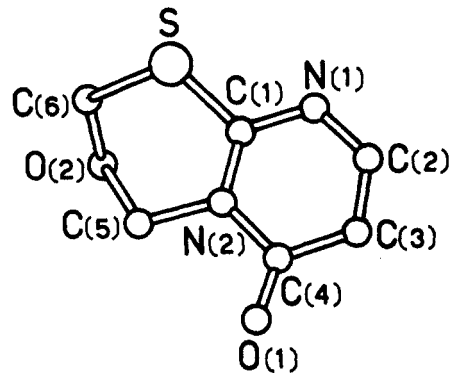

Figure 1.—A sketch of the molecule with a numbering scheme. The hydrogen atoms are not shown.

to the plane space group *pmg*. A two-dimensional analysis, carried out on the basis of 116 independent *h0l* reflections using the heavy-atom method, allowed the location of all the non-hydrogen atoms. After three cycles of isotropic block-diagonal least-squares refinement the *R* factor was 0.21. This value suggests that the deduced model is essentially correct, as shown by the Fourier projection calculated on the basis of these data. Since the geometry of the molecule was univocally determined, no attempt was made to locate the hydrogen atoms in order to inprove the refinement.

Thus the results showed that the orthorhombic needles and the monocline crystals were two crystalline modifications of a single substance having the assigned structure **2a**.

6*H*-Pyrimido[2,1-*d*][1,3,5]oxathiazin-6-one (2a).—The procedure reported in literature[1] for the homolog **2b** has been followed. 2-Thiouracil (18 g) was dissolved in a mixture of 40 ml of water, 130 ml of concentrated sulfuric acid, and 30 ml of 35% formaldehyde. The solution was allowed to stand at room temperature for 24 hr and was stirred occasionally. After dilution with 800 ml of water, the pH was adjusted to about 8 with diluted ammonia. The precipitate that formed was collected by filtration and crystallized from water. A mixture of monoclinic crystals, mp 132°, and fibrous aggregates of orthorhombic needles, mp 131.5°, was obtained. The monoclinic crystals could be converted into needles by recrystallization from aqueous solutions. The two crystalline forms had identical nmr[17] and uv spectra: λ_{max}^{hexane} 298 mμ (ε 7496), 228 (6283); λ_{max}^{water} 293, 240, 226 at pH 6.5; $\lambda_{max}^{95\%\ ethanol}$ 296.5 (240 mμ sh), 228; $\lambda_{max}^{methanol}$ 296 (240 sh), 229; $\delta_{TMS}^{CDCl_3}$ 7.78 (d, 1 H, CH), 6.21 (d, 1 H, CH), 5.58 (s, 2 H, CH_2), 5.31 (s, 2 H, CH_2). The ir spectra were different: *e.g.*, monoclinic crystals, ν_{max}^{Nujol} 1690 and 1666 (C=O); needles, ν_{max}^{Nujol} 1678 and 1664 (C=O); $\nu_{max}^{CHCl_3}$ 1680 cm^{-1} (C=O) for both forms.

The R_f values obtained by thin layer chromatography for both these crystalline forms were identical.

Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 3.55; N, 16.46; O, 18.80; S, 18.84. Found: C, 42.21; H, 3.59; N, 16.46; O, 19.01; S, 18.76.

The hydrochloride of the base described above has been obtained from 2-thiouracil itself in a 55% yield; the procedure followed was that reported for chloromethylating uracil;[9] and the product was precipitated by addition of acetone to the reaction mixture. After recrystallization from alcohol–ether, the compound had mp 187° with decomposition, depending on the heating speed. This hydrochloride can also be obtained from chloroform solutions of the base by precipitation with hydrogen chloride.

Anal. Calcd for $C_6H_7ClN_2O_2S$: C, 34.88; H, 3.41; N, 13.55; Cl, 17.15; S, 15.51. Found: C, 34.92; H, 3.50; N, 13.48; Cl, 17.03; S, 15.64.

