH); 4.49 and 4.59 (N_3); 5.8–6.0 (uracil C=O); 6.13 and 6.68 (pyrimidine ring); no satisfactory paper chromatographic solvent system was found for this compound.

Anal. Calcd. for $C_5H_3N_5O_3.1/2\ H_2O$: C, 31.6; H, 2.12; N, 36.8. Found: C, 32.0; H, 2.58; N, 37.4.

N-(2-Hydroxyethyl)orotamide (IV). A mixture of 1.0 g. (4.71 mmoles) of the ester (I), 1.0 g. (16.3 mmoles) of 2-aminoethanol, and 20 ml. of absolute ethanol was heated in a stainless steel bomb at 100° for 14 hr. After cooling to room temperature, the contents of the bomb were transferred and evaporated *in vacuo*. The solid residue was slurried with 20 ml. of reagent methanol and the suspension filtered to give 0.80 g. (85%) of solid product, m.p. 272–274° dec. The solid was dissolved in 10 ml. of water, the solution treated with Norit and filtered. Hot methanol (20 ml.) was added to the filtrate and, on chilling, 0.60 g. (64%) of product was obtained, m.p. 278–280°; $\lambda^{Nujol}_{max(\mu)}$ 2.98 and 6.57 (NH), 6.00 (uracil C=O); 6.10 (amide C=O); 9.41 (C—OH); surprisingly, there was no OH absorption near 3.0 μ; $\lambda^{pH\ 1}_{max(m\mu)}$ 280 (ϵ 6500); $\lambda^{pH\ 7}_{max(m\mu)}$ 280–295 (ϵ 4900); $\lambda^{pH\ 13}_{max(m\mu)}$ 312 (ϵ 6600). On paper chromatography in solvent A the compound moved as a single spot with R_{Ad} 0.70.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.55; N, 21.0. Found: C, 42.2; H, 4.71; N, 21.0.

N-Butyl orotamide (V). A stirred mixture of 4.50 g. (2.12 mmoles) of the ester (I), 4.25 g. (58.8 mmoles) of *n*-butylamine, and 50 ml. of absolute ethanol was heated under reflux for 7 hr. and evaporated *in vacuo* to a semi-solid slurry. Water (25 ml.) was added and the mixture was warmed until complete solution was attained. The hot solution was treated with Norit and filtered. The chilled filtrate deposited 2.0 g. (45%) of crystalline solid, m.p. 275–276°. The solid was recrystallized from 25 ml. of water to give 1.80 g. (41%) of product with unchanged melting point; $\lambda^{Nujol}_{max(\mu)}$ 3.04 and 6.43 (NH), 5.74 (uracil C=O), 6.00 (uracil C=O and amide C=O), 6.12 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 279 (ϵ 6400); $\lambda^{pH\ 7}_{max(m\mu)}$ 307 (ϵ 4900); $\lambda^{pH\ 13}_{max(m\mu)}$ 311 (ϵ 6400). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 1.50.

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.1; H, 6.20; N, 19.8. Found: C, 51.5; H, 6.58; N, 20.2.

Mono-6-uracilylhydrazone of 1,3-pentanedione (VI). A stirred mixture of 0.50 g. (2.95 mmoles) of the hydrazide (II), 0.30 g. (3.00 mmoles) of 1,3-pentanedione, and 35 ml. of *N,N*-dimethylformamide was heated at 80° for 3 hr. The solvent was evaporated *in vacuo* at 80–90°, benzene (20 ml.) was added to the residue, and the evaporation was repeated, leaving 0.30 g. of solid, m.p. 184–188° dec. The solid was extracted with 10 ml. of boiling absolute ethanol, the mixture was filtered, and the filtrate was chilled to give a small amount of crystalline product, m.p. 228–230° dec.; $\lambda^{Nujol}_{max(\mu)}$ 2.97 and 3.07 (NH), 5.82 and 5.98 (uracil C=O), 6.10 and 6.85 (pyrimidine ring); $\lambda^{pH\ 1}_{max(m\mu)}$ 273 (ϵ 8800); $\lambda^{pH\ 7}_{max(m\mu)}$ 276 (ϵ 7900); $\lambda^{pH\ 13}_{max(m\mu)}$ 242 (shoulder, ϵ 8700), 285 (ϵ 6100). On paper chromatography in solvent D the compound moved as a single spot with R_{Ad} 1.90.

Anal. Calcd. for $C_{10}H_{12}N_4O_4$: C, 47.6; H, 4.76; N, 22.2. Found: C, 47.3; H, 4.70; N, 21.6.

