Pyrimido[5,4-*e*]-*as*-Triazines. III. The Preparation and Some Reactions of 5-Substituted Pyrimido[5,4-*e*]-*as*-Triazines[1]

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Reaction of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (**1**) with NaN_3 gave directly the heteroaromatic 5-aminopyrimido[5,4-*e*]-*as*-triazine (**2**). The amino group of **2** underwent exchange with both $EtNH_2$ and H_2N-NH_2 in the presence of HCl to give 5-ethylamino- and 5-hydrazinopyrimido[5,4-*e*]-*as*-triazine (**7** and **8**), respectively. In the absence of acid the pyrimidine ring was opened to give 6-amino-*as*-triazine-5-carboxamidine derivatives **9** and **10**. Alkylation of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine with $C_6H_5CH_2Cl$ gave the corresponding 5-benzylamino derivative **11**. Treatment of **2** with aqueous NaOH hydrolyzed the amino group to give pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one (**12**). Reduction of **12** with $Na_2S_2O_4$ in HOAc resulted in ring contraction to give 9-acetamidohypoxanthine (**14**). Reaction of **12** with Et_3N cleaved the pyrimidine ring to give 6-amino-*as*-triazine-5-carboxamide (**20**), which was cyclized with diethoxymethyl acetate to give **12** and with the phosgene–pyridine complex to give pyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione (**23**). Methylation of **23** gave the antibiotic, fervenulin (**24**).

The identification of the biologically active antibiotics toxoflavin and fervenulin[2-4] has stimulated interest in the chemistry of the pyrimido[5,4-*e*]-*as*-triazine (7-azapteridine) ring system. The difficulties encountered in the preparation and cyclization of 5-amino-4-hydrazinopyrimidines[2,4] to give pyrimido[5,4-*e*]-*as*-triazines led us to examine some of the reactions of both the 1,2-dihydro and heteroaromatic derivatives of this ring system and to synthesize the parent ring system, pyrimido[5,4-*e*]-*as*-triazine-5,7(6H,8H)-dione (**23**)[5] from the previously unknown 6-amino-*as*-triazine-5-carboxamide (**20**).

Although the ultraviolet (uv) spectrum indicated that treatment of 4,5-diamino-6-hydrazinopyrimidine[6] with the $(EtO)_3CH$–HCl reagent[7] gave some 5-aminopyrimido[5,4-*e*]-*as*-triazine (**2**), this compound was not separated pure from the other reaction products. However, the reaction of 5-chloro-1,2-dihydropyrimido-[5,4-*e*]-*as*-triazine (**1**)[7] with NaN_3 in aqueous EtOH, either at room temperature or at reflux, gave directly the 5-amino compound **2** (Scheme I). Although the intermediates and the order of their occurrence in this reaction are unknown, this transformation probably involves either (1) oxidation of **1** by the azide group[8] to give **3** and ammonia which then combine to give **2** or (2) azido-5-dechlorination of **1** followed by oxidation of the 1,2-dihydro-*as*-triazine ring and conversion of the azido group into an amino group. The latter could occur either by autoxidation or disproportionation. Prior air oxidation of **1** to **3** was eliminated from consideration by treatment of **1** with aqueous ethanolic NaCl, which resulted in ring opening of the 1,2-dihydrotriazine ring to give the pyrimidine **5**. Reaction sequence 2 is supported by (a) the nitrosation of the 5-hydrazino compound **8** (see below) at room temperature to give **2**, presumably *via* an azido intermediate, (b) the formation of a dihydro derivative by reaction of **1** with a nucleophile in a reducing medium (NaSH),[9] and (c) the reaction of **1** with diethylamine to give a 17% yield of **6** presumably formed *via* oxidation of a dihydro intermediate of **6**.[10] The recovery of 1-benzyl-5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine[11] in 79% yield from its reaction with NaN_3 would appear to provide support for route **1**; however, this result might indicate that the facility with which **1** and NaN_3 react is related to the delocalization of the charge at N-1 as in the intermediate anionic adduct **4**. The importance of charge delocalization in the adjoining ring has been noted in other heterocyclic systems.[12]

Previously it was shown that the 5-amino group of heteroaromatic pyrimido[5,4-*e*]-*as*-triazines will undergo exchange with primary amines.[13] Treatment of **2** with excess alcoholic $EtNH_2$ in a bomb at 125° gave a mixture containing the 5-ethylamino compound **7** as a minor component. The major component was identified as the *as*-triazine-5-carboxamidine **9** by elemental analyses and its pmr spectrum. Reaction of **2** with $EtNH_2$ at 65° gave a 69% yield of recovered **2** and a 22% yield of crude **7**. Addition of HCl to this reaction, however, gave a 63% yield of **7**, identified by elemental analyses and its pmr spectrum. At this temperature it appears that the exchange reaction, but not the cleavage reaction, is catalyzed by HCl.[14] Also the results described above indicate that only **7** and not **2** is involved in the cleavage reaction. Similar products were obtained by treatment of **2** with alcoholic hydrazine. In hot propanol, **2** and hydrazine gave the *as*-triazine-5-carboxamide hydrazone **10**. Although little or no reaction occurred between **2** and hydrazine in hot MeOH, addition of HCl to this reaction gave a 59% yield of the 5-hydrazino compound **8**. As described

(1) This work was supported by the C. F. Kettering Foundation and by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, **84**, 1724 (1962).