6*H*-8-Methylpyrimido[2,1-*d*][1,3,5]oxathiazin-6-one (2b).—The procedure reported for **2a** was followed starting from 6-methyl-2-thiouracil. After recrystallization from water, the yield was 84%; mp 140° (lit.[1] mp 140–141°); λ_{max}^{hexane} 294 mμ (ε 6915), 228 (6409); $\lambda_{max}^{95\%\ ethanol}$ 293.5, 240 (230 mμ sh); λ_{max}^{water} 290, 243.5 (225.5 sh); $\delta_{TMS}^{CD_3SO}$ 6.00 (s, 1 H, CH), 5.46 (s, 2 H, CH_2), 5.40 (s, 2 H, CH_2), 2.08 (s, 3 H, CH_3); $\nu_{max}^{CHCl_3}$ 1679 cm^{-1} (C=O).

Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.37; N, 15.20. Found: C, 45.45; H, 4.20; N, 15.32.

(17) J. P. Kokko, L. Mandell, and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 1042 (1962).

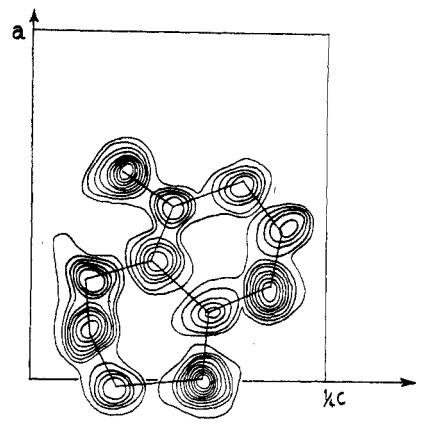

Figure 2.—Fourier projection of the electron density onto (010). Contours are drawn at intervals of 2 e $Å^{-2}$ for the S atom and of 1 e $Å^{-2}$ for the O, N, and C atoms.

6*H*-8-Propylpyrimido[2,1-*d*][1,3,5]oxathiazin-6-one (2c).—The procedure reported for **2a** was followed starting from 6-propyl-2-thiouracil. After recrystallization from water, the product had mp 97°; λ_{max}^{hexane} 295 mμ (ε 6770), 229 (ε 6498); λ_{max}^{water} 288, 242 (221.5 sh); $\lambda_{max}^{95\%\ ethanol}$ 294.5, two overlapping maxima 235; $\delta_{TMS}^{CDCl_3}$ 6.0 (s, 1 H, CH), 5.5 (s, 2 H, CH_2), 5.26 (s, 2 H, CH_2), and with approximated first order 2.37 (tr, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 0.87 (tr, 3 H, CH_3); $\nu_{max}^{CHCl_3}$ 1675 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.87; H, 5.60; N, 13.28.

8-Methyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (5)[4] had λ_{max}^{water} 292 mμ, 247; $\lambda_{max}^{95\%\ ethanol}$ 295 (240 sh), 228; $\lambda_{max}^{methanol}$ 294, 243.5, 229. The hydrochloride precipitated from a chloroform solution of the base with hydrogen chloride had mp 268–270° (uncor).

Anal. Calcd for $C_8H_{11}N_2ClOS$: C, 43.93; H, 5.07; N, 12.81. Found: C, 43.69; H, 4.98; N, 12.90.

7-Methyl-2*H*,5*H*-thiazolo[3,2-*a*][1,3]pyrimidin-5-one (6)[4] had λ_{max}^{water} 284.5 mμ (243 and 227 mμ sh); $\lambda_{max}^{95\%\ ethanol}$ 285.5, 227; $\lambda_{max}^{methanol}$ 285 (240 mμ sh), 228.

5-Methyl-2*H*,7*H*-thiazolo[3,2-*a*][1,3]pyrimidin-7-one (7)[4] had λ_{max}^{water} 262 mμ, 229; $\lambda_{max}^{95\%\ ethanol}$ (257 sh), 229.5; $\lambda_{max}^{methanol}$ 264, 228.5.

Registry No.—**2a**, 27092-97-3; **2a** HCl, 27092-98-4; **2b**, 27092-99-5; **2c**, 27093-00-1; **5** HCl, 27093-01-2; 2-thiouracil, 156-82-1; formaldehyde, 50-00-0.

Acknowledgment.—The authors are very indebted to Dr. E. Trivellone for preliminary nmr spectroscopy and to Mrs. A. Andreassi for her cooperation. This work has been partly supported by Italian National Research Council.

