Pyrimido[4,5-*c*]isoquinolines. 1. Synthesis of the Parent Compound and Some 6-Substituted Derivatives (1)

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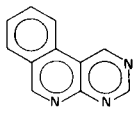
As part of a larger program directed toward the synthesis of aza analogs of the 1,3-diaminobenzo[*f*]-quinazoline antifolates (2,3) as candidate experimental antitumor agents (4), we were interested in obtaining pyrimido[4,5-*c*]isoquinoline (**1**), the parent member of an as yet still sparsely studied heterocyclic ring system (5-10), in order to compare its properties with those reported earlier for benzo[*f*]quinazoline (**2**) (11-13), which differs from compound **1** only in the absence of a nitrogen atom in the central ring. In this Note we should like to describe the preparation of compound **1** and several 6-substituted derivatives thereof.



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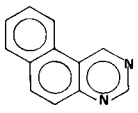

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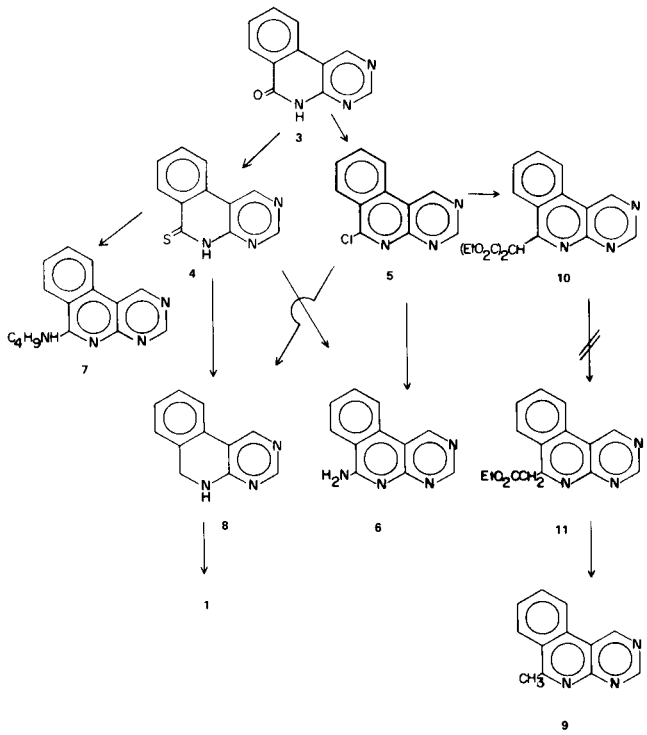
A facile entry into the pyrimido[4,5-*c*]isoquinoline ring system was available via the condensation of homophthalic acid and formamide, a reaction similar to one reported in 1966 by Bellomonte and coworkers (5) utilizing homophthalic anhydride instead of the acid. The product, pyrimido[4,5-*c*]isoquinolin-6(5*H*)one (**3**, 49% yield), was a high-melting, sparingly soluble yellow solid displaying prominent infrared absorption at 1690 cm^{-1} (lactam C=O) and other bands conforming in every respect to the values given in the literature (5). Further transformations of lactam **3** which corroborate its assigned structure are shown in Scheme I.

Thiation of **3** with phosphorus pentasulfide in refluxing pyridine gave the corresponding 6-thione (**4**, 83% yield) as a high-melting bright yellow solid exhibiting strong ultraviolet absorption bands in 95% ethanol at 287, 317, 333, and 347 nm. Comparison with the spectrum of lactam **3** in the same solvent (λ max 266, 294, 309, 322 nm) revealed a 20-25 nm bathochromic shift consistent with the change of an oxo function to a thione. Infrared spectra of compounds **3** and **4** differed chiefly in the presence, in the latter instance, of a prominent band at 1150 cm^{-1} which we ascribe to the C=S stretching mode (14).

Scheme I



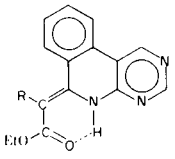
Chlorination of compound **3** with thionyl chloride in a mixture of chloroform and dimethylformamide furnished the 6-chloro derivative **5** (44% yield) as a readily sublimable solid with the expected easy solubility in organic solvents. Compounds **4** and **5** were each found to undergo amination when heated under pressure in aqueous or ethanolic ammonia. 6-Aminopyrimido[4,5-*c*]isoquinoline (**6**) was formed in 22% yield from **4** and 60% yield from **5**, suggesting that a chloro substituent is superior to a mercapto group for nucleophilic displacement reactions at the 6-position of this ring system. That amination of the 6-position can be accomplished equally well with alkylamines was also indicated, in one experiment, when attempted recrystallization of thiolactam **4** from hot butylamine yielded as the sole product a compound analyzing correctly for 6-*N*-butylaminopyrimido[4,5-*c*]-isoquinoline (**7**).