(3) E. C. Taylor and F. Sowinski, *ibid.*, **90**, 1374 (1968) and references therein.

(4) T. K. Liao, F. Baiocchi, and C. C. Cheng, *J. Org. Chem.* **31**, 900 (1966), and references therein.

(5) Part of this work has appeared as a preliminary report. See C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Heterocycl. Chem.*, **5**, 581 (1968).

(6) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **30**, 829 (1965).

(7) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *ibid.*, **28**, 923 (1963).

(8) E. S. Gould, "Inorganic Reactions and Structure," Henry Holt and Co., New York, N. Y., 1955, p 236.

(9) This reaction gave 1,2-dihydropyrimido[5,4-*e*]-*as*-triazine-5(6*H*)-thione; it will be described in a forthcoming paper.

(10) The oxidation of reduced pteridines is retarded by chloro groups and accelerated by amino groups. See E. C. Taylor and W. R. Sherman, *J. Amer. Chem. Soc.*, **81**, 2464 (1959).

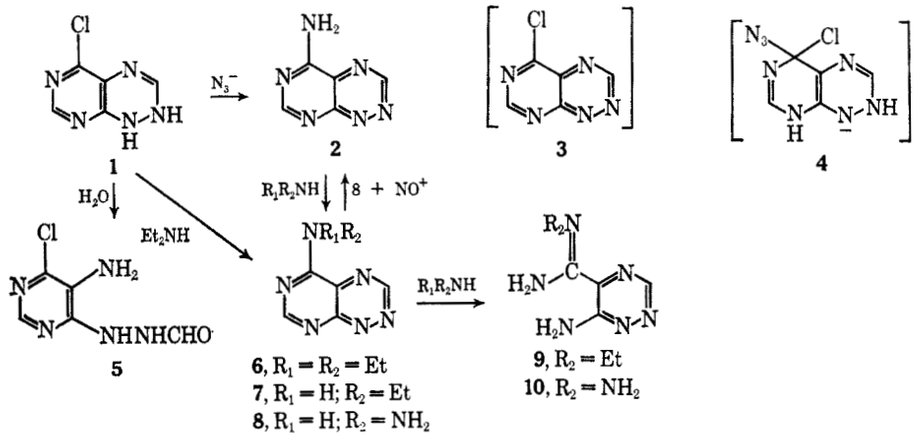
(11) J. A. Montgomery and C. Temple, Jr., *ibid.*, **82**, 4592 (1960).

(12) E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *ibid.*, **82**, 6058 (1960).

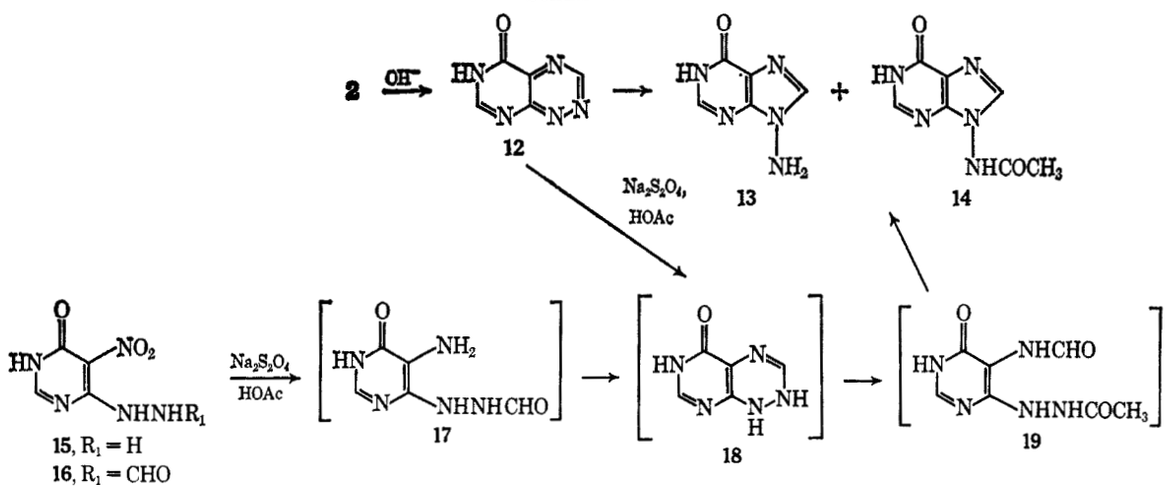
(13) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **28**, 3038 (1963).

(14) C. W. Whitehead and J. J. Traverso, *J. Amer. Chem. Soc.*, **82**, 3971 (1960).