Cyclization of Some 2-(Haloacylamino)pyrimidines

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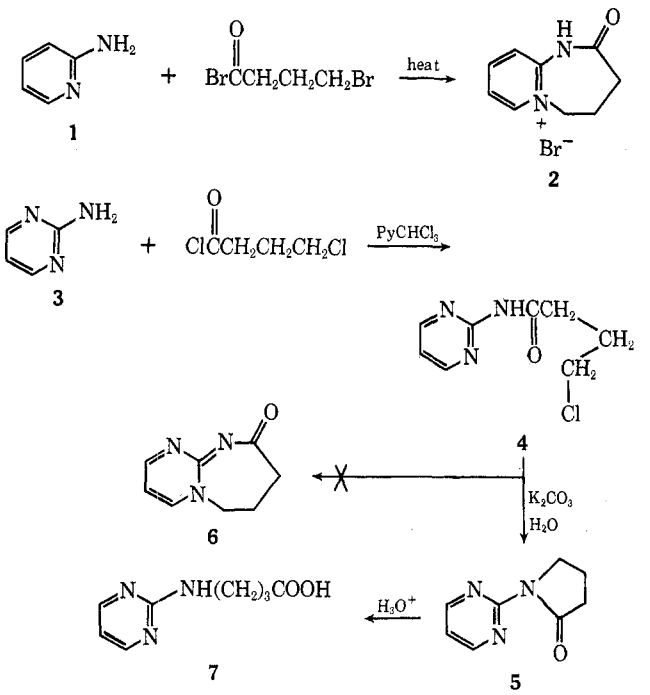
Fozard and Jones[2] reported that heating 2-aminopyridine (**1**) with 4-bromobutyryl bromide led to the formation of 2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*]-diazepinium bromide (**2**, Scheme I). When we at-

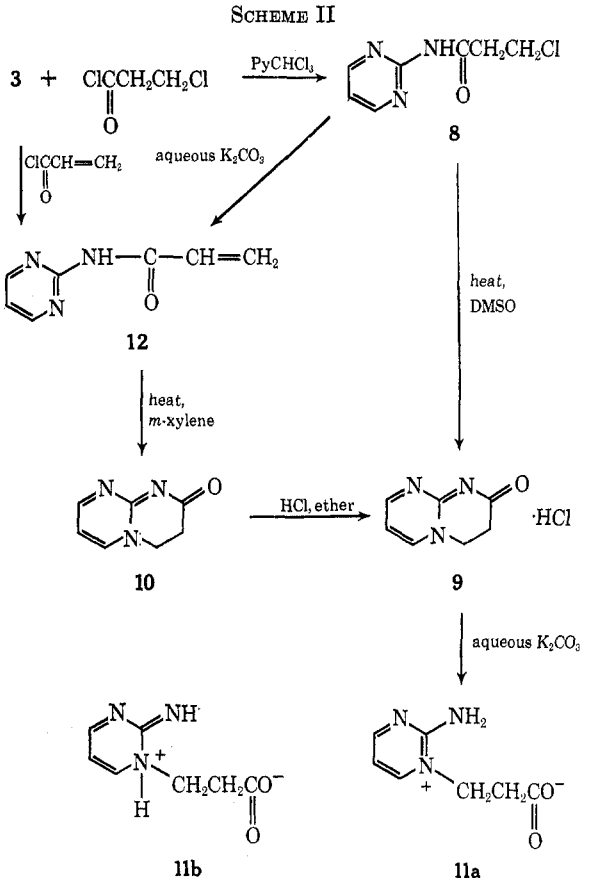
(1) To whom inquiries should be addressed.

(2) A. Fozard and G. Jones, *J. Chem. Soc.*, 2763 (1964).

