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Esters and Amides of 5-Amino-2-aryl-4-pyrimidinecarboxylic Acid

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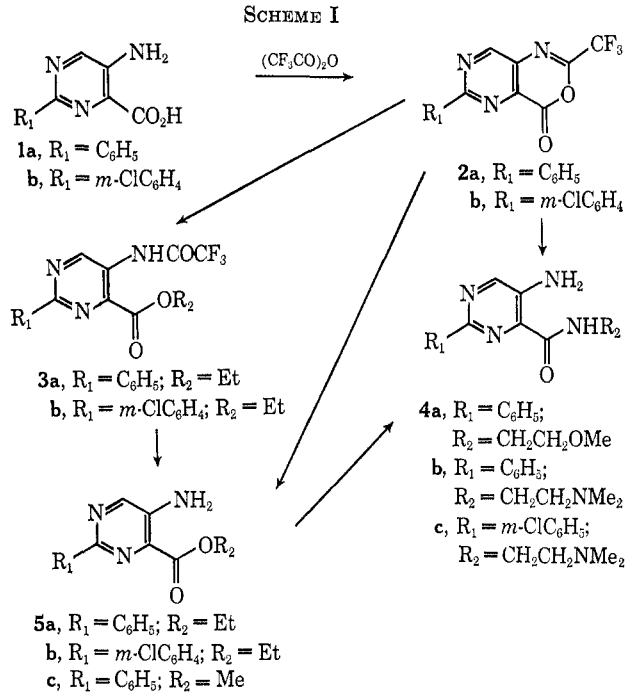
Although 5-amino-2-phenyl-4-pyrimidinecarboxylic acid (**1**)[1] has been known since 1902, surprisingly, none of its esters or amides has been reported thus far. A review of the literature, furthermore, revealed that neither esters nor amides of 5-amino-4-pyrimidinecarboxylic acids, in general, have been described. The importance of esters and amides of *o*-aminocarboxylic acids as synthetic intermediates for the construction of other heterocycles fused to the original nucleus has been widely recognized for many years.[2]

An application of the conventional Fischer esterification method to **1b** caused extensive decarboxylation, resulting in the formation of 5-amino-2-(*m*-chlorophenyl)pyrimidine. Price, *et al.*,[3] obtained 4-amino-2-methyl-5-pyrimidinecarboxylic acid methyl ester by adding a mixture of methanol and sulfuric acid to a warm solution of the corresponding carboxylic acid in sulfuric acid. An attempt to esterify **1b** by the Price method, however, caused the pyrimidine to suffer the same decarboxylation experienced with the Fischer method. Apparently, decarboxylation of these 5-amino-4-pyrimidinecarboxylic acids occurs with such facility that it presents a major problem in preparing derivatives.

We now wish to report a convenient two-step synthesis of esters and amides of 5-amino-4-pyrimidinecarboxylic acids (see Scheme I). Treatment of **1a,b** with trifluoroacetic anhydride produced in excellent yield the pyrimido[5,4-*d*][1,3]oxazines **2a,b**, the first examples of a previously undescribed heterocyclic ring system. The structures of **2a,b** were supported by elemental analyses and spectral data; their infrared carbonyl absorption bands were exhibited at 5.5 μ. When the intermediates **2a,b** were treated with an appropriate alcohol in the presence of a catalytic amount of base and HCl gas was then introduced, the desired esters **5a–c** were obtained. The products exhibited their ester carbonyl absorption bands at 5.85–5.95 μ. The conversion of **2a,b** into the esters **5a,b** appears to involve a base-catalyzed initial cleavage of the oxazine ring followed by detrifluoroacetylation in the presence of acid. Intermediates **3a,b** were isolated

SCHEME I



when the conversion reaction of **2a,b** into **5a–c** was interrupted prior to the acid treatment. Subsequent treatment of **3a,b** with ethanolic HCl produced **5a** and **5b**. Treatment of **2a** with an excess of 2-methoxyethylamine afforded, in 90% yield, the pyrimidinecarboxamide **4a**, which was identical with the compound obtained from **5a** by refluxing the latter compound with 2-methoxyethylamine. Compounds **4b,c** were prepared similarly by treating **2a,b** with appropriate amines.

Experimental Section

The melting points were taken in capillary tubes (Thomas–Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. No effort was made to obtain optimum reaction conditions and yields.

5-Amino-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid (1b) was prepared according to the literature method[1] from 5-bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid: yield 50%, mp 240–242° dec.