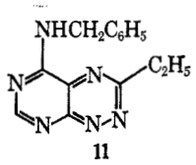
SCHEME I



SCHEME II



above, the nitrosation of **8** gave **2** in 42% yield. Addition of **2** to 10% NaOH gave a precipitate, presumably a sodium salt of a hydrated derivative of **2**.[15] That the 5-amino group of this ring system was acidic, however, was shown by alkylation of 5-amino-3-ethylpyrimido-[5,4-*e*]-*as*-triazine with NaH and $C_6H_5CH_2Cl$ in DMF to give a 16% yield of pure **11**.[13]



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Reaction of **2** with an equivalent amount of aqueous NaOH at room temperature hydrolyzed the amino group to give **12** (Scheme II).[13] An earlier study on the preparation of **12** from the 4-hydrazinopyrimidine **15**[6] was unsuccessful. Formylation of **15** with formic acid to give **16**, followed by the reductive cyclization of **16** with $Na_2S_2O_4$ in HOAc, gave mainly 9-acetamidohypoxanthine (**14**), which was also prepared from 9-aminohypoxanthine (**13**)[11] and acetic anhydride. In addition acid hydrolysis of the reaction product gave **13**, which on nitrosation gave hypoxanthine. Apparently the conversion of **16** into **14** involved (1) reduction of the nitro group of **16** to give **17**, (2) cyclization of **17** to give **18**, (3) acetylation and opening of the *as*-triazine of **18** to give **19**, and (4) recyclization of **19** to give **14**.[16] Support for this mechanism was obtained by treatment of **12** with $Na_2S_2O_4$ in HOAc to give a mixture of **13** and **14**, presumably formed *via* **18** and **19**. In other studies reaction of (1) 5-amino-4-hydrazinopyrimidin-6(1H)-one[6] with the $(EtO)_3CH$–HCl reagent, (2) 4-chloro-5-ethoxymethyleneaminopyrimidin-6(1H)-one with hydrazine,[13] and (3) compound **1** with aqueous NH_4OH gave only low yields of crude **12**.

Treatment of **12** with aqueous ethanolic Et_3N cleaved the pyrimidine ring to give 6-amino-*as*-triazine-5-carboxamide (**20**) (Scheme III).[17] A 6% yield of the corresponding carboxylic acid **21** was also obtained in this reaction. The recyclization of **20** to **12** was carried out with hot diethoxymethyl acetate. Also, treatment of **20** with a HCO_2H–Ac_2O mixture gave **22**, which was converted into **12** (tlc) in DMF containing K_2CO_3. No reaction occurred on treatment of **20** with hot formic acid, which was explained when it was found that the formamide group of **22** was hydrolyzed in hot formic acid to give **20**. Although the fusion of **20** with urea gave mainly decomposition products containing a trace amount of **23**, the reaction of **20** with the phosgene–pyridine complex[18] gave a 37% yield of pure **23**.[5]

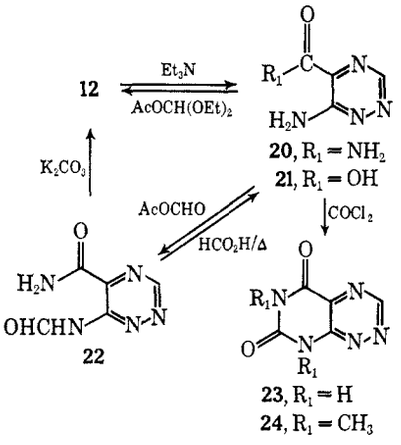
(15) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951), reported that 4-aminopteridine forms an anion in 0.2 *N* NaOH.

(16) A similar sequence of reactions for the conversion of 5-amino-4-chloro-6-hydrazinopyrimidine into 9-formamidohypoxanthine has been demonstrated. See ref 7.

(17) J. Clark and G. Neath, *J. Chem. Soc., C*, 1112 (1966).

(18) C. Scholtissek, *Ber.*, **89**, 2562 (1956).

SCHEME III



This structure was confirmed by alkylation with CH_3I in DMF containing K_2CO_3 to give the antibiotic, fervenulin **24**.[2,3]

Experimental Section

Melting points were determined on a Kofler Heizbank apparatus and are corrected. The uv absorption spectra of solutions were determined with a Cary Model 14 spectrophotometer, whereas the infrared (ir) absorption spectra were determined in pressed potassium bromide disks with Perkin-Elmer Models 221-G and 521 spectrophotometers. The proton magnetic resonance (pmr) spectra were obtained on a Varian A-60A spectrometer in DMSO-d_6 using tetramethylsilane as an internal reference. Descending paper chromatograms were developed in water saturated butanol (A), butanol–glacial acetic acid–water (5:2:3, v/v) (B), isopropyl alcohol–concentrated ammonium hydroxide–water (70:5:25, v/v) (C), and acetate buffer pH 6.1 (D). Thin layer chromatograms were prepared from silica gel H (Brinkmann) and were usually developed with mixtures of chloroform and methanol.

5-Aminopyrimido[5,4-*e*]-*as*-triazine (2). A.—A mixture of **1**[7] (32 g) and NaN_3 (20 g) in 1:1 EtOH–H_2O (1300 ml) was refluxed with stirring for 2 hr. After cooling the solid was collected by filtration, washed with water, and dried *in vacuo* over P_2O_5 to give practically pure product: yield 26 g (93%). The analytical sample was obtained by recrystallization from MeOH: mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 217 (13.8), 243 (10.0), 353 (10.5), 358 (sh) (10.3); $\bar{\nu}_{max}$ in cm^{-1}, 3225, 3045 (NH), 1670 (NH_2), 1650, 1575, 1540, 1500 (C=C, C=N); pmr, τ −0.11, 1.32 (1, 1, CH), 1.12 (2, NH).