SCHEME I



SCHEME II



tempted reaction of 2-aminopyrimidine (**3**) with either 4-iodobutanoic acid[3] or 4-chlorobutyryl chloride under similar conditions,[2] only the respective hydrohalide salts of **3** were isolated. The precursor haloamide, 2-(4-chlorobutyryl)aminopyrimidine (**4**), however, could be readily prepared by treating **3** with 4-chlorobutyryl chloride in chloroform–pyridine solution. Heating **4** at 140° in an oil bath afforded only intractable tars. Reaction of **4** with aqueous potassium carbonate or ethanol–triethylamine solution or sodium hydride in refluxing xylene led to 1-(2-pyrimidinyl)-2-pyrrolidine (**5**) rather than the pyrimido[1,2-*a*]diazepinone **6**. It was unusual that the potassium carbonate method, which gave the highest yield, succeeded at all since cyclizations of haloamides generally proceed under anhydrous conditions in the presence of a strong base as sodium hydride or potassium *tert*-butoxide.[4] The structure of **5** was assigned on the basis of (1) the nmr spectrum, which showed two of the three pyrimidine ring protons as being equivalent and the presence of three adjacent methylene groups; (2) 5.84-μ ir absorption, attributed to the pyrrolidone carbonyl group; (3) acid hydrolysis to the amphoteric 2-(3-carboxypropyl)aminopyrimidine (**7**); and (4) the mass spectrum, which showed a fragmentation pattern common to pyrrolidones.[5] An attempt to prepare **5** from 2-chloropyrimidine and 2-pyrrolidone in the presence of sodium hydride was not successful.

Treatment of **3** with 3-chloropropionyl chloride in chloroform–pyridine solution at 0–5° led exclusively to 2-(3-chloropropionyl)aminopyrimidine (**8**, Scheme II).[6] Treatment of **8** with an equimolar amount of aqueous potassium carbonate solution caused dehydrochlorination to 2-acryloylaminopyrimidine **12**. This structure was supported by (1) the olefinic absorption and the equivalence of two of the three pyrimidine ring protons as exhibited in its nmr spectrum, and (2) an alternate synthesis by reaction of **3** with acryloyl chloride (Scheme II).

Heating **8** in chloroform, dimethylformamide, or dimethyl sulfoxide produced 3,4-dihydro-2*H*-pyrimido-[1,2-*a*]pyrimidin-2-one hydrochloride (**9**). We are aware of only one other report on the synthesis of this class of compound. Hurd and Hayao[7] prepared the 6,8-dimethyl analog by fusion of 4,6-dimethyl-2-aminopyrimidine with 3-bromopropionic acid.[8] The nmr spectrum of **9** exhibited the three pyrimidine ring hydrogens as multiplets at δ 9.3–9.1, 9.0–8.8, and 7.9–7.6. Brown[9] observed similar multiplet absorptions for the nonequivalent protons in 1-alkyl-2-alkylimino-1,2-dihydropyrimidines. Attempts to isolate the free base **10** from **9** were unsuccessful.[10] With either equimolar or excess aqueous potassium carbonate solution, **9** was hydrolyzed to 2-amino-1-(2-carboxyethyl)pyrimidinium betaine **11a**. The absence of a significant bathochromic shift[11] in the uv spectrum in 0.001 *N* sodium hydroxide [λ_{max} 263 nm (ϵ 2780), 305 (3180)] from the spectral absorptions in methanol [266 nm (ϵ 3490), 310 (2920)], and the absence of any absorption around 345 nm which could be attributed to an imino moiety[11] led

(3) F. L. M. Pattison, J. B. Stothers, and R. G. Woolford, *J. Amer. Chem. Soc.*, **78**, 2255 (1956).

(4) M. S. Manhas and S. J. Jeng, *J. Org. Chem.*, **32**, 1246 (1967).

(5) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 5536 (1964).

(6) At room temperature, a mixture of **8** and the pyrimidopyrimidine **9** was obtained; the isomers were separable by sublimation.

(7) C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, **77**, 117 (1955).

(8) Compound **9** was also obtained by fusion of **3** with 3-chloropropionic acid.

(9) D. J. Brown, B. T. England, and J. S. Harper, *J. Chem. Soc. C*, 1165 (1966).

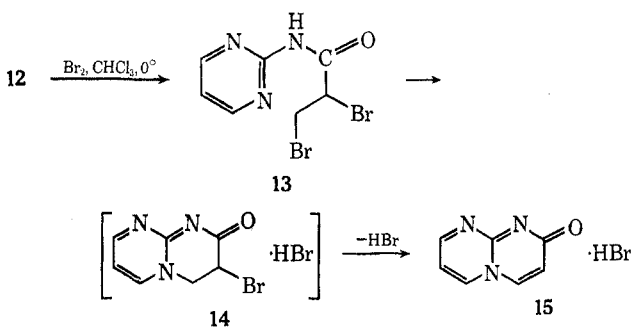
(10) The pyridopyrimidone analog was isolable by neutralization of its hydrochloride salt. *Cf.* R Adams and I. J. Pachter, *J. Amer. Chem. Soc.*, **74**, 4906 (1952).