Dethiation of compound **4** with Davison sponge nickel (15) in refluxing ethanol yielded a product whose spectral properties and microanalytical values indicated the formation of 5,6-dihydropyrimido[4,5-*c*]isoquinoline (**8**, 41% yield) in place of the desired product, **1**. The same 5,6-dihydro derivative was obtained in 58% yield when chloro compound **5** was hydrogenated in the presence of 10% palladium-charcoal and magnesium oxide. The nmr spectrum of **8** in deuteriochloroform showed only *two* deshielded aromatic singlets at δ 8.45 and δ 8.63 (the pyrimidine protons), a two-proton singlet at δ 4.80 (the benzylic protons at C-6), and a broad NH signal at δ 6.0. The uv spectrum (λ max (ethanol) 281, 335 nm) differed significantly from the data published for 4-amino-5-phenylpyrimidine (λ max (ethanol) 248, 282 nm) (16), but could be rationalized on the basis of the likely bathochromic effects of *N*-alkyl substitution and the concomitant increase in coplanarity of the phenyl and pyrimidine chromophores as a result of bridging (17).

Aromatization of compound **8** was accomplished by treatment with potassium ferricyanide in refluxing aqueous dioxan. The product (**1**, 28% yield) was a readily sublimable light-yellow solid whose nmr spectrum in deuteriochloroform contained *three* deshielded aromatic singlets at δ 9.56, δ 9.66, and δ 10.10 (three *N*-adjacent protons), and whose uv spectrum (λ max (ethanol) 221, 240, 287 infl., 315 infl., 328, 343 nm) bore a resemblance to that of compound **2** (11) and was consistent with an extension of conjugation relative to compound **8**. Like compound **8**, **1** could be converted into a stable hydrochloride salt which was higher-melting and more convenient to store than the free base.

In addition to the aforementioned compounds bearing electronegative substituents at position 6, we also desired to prepare 6-methylpyrimido[4,5-*c*]isoquinoline (**9**). Inasmuch as trial experiments involving metallation of the chloro compound **4** with *n*-butyl lithium appeared unpromising, it was decided to adopt the procedure described in the literature for the conversion of 4-chloroquinazoline into 4-methylquinazoline (18). Alkylation of **4** with diethyl sodiomalonate in refluxing ether afforded the expected malonate derivative **10** (81% yield). However, we were disappointed to find that hydrolysis and decarboxylation of **10** in alcoholic alkali under the usual conditions (18) failed to proceed beyond the loss of one carboxyl group. The sole product proved to be the monoester derivative **11** (89% yield). All efforts to obtain **9** under more vigorous alkaline or acid conditions (see Experimental) failed to produce the desired effect. The only product formed on further breakdown of the monoester **11** was the lactam **3**.

A plausible explanation for these unanticipated properties of monoester **11** is that this compound exists mainly, if not entirely, in tautomeric form **11A**, which is strongly stabilized by intramolecular hydrogen bonding. Strong support for this view was provided by the ir spectrum of **11** which showed a hydrogen-bonded enolic ester C=O stretching band at 1670 cm^{-1} (rather than the more usual absorption for unconjugated aliphatic esters at 1620 cm^{-1}), and by the nmr spectrum (deuteriochloroform solution) which showed a prominent vinyl proton singlet at δ 5.71 and no trace of benzylic methylene absorption. Correspondingly, the ir spectrum of the malonate derivative **10** contained *two* C=O peaks, at 1670 cm^{-1} (H-bonded enolic ester) and 1620 cm^{-1} (normal ester), and no methinyl proton absorption was discernible in the nmr spectrum. These data suggest that, in addition to the tautomeric form **11A** for compound **11**, there is a corresponding structure, **10A**, for the malonate derivative **10**.



10A, R = CO_2Et
11A, R = H

EXPERIMENTAL

Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Nmr spectra were determined on a Varian A-60 instrument, with tetramethylsilane as the internal reference. Analytical samples were dried over phosphorus pentoxide in an Abderhalden apparatus at 70-100° (0.05 mm). Melting points were measured in Pyrex capillary tubes by means of a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Massachusetts) and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Pyrimido[4,5-*c*]isoquinolin-6(5*H*)one (**3**).

Homophthalic acid (100 g., 0.555 mole) and formamide (1 kg.) were refluxed in 1-octanol (500 ml.) for 4 hours. The mixture was allowed to cool and the solid was filtered, washed with 95% ethanol, rinsed with dichloromethane, and dried. Recrystallization of the crude product (53.5 g., 49% yield) from dimethyl sulfoxide gave light yellow needles, m.p. 357-360° dec. [lit. (5) m.p. 363°].

Pyrimido[4,5-*c*]isoquinoline-6(5*H*)thione (**4**).