Anal. Calcd for $C_5H_4N_6$: C, 40.55; H, 2.70; N, 56.75. Found: C, 40.57; H, 2.80; N, 56.87.

At room temperature for 24 hr 1 (1.0 g) and NaN_3 (0.61 g) gave an 87% yield of **2**.

B.—To a suspension of **8** (500 mg) in 1:1 EtOH–H_2O (20 ml) was added with stirring a solution of $NaNO_2$ (250 mg) in 1 *N* HCl (3.1 ml). After 18 hr the solid (190 mg, 42%) was collected by filtration and identified as **2** by comparison of its uv spectrum and chromatographic behavior (tlc) with those described in A.

C.—A suspension of 4,5-diamino-6-hydrazinopyrimidine[6] (1.0 g) and ethyl orthoformate (20 ml) containing concentrated HCl (0.62 ml) was stirred at room temperature for 20 hr. The solid (1.15 g) was collected by filtration and was shown to contain **2** by comparison of its uv spectrum and chromatographic behavior (tlc) with those described in A. The isolation of pure **2** from this solid by recrystallization was unsuccessful.

5-Amino-4-chloro-6-(2-formylhydrazino)pyrimidine (5).[7]—A suspension of **1** (1.0 g) in 1:1 EtOH–H_2O (64 ml) containing NaCl (0.52 g) was refluxed for 2.5 hr. The unreacted **1** (0.47 g) was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Tlc (9:1 $CHCl_3$–MeOH) showed that the resulting solid contained mainly **5** contaminated with **1** and **12**. Extraction of this residue with hot EtOAc (25 ml) and recrystallization of the solid from the extract from C_6H_6 gave the product containing a trace amount of **1**: yield 0.22 g (38% based on recovered **1**).

Anal. Calcd for $C_5H_6ClN_5O$: C, 32.00; H, 3.20; N, 37.30. Found: C, 32.25; H, 3.17; N, 37.01.

5-Diethylaminopyrimido[5,4-*e*]-*as*-triazine (6).—A suspension of **1** (5.0 g) in *n*-PrOH (100 ml) containing Et_2NH (15 ml) was refluxed for 5 hr. After filtration the dark filtrate was evaporated to dryness, and the residue was triturated with H_2O (20 ml). The remaining solid (1.2 g) was extracted with EtOAc, and the extract was evaporated to dryness to give **6**: yield 1.0 g (17%); mp 123° (recrystallization of a portion of this sample from hexane raised the melting point to 127°); λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 233 (11.6), 373 (11.6); $\bar{\nu}_{max}$, in cm^{-1}, 2975, 2930 (aliphatic CH), 1570, 1515 (C=C, C=N).

Anal. Calcd for $C_9H_{12}N_6$: C, 52.93; H, 5.92; N, 41.15. Found: C, 52.98; H, 6.03; N, 41.15.

5-Ethylaminopyrimido[5,4-*e*]-*as*-triazine (7).—A suspension of **2** (1.0 g) in MeOH (20 ml) and 1.0 *N* HCl (6.8 ml) containing $EtNH_2$ (1.0 ml) was heated with stirring at 68° for 8 hr. The resulting solution was evaporated to dryness, and the residue was recrystallized from benzene: yield 0.75 g (63%); mp 170° with presoftening from 130°. Recrystallization of a portion of this solid from petroleum ether (bp 85–105°) gave the analytical sample: mp 172°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 224 (12.5), 249 (sh) (4.51), 363 (10.7); $\bar{\nu}_{max}$, in cm^{-1}, 2975, 2950 (aliphatic CH), 1605 (NH), 1565, 1490 (C=C, C=N); pmr, τ −0.15, 1.22 (1, 1, CH), 0.44 (m, 1, NH), 6.35 (m, 2, CH_2), 8.73 (t, 3, CH_3).

Anal. Calcd for $C_7H_8N_6$: C, 47.72; H, 4.58; N, 47.71. Found: C, 47.99; H, 4.55; N, 47.61.

A similar reaction without HCl gave 0.69 g of recovered **2** and only 0.26 g (22%) of impure **7**.

5-Hydrazinopyrimido[5,4-*e*]-*as*-triazine (8).—A suspension of **2** (1.0 g) in MeOH (20 ml) and 1.0 *N* HCl (6.8 ml) containing 95+% hydrazine (0.5 ml) was heated with stirring at 80° for 5 hr. After the mixture was cooled, the solid was collected by filtration, washed with MeOH, and dried *in vacuo* over P_2O_5: yield 0.65 g (59%); mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] 0.1 *N* HCl, 365 (7.33); $\bar{\nu}_{max}$, in cm^{-1}, 3400, 3270 (NH), 1625 (NH), 1610, 1550 (C=C, C=N); pmr, τ 1.03, 2.63 (1, 1, CH), *ca.* 1.5 (NH).

Anal. Calcd for $C_6H_5N_7$: C, 36.81; H, 3.09; N, 60.10. Found: C, 37.00; H, 3.41; N, 59.81.