(11) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963).

to the exclusion of the imino tautomer **11b**. Also our structural assignment of **11a** was based on the similarity of the uv[10] and ir[7] spectra to the corresponding 2-amino-1-(2-carboxyethyl)pyridinium betaine. The free base **10** was finally obtained by heating **12** in *m*-xylene. On treatment with ether–hydrogen chloride, **10** was converted to **9**.

Bromination of **12** gave 2-(2,3-dibromopropionyl)-aminopyrimidine (**13**, Scheme III). At room tempera-

SCHEME III



ture, the bromination procedure led to a solid which tlc analysis showed to be a binary mixture, the major component being **13**, minor component **14**. On heating of this mixture in dimethylformamide, 2*H*-pyrimido-[1,2-*a*]pyrimidin-2-one hydrobromide (**15**) was prepared. An attempt to obtain **15** by fusion of **3** with 1,3-dibromopropionic acid was not successful. Heating **13** in dimethylformamide at 100–110° for about 45 min gave a high yield of **15**. A characteristic feature of the nmr spectrum of **15** was the AB pattern with the more shielded doublet centered at δ 6.85 and the less shielded doublet at δ 8.40. The latter resonance also showed secondary splitting due to coupling with the peri hydrogens at the 4 and 6 positions.[12,13]

Experimental Section[14]

2-(3-Chloropropionyl)aminopyrimidine (8).—**3** (10 g, 0.105 mol) and 8.4 ml (8.3 g, 0.105 mol) of pyridine were added to 50 ml of chloroform. To this mixture at 0–5°, 9.2 ml (13.4 g, 0.105 mol) of 3-chloropropionyl chloride in 50 ml of chloroform was added dropwise over a 1-hr period. After dilution with 150 ml of chloroform, the solution was allowed to warm to room temperature and was washed with 300 ml of 5% aqueous potassium carbonate. The aqueous layer was then extracted with chloroform until the pink coloration was removed. The dried ($MgSO_4$) combined extracts were filtered, reduced *in vacuo* below 40° to 75 ml, and cooled. White crystals (5.5 g, 28.3%) of **8** precipitated: mp 280–285° dec; $\nu_{C=O}$ 5.98 μ; nmr (TFA) 3.30 (t, 2 H, CH_2CO), 3.96 (t, 2 H, CH_2Cl), 7.78 (t, 1 H, 5 proton of pyrimidine ring), 9.08 (d, 2 H, 4,6 protons of pyrimidine ring).

Anal. Calcd for $C_7H_8ClN_3O$: C, 45.29; H, 4.35; Cl, 19.10; N, 22.64. Found: C, 45.45; H, 4.47; Cl, 19.34; N, 22.48.

2-(4-Chlorobutyryl)aminopyrimidine (4).—Using 4-chlorobutyryl chloride in the above procedure gave a 72% yield of **4** as a white solid after two recrystallizations from 2-propanol: mp 97–99°; $\nu_{C=O}$ 5.95 μ; nmr ($CDCl_3$) 2.26 (m, 2 H, CH_2), 3.04 (t, 2 H, CH_2CO), 3.72 (t, 2 H, CH_2Cl), 7.04 (t, 2 H, 5 proton on pyrimidine ring), 8.66 (d, 2 H, 4,6 protons on pyrimidine ring), 10.06 (s, 1 H, NH).

Anal. Calcd for $C_8H_{10}ClN_3O$: C, 48.12; H, 5.01; Cl, 17.50; N, 21.05. Found: C, 48.41; H, 4.98; Cl, 17.50; N, 21.28.

2-Acryloylaminopyrimidine (12).—To 2.0 g (0.015 mol) of potassium carbonate in 50 ml of water was added 2.7 g (0.015 mol) of amide **8**, and the mixture heated on a steam bath until all solids dissolved. The cooled soluion (pH about 7) was saturated with sodium chloride and extracted with chloroform. The dried (Na_2SO_4) extracts were filtered and evaporated at reduced pressure to yield 1.4 g (63%) of an off-white solid. Purification by sublimation (90°, 0.5 mm) or recrystallization (1-butanol–benzene) gave **12**: mp (partial) 125–126°, resolidification and decomposition 195–200°; $\nu_{C=O}$ 5.99 μ; nmr ($CDCl_3$) 7.40–5.76 (m, 4 H, three vinylic and one for 5 position on pyrimidine ring), 8.62 (d, 2 H, 4,6 protons on pyrimidine ring) 10.70 (s, 1 H, NH).