A mixture of lactam **3** (2 g., 0.01 mole) and purified phosphorus pentasulfide (4 g., 0.018 mole) (19) in dry pyridine (25 ml.) was stirred under reflux for 1.5 hours and at room temperature overnight. Benzene (100 ml.) was added and the solid was filtered, washed with dichloromethane, digested with boiling water (250 ml.) for 1 hour, filtered again, washed with water and dichloromethane, and dried to a yellow powder (1.8 g., 83% yield). Recrystallization from dimethyl sulfoxide afforded yellow needles, m.p. 329-331° dec.; λ max (ethanol) (nm) 222 (ε 25,270), 237 (33,490), 287 (11,110), 317 (10,350), 333 (14,280), 347 (13,830).

Anal. Calcd. for $C_{11}H_7N_3S$: C, 61.95; H, 3.31; N, 19.70; S, 15.04. Found: C, 61.84; H, 3.40; N, 19.92; S, 14.65.

6-Chloropyrimido[4,5-*c*]isoquinoline (**5**).

A stirred mixture of lactam **3** (19.7 g., 0.1 mole), chloroform (250 ml.), and dimethylformamide (73 g.) was treated dropwise with thionyl chloride (119 g.). When addition was complete and the initial exothermic effect subsided the mixture was refluxed for 2 hours, cooled, and filtered. The solid was washed with dichloromethane until colorless, suspended in 50% aqueous ethanol (400 ml.), treated with sufficient concentrated ammonia to bring the *p*H above 8.0, filtered, washed thoroughly with cold water, and dried to a very pale yellow powder (8 g., 44% yield). For microanalysis a small sample of this material was sublimed at 115-120° (0.05 mm) (bath temperature); m.p. 210-212° dec. (with sublimation).

Anal. Calcd. for $C_{11}H_6ClN_3$: C, 61.27; H, 2.80; Cl, 16.44; N, 19.49. Found: C, 60.93; H, 2.27; Cl, 16.54; N, 19.26.

6-Aminopyrimido[4,5-*c*]isoquinoline (**6**).

Method A.

A solution of compound **5** (1 g., 0.0055 mole) in ammonia-saturated ethanol (100 ml.) was heated overnight in a glass pressure bottle on the steam bath. Cooling produced small colorless needles (0.65 g., 60% yield), m.p. 324-325° dec.

Method B.

Similar treatment of compound **4** (3 g., 0.014 mole) in concentrated ammonium hydroxide (100 ml.) and recrystallization of the crude product from ethanol (charcoal) gave 0.6 g. (22% yield) of solid whose infrared and ultraviolet spectra were superimposable on those of the material obtained from compound **5** in the foregoing experiment. The analytical sample, m.p. 324-326° dec., was prepared by sublimation at 205° (0.005 mm) (bath temperature); λ max (95% ethanol) (nm) 237 (ε, 46,240), 282 (11,760), 315 infl. (8,840), 328 (14,280), 343 (14,800); λ max (*p*H 1, ethanol) (nm) 231 (ε, 36,130), 238 (36,130), 257 (19,140) 286 infl. (8,870), 310 infl. (7,590), 322 (12,510), 336 (13,390).

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.33; H, 4.11; N, 28.56. Found: C, 67.35; H, 4.18; N, 28.46.

6-(*N*-Butylamino)pyrimido[4,5-*c*]isoquinoline (**7**).

Attempted recrystallization of thiolactam **4** from hot aqueous *n*-butylamine (charcoal) yielded small yellow needles, m.p. 110-115°, as the sole product.

Anal. Calcd. for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.70; H, 6.95; N, 21.72.

5,6-Dihydropyrimido[4,5-*c*]isoquinoline (**8**).

Method A.

A mixture of compound **4** (1 g., 0.0047 mole), Davison sponge nickel (10 ml. of settled solid) (15), and ethanol (100 ml.) was refluxed for 20 minutes, cooled to room temperature, and filtered. Solvent evaporation and sublimation of the residue (0.5 g.) at 130° (0.05 mm) (bath temperature) gave a pale yellow solid (0.35 g., 41% yield), m.p. 170-175° dec; λ max (ethanol) (nm) 218 (ε 12,400), 273 infl. (4,700), 282 (5,550), 325 infl. (8,280), 336 (8,840); λ max (*p*H 1, ethanol) (nm) 218 (ε 28,190), 285 infl. (7,300), 310 (9,230), 323 (9,410); nmr (deuteriochloroform): δ 4.80 (singlet, $NHCH_2$), 6.0 (broad, NH), 7.0-7.8 (complex multiplet, benzene ring protons), 8.45 and 8.63 (singlets, pyrimidine ring protons).

Method B.