In a similar reaction without HCl 0.84 g of **2** was recovered after 20 hr.

6-Amino-N-ethyl-*as*-triazine-5-carboxamidine (9).—A mixture of **2** (5.2 g), ethylamine (25 ml), and *n*-PrOH (170 ml) in a Parr bomb was heated at 100° for 9 hr, then at 125° for 4 hr. The resulting solution was evaporated to dryness, and the residue was recrystallized from C_6H_6 to give **9** in two crops: yield 2.0 g (35%) mp 179°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 240 (9.34), 347 (4.06); $\bar{\nu}_{max}$, in cm^{-1}, 2965, 2930, 2865 (aliphatic CH), 1640 (NH), 1600, 1585, 1520 (C=C, C=N); pmr, τ 0.98 (1, CH), 1.53, 3.20 (2, 2, NH), 6.76 (q, 2, CH_2), 8.76 (t, 3 CH_3).

Anal. Calcd for $C_6H_{10}N_6$: C, 43.36; H, 6.06; N, 50.57. Found: C, 43.43; H, 6.03; N, 50.39.

The C_6H_6 filtrate gave 0.87 g (14%) of crude **7**, mp 160–163°.

6-Amino-*as*-triazine-5-carboxamide Hydrazone (10).—A mixture of **2** (1.0 g) and 95+% anhydrous hydrazine (1.0 ml) in *n*-PrOH (20 ml), protected with drying a tube, was refluxed under a Dry Ice condenser for 20 hr. The solid was collected by filtration and recrystallized from MeOH: yield 0.32 g (31%); mp 245° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 357 (9.04); $\bar{\nu}_{max}$, in cm^{-1}, 3420, 3370, 3340, 3315, 3185 (NH), 1640, 1600 (NH_2), 1560, 1495 (C=C, C=N); pmr, τ 1.05 (1, CH), 2.15, 3.83, 4.10 (2,2,2, NH).

Anal. Calcd for $C_4H_7N_7$: C, 31.37; H, 4.60; N, 64.03. Found: C, 31.44; H, 4.62; N, 63.98.

5-Benzylamino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (11).[13]—Solid NaH (0.30 g), 51.5% dispersed in mineral oil, was added with stirring to a suspension of 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine[13] (1.0 g) in DMF (10 ml), which was cooled in an ice bath. After the initial reaction had subsided, benzyl chloride (0.8 ml) was added. Then the mixture was stirred at room temperature for 1.5 hr and evaporated *in vacuo* to give a gum. This residue was extracted with CCl_4 (50 ml), the extract was evaporated to dryness *in vacuo*, and the resulting oil was extracted with three 300-ml portions of hot petroleum ether (bp 85–105°). The combined extracts were decanted from the gum that deposited, then evaporated to dryness to give the crude

(19) Each solution contains 10% dissolving solvent and 90% appropriate aqueous solvent: a, MeOH; b, 8%methanolic DMSO; c, H_2O.

product: yield 0.40 g; mp ~141° dec. Two recrystallizations of this material from petroleum ether gave the pure product: yield 0.25 g (16%); mp 152–153° dec (lit.[13] mp 153–154° dec); pmr, τ 0.18 (t,1, NH), 1.30 (1, CH), 2.65 (5, C_6H_5), 5.17 (d,2, CH_2), 6.63 (q,2, CH_2), 8.51 (t,3, CH_3).

Pyrimido[5,4-e]-as-triazin-5(6H)-one (12). **A.**—A suspension of **2** (10 g) in H_2O (100 ml) containing 1 *N* NaOH (73 ml) was stirred at room temperature for 3 hr. A trace amount of solid was removed by filtration, and with cooling and stirring the filtrate was acidified with 1 *N* HCl (146 ml). After 0.5 hr the product was collected by filtration: yield 5.7 g (57%). The analytical sample was obtained by recrystallization from H_2O: mp 256° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* HCl, 232 (8.19), 264 (4.49), 329 (5.42); $\bar{\nu}_{max}$, in cm^{-1}, 1715 (CO), 1605, 1595, 1535 (C=C, C=N); pmr, τ −0.08, 1.52 (1,1, CH), *ca.* −2.0 (NH).

Anal. Calcd for $C_5H_3N_5O$: C, 40.27; H, 2.03; N, 46.97. Found: C, 40.48; H, 2.28; N, 47.16.

B.—A suspension of 5-amino-4-hydrazinopyrimidin-6(1H)-one[6] (500 mg) in $(EtO)_3CH$ (10 ml) containing concd HCl (0.3 ml) was stirred at room temperature for 6 hr. The solid was collected by filtration, washed with hot CH_3OH (25 ml), and dissolved in 0.1 *N* NaOH (20 ml). After filtration the filtrate was acidified to pH 1 with 1 *N* HCl to give 25 mg of **12**.

C.—A suspension of **1** (500 mg) in 1 *N* NH_4OH (10 ml) was stirred at room temperature for 1 hr. The solid was collected by filtration and washed with H_2O (10 ml) and EtOH (10 ml), to give 250 mg of crude **12**.