Anal. Calcd for $C_7H_7N_3O$: C, 56.36; H, 4.74; N, 28.17. Found: C, 56.33; H, 4.74; N, 28.09.

Compound **12** was also prepared in lower yield (27%) by reacting equimolar quantities of **3**, acryloyl chloride, and triethylamine in acetonitrile essentially according to the procedure described for compound **8**.

2-(2,3-Dibromopropionyl)aminopyrimidine (13).—A solution of **12** (1.25 g, 0.0084 mol) in 200 ml of chloroform at 0° was treated with a chloroform (30 ml) solution of bromine (1.36 g, 0.0085 mol) dropwise over a 2-hr period. The resulting mixture became colorless after 48 hr of refrigeration and was filtered to afford 0.65 g of a pale yellow solid. Tlc examination (silica gel, 30:70 chloroform:methanol) showed this solid to be mainly **13** contaminated with **14**. The reaction filtrate was evaporated below room temperature under reduced pressure to about 15 ml, chilled overnight, and filtered to afford 1.18 g (45.4%) of **13** as a white solid: mp 135–140° bubbling, resolidification on further heating, 290° dec; $\nu_{C=O}$ 5.91 μ; nmr (TFA) 4.29–3.67 (m, 2 H, CH_2), 4.92 (q, 1 H, CH), 7.84 (t, 1 H, 5 proton on pyrimidine ring), 9.18 (d, 2 H, 4,6 protons on pyrimidine ring).

Anal. Calcd for $C_7H_7Br_2N_3O$: C, 27.21; H, 2.29; Br, 51.73; N, 13.60. Found: C, 27.22; H, 2.47; Br, 51.53; N, 13.45.

1-(2-Pyrimidinyl)-2-pyrrolidone (5).—**4** (6 g, 0.03 mol) was dissolved in a solution of 4.14 g (0.03 mol) of potassium carbonate in 200 ml of water by briefly heating on a steam bath. The cooled solution (pH 7–8) was extracted with chloroform, and the extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude residue recrystallized from hot ether to yield 3.7 g (76%) of a white solid: mp 107.5–110°; $\nu_{C=O}$ 5.84 μ; nmr ($CDCl_3$) 2.12 (m, 2 H, CH_2), 2.56 (t, 2 H, CH_2CO), 3.96 (t, 2 H, CH_2N), 6.82 (t, 1 H, 5 proton on pyrimidine ring), 8.46 (d, 2 H, 4,6 protons on pyrimidine ring).

Anal. Calcd for $C_8H_9N_3O$: C, 58.90; H, 5.52; N, 25.77; mol wt, 163. Found: C, 58.95; H, 5.54; N, 26.09; mol wt, 163 (mass spectrometric).

2-(3-Carboxypropyl)aminopyrimidine (7).—To 15 ml of a 10% solution of sulfuric acid was added 0.6 g (0.0037 mol) of **5**, and the solution was heated at 100° for 24 hr. Adjustment of the pH to 6 precipitated a white solid. The mixture was evaporated to dryness and the residue extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residual solids were recrystallized from absolute alcohol–ether to afford 0.44 g (65.6%) of **7**, mp 120–124°. Sublimation at 96° (0.1 mm) gave the analytical sample, mp 124.5–126°.

Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.04; H, 6.08; N, 23.21; mol wt, 181. Found: C, 53.31; H, 6.25; N, 23.10; mol wt, 181 (mass spectroscopic).

3,4-Dihydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-one Hydrochloride (9).—To 5 ml of dimethyl sulfoxide was added 0.5 g (0.0027 mol) of **8**, and the mixture heated 10 min on a steam bath and then cooled. The solids were filtered off and washed with fresh dimethyl sulfoxide followed by chloroform to give a nearly quantitative yield of **9**: mp 290–291° dec; $\nu_{C=O}$ 5.74 μ; uv λ_{max}^{MeOH} 233 nm (ϵ 6000), 268 (3300), 300 (2360); nmr (TFA) 3.44 (t, 2 H, CH_2), 5.10 (t, 2 H, CH_2), 7.76 (q, 1 H, pyrimidine ring), 8.96 (q, 1 H, pyrimidine ring), 9.20 (q, 1 H, pyrimidine ring).