Subsequent preparations using 1.00 of the hydrazide II and recrystallizing the crude residue from hot water gave a 51% yield of material, m.p. 225–228° dec., whose infrared spectrum was identical with that of the analytical sample.

When the hydrazone (VI), dissolved in aqueous ethanol containing a few drops of glacial acetic acid, was heated on the steam bath for 10 min. with an excess of either phenylhydrazine or *p*-nitrophenylhydrazine and the solution chilled, the solid product obtained in good yield was the hydrazide (II), m.p. >300° and identical with authentic II in infrared spectrum and paper chromatographic behavior.

5-Carbo-n-butoxyuracil (VIII). A stirred suspension of 1.0 g. (2.8 mmoles) of uracil-5-carboxylic acid, 50 ml. of *n*-butyl alcohol, and 0.30 ml. of concd. sulfuric acid in an apparatus equipped with a water separator was heated

(6) M. M. Stimson, *J. Am. Chem. Soc.*, **71**, 1470 (1949).

(7) H. Vanderhaege, *Bull. soc. chem. Belg.*, **62**, 611 (1953).

(8) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus. Paper chromatography was done by the descending technique on Whatman No. 1 paper and the spots were detected by visual examination under ultraviolet light. Adenine was used as a standard and the spots were located relative to R_{Ad} 1.00. The solvent systems used were A,[9] *n*-butanol–acetic acid–water (5:2:3); B,[10] *i*-propanol–2*M* hydrochloric acid (65:35); C,[11] ammonium sulfate–*i*-propanol–water (2:28:70); D,[12] 2-methoxyethanol–water (9/1).

(9) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

(10) G. R. Wyatt, *Biochem. J.*, **48**, 584 (1951).

(11) A variant of a system used by R. Markham and J. D. Smith, *Biochem. J.*, **49**, 401 (1951).

(12) A. E. Bender, *Biochem. J.*, **48**, XV (1951) (Proc. Biochemical Society).

under reflux for 3 hr., resulting in complete solution. The chilled mixture gave 1.0 g. (74%) of crude product, m.p. 230–234°. The solid was recrystallized from 40 ml. of hot methanol to give 0.60 g. (44%) of product, m.p. 237–239°; $\lambda_{max(\mu)}^{KBr}$ 3.11 (NH); 5.70–5.80 (uracil and ester C=O), 6.60 (NH and pyrimidine ring); 6.13, and 6.99 (pyrimidine ring), 8.15 (ester C—O—C); $\lambda_{max(m\mu)}^{pH\ 1}$ 270 (ε 13300); $\lambda_{max(m\mu)}^{pH\ 7}$ 272 (ε 11900); $\lambda_{max(m\mu)}^{pH\ 13}$ 239 (ε 13700), 291 (ε 17900). On paper chromatography in solvent A, the product moved as a single spot with R_{Ad} 1.57.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.9; H, 5.70; N, 13.2. Found: C, 51.1; H, 5.79; N, 13.0.

Uracil-5-carboxyhydrazide (IX). A stirred suspension of 0.50 g. (2.36 mmoles) of the ester (VIII) in 5 ml. of hydrazine hydrate was heated under reflux for 15 min. and the resulting solution cooled to room temperature. Methanol (10 ml.) was added to the solution and, on chilling, 0.30 g. (75%) of product, m.p. >300°, was obtained. The solid was recrystallized from 40 ml. of water with the aid of Norit to give 0.20 g. (50%) of product, m.p. >300°; $\lambda_{max(\mu)}^{Nujol}$ 3.09 and 6.30 (NH_2), 3.25 and 3.30 (NH), 5.65 and 5.78 (uracil C=O), 5.99 (amide C=O), 6.65 (NH and pyrimidine ring), 6.09 and 6.92 (pyrimidine ring); $\lambda_{max(m\mu)}^{pH\ 1}$ 219 (ε 12800), 273 (ε 12000); $\lambda_{max(m\mu)}^{pH\ 7}$ 223 (ε 8500), 278 (ε 10800); $\lambda_{max(m\mu)}^{pH\ 13}$ 244 (broad ε 10200), 292 (ε 16800). On paper in solvent B the product moved as a single spot with R_{Ad} 0.43.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.2; H, 3.52; N, 32.8. Found: C, 35.3; H, 3.74; N, 32.8.