D.—A suspension of 4-chloro-5-ethoxymethyleneaminopyrimidin-6(1H)-one (1.0 g) in EtOH (20 ml) containing 95% anhydrous hydrazine (0.16 ml) was refluxed for 3 hr, and the mixture was evaporated to dryness to yield 810 mg of a slightly gummy solid. Paper chromatograms in four solvent systems indicated that this material was mainly 5-amino-4-chloropyrimidin-6(1H)-one[6] containing a trace amount of **12**.

E.—A solution of **20** (1.0 g) in diethoxymethyl acetate (20 ml) was heated at 100° for 4 hr and evaporated to dryness *in vacuo*. This residue was dissolved in 1.5 *N* NH_4OH (11 ml), and the resulting solution was acidified to pH 4 with 1 *N* HCl to deposit **12**: yield 0.82 g (77%); mp 251° dec (95% pure by uv spectrum).

4-Chloro-5-ethoxymethylenaminopyrimidin-6(1H)-one.—A suspension of 5-amino-4-chloropyrimidin-6(1H)-one hydrochloride[6] (5.0 g) in diethoxymethyl acetate (25 ml) was stirred at room temperature for 2.5 hr. An additional 5 ml of diethoxymethyl acetate was added to the mixture at the end of the first hour. The solid was collected by filtration, washed with ether (25 ml), and dried *in vacuo* over P_2O_5: yield 0.77 g; mp 181–183° dec with the evolution of gas (the melt solidified and did not remelt below 264°); λ_{max}, in mμ ($\epsilon \times 10^{-3}$), EtOH, 259 (5.50), 300 (7.92); $\bar{\nu}_{max}$, in cm^{-1}, 1700 (C=O), 1635, 1610, 1500 (C=C, C=N).

Anal. Calcd for $C_7H_5ClN_3O_2$: C, 41.65; H, 3.97; Cl, 17.61; N, 20.80. Found: C, 41.36; H, 4.30; Cl, 17.76; N, 20.82.

The diethoxymethyl acetate filtrate was evaporated to dryness under reduced pressure, and the remaining oil was distilled under high vacuum. The fraction that boiled at 121–155° was collected and extracted with petroleum ether (bp 85–105°) (35 ml), and the extract was evaporated to dryness to give an oil that solidified on cooling: yield 2.91 g; mp 181–183° dec with the evolution of fumes. The total yield was 3.67 g (66%).

9-Acetamidohypoxanthine (14). **A.**—A mixture of 9-aminohypoxanthine (**13**,[11] 900 mg) and Ac_2O (50 ml) was heated for 1 hr, the unreacted material (620 mg) was removed by filtration, and the filtrate was evaporated to dryness *in vacuo:* yield 450 mg. This residue was dissolved in 1 *N* NH_4OH, the solution was filtered, and the filtrate was evaporated to dryness *in vacuo*. The resulting residue was triturated with a small amount of H_2O and dried *in vacuo* over P_2O_5: yield 180 mg (50%, based on recovered **16**); mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* NaOH, 256 (11.8); $\bar{\nu}_{max}$, in cm^{-1}, 1715, 1700 (C=O), 1585, 1560, 1535, 1515 (C=C, C=N); paper chromatogram solvent (R_f). A (0.24), B (0.53), C (0.34), D (0.78).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.55; H, 3.63; N, 36.25. Found: C, 43.76; H, 3.66; N, 36.02.

B.—Solid sodium hydrosulfite (3 g) was added in several portions with stirring to a suspension of **16** (1.0 g) in glacial AcOH (20 ml) at 100°, and the mixture was refluxed for 18 hr. After the addition of concentrated HCl (7 ml), the solid was removed by filtration, and the filtrate was evaporated to dryness *in vacuo* to yield 1.4 g of colored solid. Chromatographic data indicated that the major absorbing spot was **14**: paper chromatogram solvent (R_f), A (0.23), B (0.51), D (0.80). Similar treatment of **12** gave **14** containing a small amount of **13**.

In another experiment the isolated solid was boiled for 10 min in 2 *N* HCl to give mainly **13**, identified by its paper chromatographic behavior: A (0.12), B (0.42), C (0.23), D (0.68). Nitrosation of this sample gave hypoxanthine: A (0.26), B (0.51), C (0.36), D (0.58).

4-(2-Formylhydrazino)-5-nitropyrimidin-6(5H)-one (16).—A suspension of **15**[6] (2.3 g) in 98% HCO_2H (20 ml) was refluxed for 30 min and diluted with methanol (75 ml). The yellow solid that deposited was collected by filtration and dried *in vacuo* over P_2O_5: yield 2.10 g (78%); mp 263–265° dec; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19b] pH 7, 260 (5.9), 335 (6.22); $\bar{\nu}_{max}$, in cm^{-1}, 1715, 1670 (C=O), 1615, 1485 (C=C, C=N).

Anal. Calcd for $C_5H_5N_5O_4$: C, 30.15; H, 2.51; N, 35.15. Found: C, 30.28; H, 2.42; N, 35.01.