Anal. Calcd for $C_7H_8ClN_3O$: C, 45.29; H, 4.35; Cl, 19.10; N, 22.64. Found: C, 45.45; H, 4.35; Cl, 19.29; N, 22.50.

3,4-Dihydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-one (10).—To 5 ml of *m*-xylene was added 0.36 g (0.0024 mol) of **12**. As the temperature was increased, the olefin slowly dissolved until *ca.* 120° a white solid began to separate which gradually yellowed while the temperature was maintained between 120 and 130° for 0.5 hr. Cooling gave a quantitative yield of crude **10**. Recrystallization (DMF) gave 0.29 g (58%) of **10**: mp 210–211°; ir strong bands at 6.18, 6.50, 6.59, 6.79, 6.96, 7.34, 7.92, 8.68,

(12) K. D. Bartle, D. W. Jones, and R. S. Matthews, *Tetrahedron*, **25**, 2701 (1969).

(13) W. W. Paudler and H. L. Blewitt, *ibid.*, **21**, 353 (1965).

(14) Spectra were obtained on the following instruments: infrared on a Perkin-Elmer Infracord 137 (KBr pellets), ultraviolet on a Bausch and Lomb Spectronic 505, nmr on a Varian A-60A [chemical shifts reported downfield from Me_4Si as an internal standard in parts per million (δ)], mass spectra at 70 eV on a CEC 21-103C. Brinkman silica gel F-254 was employed for tlc.

8.99, 12.02, 12.78, 13.27 μ; uv λ_{max}^{MeOH} 265 nm (ϵ 23,000), 314 (5070).

Anal. Calcd for $C_7H_7N_3O$: C, 56.36; H, 4.74; N, 28.17. Found: C, 56.20; H, 4.31; N, 28.04.

Solution of **10** in methanol–hydrogen chloride–ether gave **9**.

2-Amino-1-(2-carboxyethyl)pyrimidinium Betaine (11a).—To a solution of 0.75 g (0.0054 mol) of potassium carbonate in 25 ml of water was added 1.0 g (0.005 mol) of **9**. The nearly neutral solution was evaporated to dryness and the residue extracted with hot chloroform. The chloroform extracts were evaporated at reduced pressure. Recrystallization of the residue (ethanol–ether) gave 0.3 g of a light yellow solid, mp 171–172.5°.

2*H*-Pyrimido[1,2-*a*]pyrimidin-2-one Hydrobromide (15).—A mixture of 5 ml of dimethylformamide and 1.0 g (0.0032 mol) of **13** was slowly heated in an oil bath whereupon solution occurred. Near 80° a solid began to separate and heating was continued at 100–110° for *ca.* 45 min. The cooled mixture was filtered and the residue washed with dimethylformamide followed by chloroform. Recrystallization (TFA–methanol) gave 0.53 g (72.6%) of **15**: mp (darkening) 280°, bubbling 310° dec; $\nu_{C=O}$ 5.75 μ; uv λ_{max}^{MeOH} 240 nm (ϵ 9464), 320 (5986); λ_{max} (0.001 *N* NaOH) 247 (14,280), 275 (14,570), 313 (46,280); nmr (TFA) 6.85 (d, 1 H, 3 proton), 8.10–7.84 (m, 1 H, 7 proton), 8.40 (d, 1 H, 4 proton), 9.76–9.40 (m, 2 H, 6,8 protons).

Anal. Calcd for $C_7H_6BrN_3O$: C, 36.86; H, 2.66; Br, 35.04; N, 18.43. Found: C, 36.87; H, 3.09; Br, 35.03; N, 18.43.

If the resulting solid formed at 80° was filtered off and washed with chloroform, tlc analysis showed the presence of only a small amount of **15**, the major component being the intermediate **14**.

Registry No.—**4**, 27179-31-3; **5**, 27179-32-4; **7**, 27179-33-5; **8**, 27179-34-6; **9**, 27248-73-3; **10**, 27179-35-7; **11**, 27179-36-8; **12**, 27179-37-9; **13**, 27179-38-0; **15**, 27179-39-1.