Anal. Calcd for $C_{11}H_8ClN_3O_2$: C, 52.92; H, 3.23; Cl, 14.20; N, 16.83. Found: C, 52.90; H, 3.33; Cl, 14.2; N, 16.77.

5-Bromo-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic acid was prepared from *m*-chlorobenzamidine hydrochloride[4] and mucobromic acid according to the literature method.[5] Recrystallization from 95% EtOH gave a product with mp 162–163° dec.

Anal. Calcd for $C_{11}H_6BrClN_2O_2$: C, 42.14; H, 1.93; N, 8.94; Cl, 11.31. Found: C, 42.36; H, 1.95; N, 8.80; Cl, 11.32.

5-Amino-2-(*m*-chlorophenyl)pyrimidine.—Dry HCl gas was introduced into a mixture of **1b** (1.0 g) and absolute EtOH (70 ml) for 0.5 hr, with occasional cooling, and the resulting mixture was heated on a steam bath for 2 hr. Chilling of the reaction mixture caused separation of a precipitate, which was collected on a filter and treated with 1 *N* aqueous NaOH solution to give a product: mp 154–160° (recrystallization from EtOH–water raised the melting point to 159–161°); ir, no carbonyl absorption band.

Anal. Calcd for $C_{10}H_8ClN_3$: C, 58.40; H, 3.92; N, 20.43; Cl, 17.24. Found: C, 58.67; H, 3.89; N, 20.67; Cl, 17.21.

6-Phenyl-2-trifluoromethyl-4H-pyrimido[5,4-*d*][1,3]oxazin-4-one (2a).—5-Amino-2-phenyl-4-pyrimidinecarboxylic acid (**1a**)

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TABLE I
5-AMINO-N-SUBSTITUTED 4-PYRIMIDINECARBOXAMIDES

Compd	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	112–114	A	90	$C_{14}H_{16}N_4O_2$	61.75	5.92	20.58	62.09	5.99	20.30
5b	141–143	B	89	$C_{15}H_{19}N_5O$	63.14	6.71	24.55	63.19	6.78	24.73
4c	137–139	C	74	$C_{15}H_{18}ClN_5O$	56.33	5.67	21.90	56.29	5.28	21.89

[a] A = absolute ethanol, B = cyclohexane, C = ethanol + water.

(2.5 g) was added in small portions to trifluoroacetic anhydride (30 ml). The resulting mixture was refluxed for 7.5 hr and set overnight at room temperature, during which time a precipitate separated. The precipitate was collected on a filter and washed with trifluoroacetic anhyride to give 3.2 g of product, mp 210–212°.

Anal. Calcd for $C_{13}H_6F_3N_3O_2$: C, 53.25; H, 2.06; N, 14.33. Found: C, 53.33; H, 2.03; N, 14.55.

6-(*m*-Chlorophenyl)-2-trifluoromethyl-4H-pyrimido[5,4-*d*][1,3]-oxazin-4-one (2b) was prepared similarly from **1b** and trifluoroacetic anhydride: yield 94%, mp 176–178°.

Anal. Calcd for $C_{13}H_5ClF_3N_3O_2$: C, 47.65; H, 1.54; N, 12.82. Found: C, 47.79; H, 1.45; N, 12.77.

2-Phenyl-5-(2,2,2-trifluoroacetamido)-4-pyrimidinecarboxylic Acid Ethyl Ester (3a).—To a refluxing mixture of **2a** (7.0 g) and absolute EtOH (70 ml) was added a catalytic amount of sodium ethoxide, and the resulting solution was refluxed for 10 min. Concentration of the reaction mixture under reduced pressure and chilling in ice caused separation of a precipitate which was collected on a filter to give 7.5 g of product: mp 136.5–138.5°, ir 5.80 (CF_3CO) and 5.87 μ (ester CO).

Anal. Calcd for $C_{15}H_{12}F_3N_3O_3$: C, 53.10; H, 3.57; N, 12.39. Found: C, 53.52; H, 3.33; N, 12.29.

2-(*m*-Chlorophenyl)-5-(2,2,2-trifluoroacetamido)-4-pyrimidinecarboxylic acid ethyl ester (3b) was prepared similarly from **2b**: yield 85%, mp 172–174°.

Anal. Calcd for $C_{15}H_{11}ClF_3N_3O_3$: C, 48.20; H, 2.97; N, 11.24. Found: C, 48.49; H, 2.93; N, 11.50.