6-Amino-as-triazine-5-carboxamide (20).—A mixture of **12** (50 g) in 10:1 EtOH–H_2O (1100 ml) containing Et_3N (100 ml) was refluxed for 18 hr and cooled in an ice bath. The solid was collected by filtration and dried *in vacuo* over P_2O_5: yield 28 g (60%); mp 253–254° with sublimation (recrystallization from MeOH did not raise the melting point); λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 239 (11.7), 357 (4.11); $\bar{\nu}_{max}$, in cm^{-1}, 1705 (CO), 1615 (NH_2); pmr, τ 0.85 (1, CH), 1.52, 1.95, 2.20 (1,1,2, NH).

Anal. Calcd for $C_4H_5N_5O$: C, 34.53; H, 3.63; N, 50.35. Found: C, 34.64; H, 3.83; N, 50.25.

The filtrate was evaporated to dryness, and the resulting residue was recrystallized from EtOH to give crude, unreacted **12** (10 g). The ethanol filtrate was evaporated to dryness, and the residue was dissolved in H_2O (100 ml). The aqueous solution was acidified to pH 2 with concentrated HCl to deposit **21**·H_2O: yield 3.0 g (6%); this sample did not melt, but decomposed >250°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* NaOH, 244 (10.3), 342 (3.33); pmr (CF_3CO_2D), τ 0.75 (CH).

Anal. Calcd for $C_4H_4N_4O_2 \cdot H_2O$: C, 30.39; H, 3.83; N, 35.43. Found: C, 30.51; H, 3.90; N, 35.57.

6-Formamido-as-triazine-5-carboxamide (22).—A solution of **20** (1.0 g) in 2:3 Ac_2O–HCO_2H (25 ml) mixture was stirred at room temperature for 18 hr and evaporated to dryness under reduced pressure. This residue was dissolved in hot EtOAc (570 ml), and the resulting solution was evaporated to dryness to give **22**: yield 1.2 g (100%); mp 210°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19a] pH 7, 244 (16.7), 315 (3.40); $\bar{\nu}_{max}$, in cm^{-1}, 3340, 3220 (NH), 1670 (CO), 1600, 1545 (C=C, C=N); pmr, τ 0.32 (1, CH), 0.47 (m,1, CHO), −1.05 (m,1, NH), 1.18, 1.60 (1,1, NH).

Anal. Calcd for $C_5H_5N_5O_2$: C, 35.93; H, 3.02; N, 41.91. Found: C, 36.06; H, 3.18; N, 41.60.

Pyrimido[5,4-e]-as-triazine-5,7(6H,8H)-dione (23).—Phosgene was bubbled slowly for 0.5 hr into a solution of pyridine (1.8 ml) in anhydrous dioxane (225 ml), and the resulting mixture was refluxed for 15 min to remove excess phosgene. After adding **20** (3.0 g), the mixture was refluxed with stirring for 4.5 hr and evaporated to dryness *in vacuo*. This residue was extracted with hot glacial HOAc (two 125-ml portions), and the combined extracts were evaporated to dryness to give crude **23**: yield 2.5 g (70%). This solid was recrystallized once from glacial HOAc, then from water, and dried *in vacuo* over P_2O_5 at 140° to give the analytical sample: yield 1.3 g (37%); mp >264°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$),[19c] 0.1 *N* HCl, 232 (14.4), 265 (sh), 332 (4.97), pH 7, 236 (sh), 248 (11.5), 264 (sh) (9.22), 350 (2.60), 385 (2.89), 0.1 *N* NaOH, 259 (19.4), 312 (2.03), 394 (3.92); $\bar{\nu}_{max}$, in cm^{-1}, 3180, 3085, 2985, 2790 (NH), 1715 (broad) (CO), 1570, 1555 (C=C, C=N); pmr, τ 0.32 (1, CH), −2.13 (broad) (2, NH).

Anal. Calcd for $C_5H_3N_5O_2$: C, 36.37; H, 1.83; N, 42.42. Found: C, 36.14; H, 2.08; N, 42.13.

Fervenulin (24).—A solution of **23** (495 mg) in DMF (5 ml) containing K_2CO_3 (830 mg) and CH_3I (0.39 ml) was stirred at room temperature for 36 hr. An additional amount of CH_3I (0.20 ml) was added at the end of 18 hr. The mixture was evaporated to dryness *in vacuo*, the residue was treated with 1 *N* HCl (6 ml), and the solid was collected by filtration: yield 162 mg (28%); mp 176°. Extraction of the residue obtained from evaporation of the acidic filtrate with $CHCl_3$ (two 25 ml portions) gave crude product (265 mg), which was purified by recrystallization from H_2O: yield 146 mg; mp 177° (lit. mp 175.7°,[3] 178–179°[2]) [total yield 308 mg (53%)]; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), EtOH, 239 (16.8), 275 (1.60), 340 (4.33); pmr, τ 0.17 (1, CH), 6.34, 6.68 (3.3, CH_3).

Registry No.—**2**, 19359-15-0; **6**, 19359-59-2; **7**, 19359-60-5; **8**, 19359-61-6; **9**, 19359-62-7; **10**, 19359-63-8; **12**, 19359-64-9; **14**, 19359-65-0; **16**, 19359-66-1; **20**, 19359-67-2; **22**, 19359-68-3; **23**, 19359-69-4; 4-chloro-5-ethoxymethylenaminopyrimidin-6-(1H)-one, 19359-70-7.