Cyclic Lactams. II.[1] 1,7-Dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione and 3,6-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-1,4-dione from 4-Methyl-1-tetralone-4-acetic Acid

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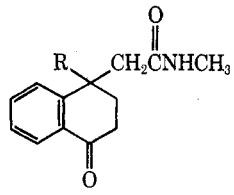
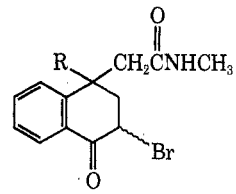
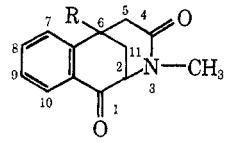
In a model study related to preparation of some benzomorphan analgesics,[3] we attempted to prepare the basic nucleus of this system from 4-methyl-1-tetralone-4-acetic acid. Various routes to this hexahydro-2,6-methano-3-benzazocine nucleus have been explored in considerable detail.[4–7] Walker and Alkalay[7] reported a successful ring closure to this skeleton from the *N*-methylamide of 4-phenyl-1-tetralone-4-acetic acid (**2**) by intramolecular displacement of the halide of the intermediate α-bromo ketone **4**. Because of the problems encountered in separation of the diastereomeric α-bromo ketones, and only partially successful cyclization using methanol–sodium methoxide, we sought to investigate the possibility of a solvolytic displacement process which would lead to benzazocine **5**. The isolation of the azabicyclo[4.3.0]nonane derivative from this process is reported.



1, R = CH_3
2, R = Ph

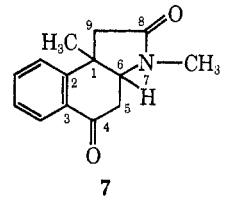


3, R = CH_3
4, R = Ph



5, R = CH_3
6, R = Ph

The necessary 4-methyl-1-tetralone-4-acetic acid was available from the Friedel–Crafts alkylation of γ-methyl-γ-(carbethoxymethyl)butyrolactone and subsequent cyclization.[8] The amide formation process was very inefficient when the mixed anhydride formed from ethyl choroformate was treated with anhydrous methylamine. However, formation of the *N*-hydroxysuccinimide ester using dicyclohexylcarbodiimide followed by treatment with aqueous methylamine resulted in the desired amide in excellent yield. Bromination was performed in acetic acid–chloroform, or in benzene–tetrahydrofuran, with the latter method being preferable. The intermediate mixture of α-bromo ketones (**3**) was refluxed in dimethylformamide to attempt intramolecular displacement. Only a single ketone amide was isolated which was identified as 1,7-dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione (**7**), based on nmr evidence, reduction, and subsequent preparation of **5** by a related method.



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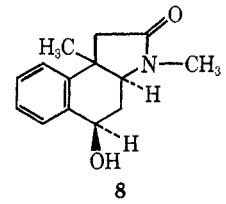

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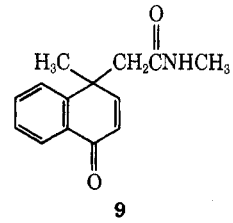

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The nmr spectrum of the isolated product showed, in addition to the expected tetralone aromatic protons, singlets for methyl groups and methylene protons adjacent to the carboxamide function, a triplet, and a doublet at δ 3.83 and 2.90 (J = 4 Hz), integrating for one and two protons, respectively. The position of the

(1) Previous paper: W. L. Nelson, D. D. Miller, and R. S. Wilson, *J. Heterocycl. Chem.*, **6**, 131 (1969).

(2) Taken in part from the Ph.D. thesis of K. F. Nelson, submitted to the Graduate School, University of Washington, July 1970.

(3) K. F. Nelson, Ph.D. Thesis, University of Washington, 1970.

(4) E. L. May and L. J. Sargent in "Analgetics," Medicinal Chemistry Monographs, Vol. 5, G. deStevens, Ed., Academic Press, New York, N. Y., 1965, pp 123–177.

(5) N. B. Eddy and E. L. May in "Synthetic Analgesics," International Series of Monographs in Organic Chemistry, Vol. 8, D. H. R. Barton and W. von Doering, Ed., Pergamon Press, London, 1966, pp 115–137.

(6) G. deStevens, *Pure Appl. Chem.*, **19**, 89 (1969).

(7) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966), and references therein.

(8) W. Herz and A. Caple, *J. Amer. Chem. Soc.*, **84**, 3517 (1962).