A mixture of compound **5** (2 g., 0.011 mole), magnesium oxide (2 g.), and 10% palladium-charcoal (0.85 g.) in 50% aqueous ethanol (100 ml.) was hydrogenated for 18 hours in a Parr apparatus at a pressure of 2.5 atmospheres. Removal of the catalyst, evaporation of the solvent, and recrystallization of the residue from ethanol gave the same product (1 g., 58% yield) as in the preceding experiment; m.p. 170-174° dec.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.29; H, 4.82; N, 22.83.

Pyrimido[4,5-*c*]isoquinoline (**1**).

The foregoing 5,6-dihydro derivative **8** (0.84 g., 0.0046 mole) was heated under reflux for 15 minutes in a mixture of potassium ferricyanide (3 g.), potassium hydroxide (2 g.), dioxan (20 ml.), and water (100 ml.). Evaporation to dryness under reduced pressure and sublimation of the residue at 135-140° (0.005 mm) (bath temperature) gave a very pale yellow solid (0.27 g., 32% yield), m.p. 161-163°; λ max (ethanol) (nm) 221 (ε 36,750), 240 (29,680), 287 infl. (5,770), 315 infl. (2,910), 328 (4,440), 343 (4,410); λ max (*p*H 1, ethanol) (nm) 221 (ε 24,020), 251 (17,260), 258 (15,200), 297 (8,530); nmr (deuteriochloroform): δ 7.6-8.8 (complex multiplet, benzene protons), 9.56, 9.66, 10.10 (singlets, pyridine and pyrimidine protons).

Anal. Calcd. for $C_{11}H_7N_3$: C, 72.92; H, 3.89; N, 23.19. Found: C, 73.33; H, 3.93; N, 22.88.

The hydrochloride salt, **1**·HCl, was prepared by dissolving the free base in dichloromethane, passing dry hydrogen chloride gas through the solution, and filtration of the precipitated solid; m.p. 252-255° dec.

Anal. Calcd. for $C_{11}H_7N_3$·HCl: C, 60.70; H, 3.70; Cl, 16.29; N, 19.31. Found: C, 61.04; H, 3.79; Cl, 16.01; N, 19.35.

Diethyl Pyrimido[4,5-*c*]isoquinolin-6-ylmalonate (**10**).

Diethyl malonate (4.0 g., 0.025 mole) was added dropwise to a slurry of sodium hydride (from 1.16 g. of 57% suspension in mineral oil) in dry ether (50 ml.), and the mixture was stirred under reflux for 15 minutes. A suspension of compound **4** (5.4 g., 0.027 mole) in ether (100 ml.) was added in a single portion, and stirring was continued under reflux overnight. After being cooled, the reaction mixture was quenched by addition of ethanol (2 ml.) and the solid was filtered, transferred to a beaker containing ice-water (400 ml.), and neutralized to *p*H 7 by careful addition of concentrated hydrochloric acid. Filtration, washing with water, and drying furnished a yellow solid (6.9 g., 81% yield), m.p. 147-150° dec. The analytical sample, m.p. 161-163°, was prepared by recrystallization from ethanol (decolorizing carbon); nmr (deuteriochloroform): δ 1.32 (triplet, CH_3CH_2O), 3.40 (quartet, CH_3CH_2O), 7.4-8.3 (complex multiplet, aromatic protons), 8.91 and 9.25 (singlets, pyrimidine protons).

Anal. Calcd. for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.81; H, 5.04; N, 12.39.

Ethyl Pyrimido[4,5-*c*]isoquinolin-6-ylacetate (**11**).

A solution of malonate ester **10** (1 g., 0.003 mole) and potassium hydroxide (1.65 g., 0.03 mole) in ethanol (100 ml.) was refluxed for 30 minutes, cooled, and neutralized with dilute hydrochloric acid. The precipitated solid was filtered (0.7 g., 89%) and recrystallized from ethanol; m.p. 193-195°; nmr (deuteriochloroform): δ 1.33 (triplet, CH_3CH_2O), 3.46 (quartet, CH_3CH_2O), 5.71 (singlet, vinyl proton), 7.5-8.5 (complex multi-

plet, benzene protons), 8.82 and 9.15 (singlets, pyrimidine protons).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.52; H, 4.89; N, 15.86.

The following conditions were unsuccessful in bringing about complete decarboxylation of compound **10** (reactions monitored at regular time intervals by ultraviolet spectral analysis): tenfold molar excess of potassium hydroxide in ethanol under reflux for up to 40 hours; refluxing in 3 *N* hydrochloric acid for 2 hours or 6 *N* hydrochloric acid for 4 hours; heating in tetralin in the presence of copper oxide at 210-220° for 15 minutes; heating in the presence of copper powder without solvent at 200° for 10 minutes. Prolonged alkaline hydrolysis yielded the starting lactam **3**, as did the thermal degradations, albeit in low yield. Acid treatment led only to the formation of **11** or the recovery of unchanged **10**.

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