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Base-Catalyzed Reactions. XXXIII.[1] Sodium- and Potassium-Catalyzed Reactions of Methylnaphthalenes with Ethylene

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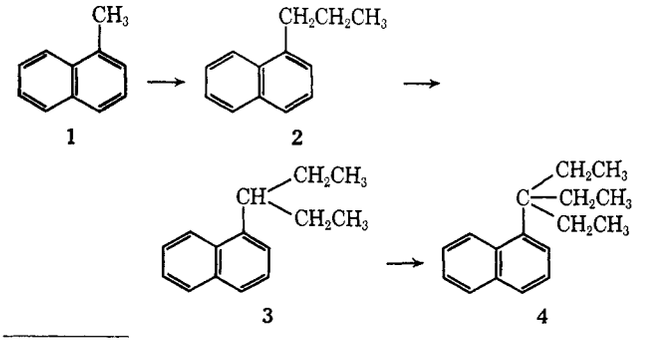
Sodium or potassium dispersed in 1- or 2-methylnaphthalene are active catalysts for the reaction of these hydrocarbons with ethylene, under pressure and at temperatures from 90 to 210°. To form an active sodium catalyst a promoter is needed, while in the case of potassium the initiator is not always required. The reaction in the presence of sodium results exclusively in side-chain ethylation (compounds **2–4**, **6**, and **8–10**). All hydrogen atoms at the α carbon of the side chain can be replaced with ethyl groups, though in case of 1-alkylnaphthalenes steric hindrance can considerably retard the reaction. The potassium-catalyzed reaction with ethylene is more complex. In addition to the side-chain ethylation reaction, products of cyclization (**12**, **17**, and **18**) and nuclear alkylation (**11** and **16**) were isolated. Also, all of these primary products undergo further alkylation (**13** and **14**) and formation of higher boiling hydrocarbons can take place.

The sodium- and potassium-catalyzed side-chain alkylation and alkenylation of alkylbenzenes and alkylpyridines have been the subject of extensive studies in this laboratory.[1,2] The present investigation is extended to the study of the reactions of ethylene with 1- and 2-alkylnaphthalenes, these being representatives of alkylpolycyclic hydrocarbons. The search of the literature had revealed only a noncatalytic reductive methylation of sodium 1- and 2-methylnaphthalenes with methyl bromide.[3]

The ethylation reactions were carried out under pressure using catalytic amounts of either sodium or potassium in the presence of small amounts of *o*-chlorotoluene as a promoter. The major reaction products were separated by a combination of fractional distillation and gas chromatography and the structures were established by nmr, by ir, and in some cases by means of mass spectra and synthesis.

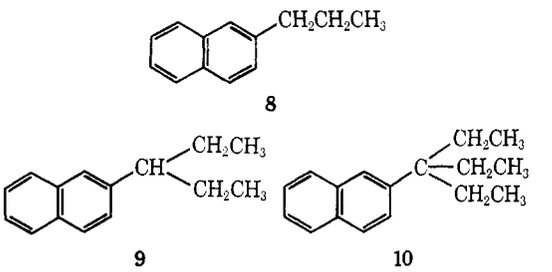
Results

Sodium-Catalyzed Reactions.—Sodium has been found to be a very selective catalyst for the side chain ethylation of alkylnaphthalenes (Table I). With 1-methylnaphthalene (**1**), mono- and diadducts of ethylene were the only products obtained (expt 1 and 2). 3-(1-Naphthyl)pentane (**3**) underwent further ethylation very slowly and only after all of the *n*-propylnaphthalene (**2**) had reacted (expt 3). Prolonged heating and stirring for several hours resulted in the formation of only 2% 3-ethyl-3-(1-naphthyl)pentane (**4**).[4]



1,5-Dimethylnaphthalene (**5**) in the presence of sodium and an excess of ethylene produced 1,5-di(3-pentyl)naphthalene (**6**) in a 94% yield (expt 5).

2-Methylnaphthalene (**7**) formed mono- (**8**), di- (**9**), and triethylated (**10**) compounds; the last one was produced in a 62% yield (expt 7, Table I).



Unlike **1**, 2-methylnaphthalene (**7**) reacts readily with three molecules of ethylene to produce 3-ethyl-3-(2-naphthyl)pentane (**10**). The difference in the reactivity of **1** and **7** is due to steric effects which in 1-methylnaphthalene had been estimated to be 1.6 kcal/mol, greater than in *o*-xylene (0.5 kcal/mol) and almost equal to that of 1,2,3-trimethylbenzene (2.0 kcal/mol).[5] Molecular models show that in compound

(1) Paper XXXII: H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3138 (1967).

(2) For general literature review, see H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(3) W. Hückel and R. Cramer, *Justus Liebigs Ann. Chem.*, **630**, 89, (1960); W. Hückel, and C. M. Jennewein, *Chem. Ber.*, **95**, 350 (1962).

(4) 1-Isopropylnaphthalene and 1-*sec*-butylnaphthalene were ethylated much more easily under the same conditions. More details about the products, 2-methyl-2-(1-naphthyl)butane and 3-methyl-3-(1-naphthyl)pentane, will be published in a separate paper.

(5) J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, **80**, 905 (1958).