N-(2-Hydroxyethyl)uracil-5-carboxamide (XI). A mixture of 1.0 g. (4.7 mmoles) of 5-carbo-*n*-butoxyuracil (VIII), 0.86 g. (14.2 mmoles) of 2-aminoethanol, and 15 ml. of absolute ethanol was heated in a stainless steel bomb at 150–155° for 15 hr. The bomb was cooled and the contents were evaporated to dryness *in vacuo* at 50–60°. Water (6 ml.) was added to the residual sirup and the solution was adjusted to *p*H 1 with 6*M* hydrochloric acid. On chilling, the solution deposited 0.45 g. (48%) of product, m.p. 244–246°. This was recrystallized from 30 ml. of hot water to yield 0.25 g. (26%) of material, m.p. 284–285°; $\lambda_{max(\mu)}^{Nujol}$ 2.98, 3.09, 3.19, 3.31 (NH, OH), 5.81 and 5.90 (uracil and amide C=O), 6.25 (pyrimidine ring), 9.38 (C—OH); $\lambda_{max(m\mu)}^{pH\ 1}$ 221 (ε 13100), 272 (ε 12700); $\lambda_{max(m\mu)}^{pH\ 7}$ 221 (ε 13100), 273 (ε 12000); $\lambda_{max(m\mu)}^{pH\ 13}$ 244 (ε 11000), 290 (ε 17000). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 0.83.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.55; N, 21.0. Found: C, 42.3; H, 4.77; N, 20.7.

N-(n-butyl)uracil-5-carboxamide (XII). A mixture of 0.50 g. (2.36 mmoles) of ester (VIII) and 2.0 g. (27 mmoles) of *n*-butylamine was heated in a stainless steel bomb at 170° for 15 hr. The bomb was cooled and the contents were evaporated to dryness *in vacuo* at 70–80°. Water (20 ml.) was added to the semi-crystalline residue and the mixture was adjusted to *p*H 1 with 6*M* hydrochloric acid, causing the precipitation of a solid, 0.35 g. (73%), m.p. 290–293°. The solid was recrystallized from 50 ml. of hot water to yield 0.30 g. (63%) of the analytical sample, m.p. 290–291°; $\lambda_{max(\mu)}^{Nujol}$ 3.06 and 3.22 (NH), 5.78 and 5.89 (uracil C=O), 6.19 (pyrimidine ring); surprisingly, there was no amide carbonyl band near 6.0 μ; $\lambda_{max(m\mu)}^{pH\ 1}$ 222 (ε 12600), 272 (ε 12200); $\lambda_{max(m\mu)}^{pH\ 7}$ 222 (ε 13000), 273 (ε 12600); $\lambda_{max(m\mu)}^{pH\ 13}$ 243 (ε 12000), 290 (ε 17600). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 1.45.

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.1; H, 6.19; N, 19.9. Found: C, 51.3; H, 6.21; N, 19.9.

Acknowledgment. The authors are indebted to Dr. P. Lim for interpretation of the infrared spectra and to his staff for the paper chromatographic results. They also wish to thank Mr. O. P. Crews, Jr., and his group for the large-scale preparation of certain intermediates.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Guanidines with Antihypertensive Activity

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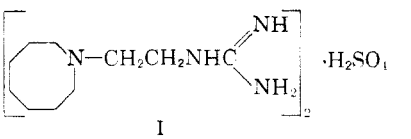
[2-(Octahydro-1-azocinyl)ethyl]guanidine sulfate was found to have protracted antihypertensive properties with the capacity to block sympathetic efferent transmission, presumably at the nerve terminals. Alterations of the ring, side chain, and terminal grouping were investigated and the relationship of these modifications to activity ascertained.

The observation that hexahydro-1-azepinylpropionamidoxime[1] possessed protracted antihypertensive activity with an unusual mechanism of action has prompted a wider search for large-membered heterocyclic compounds which might display similar unique pharmacological properties. Previous communications[2] on this study disclosed that [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate (I) markedly lowered the arterial pressure of unanesthetized renal and neurogenic dogs and



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blocked sympathetic efferent transmission, presumably at the nerve terminals. The protracted

(1) (a) R. P. Mull, R. A. Maxwell, and A. J. Plummer, *Nature*, **180**, 1200 (1957); (b) R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958); (c) R. A. Maxwell, A. J. Plummer, A. I. Daniels, F. Schneider, and H. Povalski, *J. Pharmacol. Exptl. Therap.*, **124**, 127 (1958), R. A. Maxwell, S. D. Ross, and A. J. Plummer, *J. Pharmacol. Exptl. Therap.*, **123**, 128 (1958).

(2) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959); R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniels, *J. Pharmacol. Exptl. Therap.*, **128**, 22 (1960). This compound has been assigned the generic name of guanethidine and the CIBA Trademark Ismelin™.