5-Amino-2-phenyl-4-pyrimidinecarboxylic Acid Ethyl Ester (5a). From 2a.—A mixture obtained by adding 19.3 g of **2a** to 200 ml of absolute EtOH containing a catalytic amount of sodium ethoxide was refluxed for 15 min. After the reaction mixture was cooled to room temperature, dry HCl gas was introduced for 1 hr, and then the reaction material was chilled. The precipitate that was deposited was collected on a filter and transferred to a separatory funnel containing 1 *N* aqueous NaOH solution and ether. After the mixture was shaken vigorously, the ether layer was collected, dried ($MgSO_4$), and evaporated to give 12.5 g of product, mp 78–80°.

Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.22; H, 5.36; N, 17.50.

From 3a.—A slow stream of dry HCl gas was introduced into a mixture of **3a** (3.0 g) and absolute EtOH (100 ml), with stirring for 15 min. Chilling of the resulting mixture caused separation of a precipitate, which was collected on a filter. Working up as described above afforded 1.2 g of product, mp 80–82°. A mixture melting point with the authentic sample prepared from **2a** was not depressed.

5-Amino-2-(*m*-chlorophenyl)-4-pyrimidinecarboxylic Acid ethyl ester (5b) was prepared from **3b** and absolute EtOH and recrystallized from absolute EtOH, mp 130–132°.

Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.22; H, 4.36; N, 15.13; Cl, 12.87. Found: C, 56.22; H, 4.05; N, 15.37; Cl, 12.95.

5-Amino-2-phenyl-4-pyrimidinecarboxylic acid methyl ester (5c) was prepared from **2a** and absolute methanol in 65% yield and recrystallized from cyclohexane, mp 119.5–122°.

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.56; H, 4.62; N, 18.24.

5-Amino-N-(2-methoxyethyl)-2-phenyl-4-pyrimidinecarboxamide (4a) exemplifies the preparation of 5-amino-N-substituted 2-aryl-4-pyrimidinecarboxamides (**4a–c**) (Table I).

From 2a.—To 15 ml of 2-methoxyethylamine was added 2.5 g of **2a** in small portions, and the resulting mixture was heated on a steam bath for 0.5 hr. The excess amine was removed under reduced pressure, and the solid residue was recrystallized from absolute ethanol, giving 2.1 g of product (see Table I).

From 5a.—A mixture of **5a** (1.5 g) and 2-methoxyethylamine (20 ml) was refluxed for 7 hr and then the solution was concentrated under reduced pressure. Chilling caused separation of crystals which were collected on a filter and washed with EtOH to give 1.3 g of product, mp 113–115°. A mixture melting point with the authentic sample prepared from **2a** was not depressed.

Registry No.—5-Amino-2-(*m*-chlorophenyl)pyrimidine, 23788-75-2; **2a**, 23788-76-3; **2b**, 23788-77-4; **3a**, 23788-78-5; **3b**, 23877-35-2; **4a**, 23788-79-6; **4b**, 23843-57-4; **4c**, 23788-80-9; **5a**, 23788-81-0; **5b**, 23788-82-1; **5c**, 23788-83-2.

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Preparation of 16-Unsaturated Steroids by Elimination of 17α-Acyloxyl

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Two methods are known for elimination of the 17α-hydroxyl from the dihydroxyacetone side chain of the corticoids. Allen and Bernstein[1] have reported 16,17 dehydration of 20-dioxolane derivatives using thionyl chloride in pyridine at −5°. The dehydration yield is ~45%; the dioxolane must be subsequently converted into the 20 ketone. Slates and Wendler,[2] *et al.*, reported an improved procedure involving activation of the 17α-hydroxyl by the 20-semicarbazone. Almost quantitative dehydration is effected and conversion into the 20 ketone is facile. Both methods are unsatisfactory, however, when the 11β-hydroxyl is present. Thionyl chloride causes 9,11 dehydration. In the semicarbazone method, C-18 methyl migration[2b] takes place when an 11β-hydroxyl is present and little Δ^{16} steroid is isolated.

We wish to report the removal of a 17α-hydroxyl, in good yield, by reacting a 17α-acyloxy derivative with potassium acetate in dimethylformamide. Thus prednisolone 17,21-diacetate (**1**), when heated for 8 hr at 105° with potassium acetate in dimethylformamide, is almost quantitatively converted into 16,17-anhydroprednisolone 21-acetate (**5**). Prednisolone 17-caproate 21-acetate also gives **5** but in lesser yield, 52.6%. The

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