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INVESTIGATION ON POSSIBILITY OF REARRANGEMENT OF PYRIMIDINE-5-CARBOXYLIC ACIDS ESTERS

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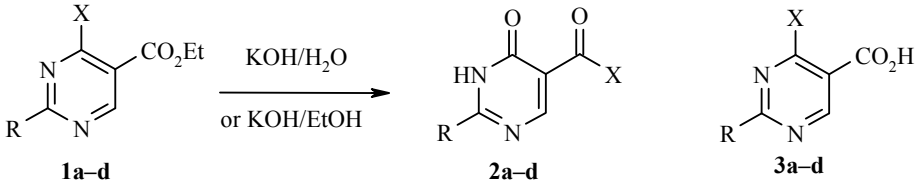
A previously reported rearrangement of pyrimidine-5-carboxylic acids esters to 5-acylpyrimidones does not, in fact, occur in any of the examples studied by us.

Keywords: pyrimidine-5-carboxylic acids esters, hydrolysis, pyrimidine rearrangements

A report appeared in 1933 regarding the rearrangement of a pyrimidine-5-carboxylic acid ester (**1b**) which occurred in aqueous alkali medium to give the 5-acetylpyrimidone (**2b**) [1]. The presence of a ketone in the reaction mixture was confirmed by the formation of its oxime and phenylhydrazone. In the years 1982-2005 a series of papers appeared in which it was confirmed that the rearrangement has a very general character and occurs for a broad range of differently substituted pyrimidine-5-carboxylic acids esters **1a-d** [2-5].



1a–d **2a–d** **3a–d**

1–3 a X = Me, R = Bn; **b** X = Me, R = OH; **c** X = Me, R = SH; **d** X = NH_2, R = SH

There is also work reported in which alkaline hydrolysis of the same pyrimidine-5-carboxylic acids esters gives the trivial result of formation of the corresponding acids which are isomers of 5-acetylpyrimidones. This reaction occurs under similar conditions and the substances obtained by different authors have very similar characteristics. The structure of the acids was quite reliably demonstrated and included a chemical route. Decarboxylation of the acids gives simple pyrimidines [6]. At the same time, proofs of the structure of the 5-acetylpyrimidones given in the articles [2-5] did not appear fully reliable.

In our laboratory repeated attempts were made to synthesize certain 5-acetylpyrimidones by methods [2-5]. All proved to be unsuccessful. Against the authors claims, only the acids were obtained in the examples studied [7].

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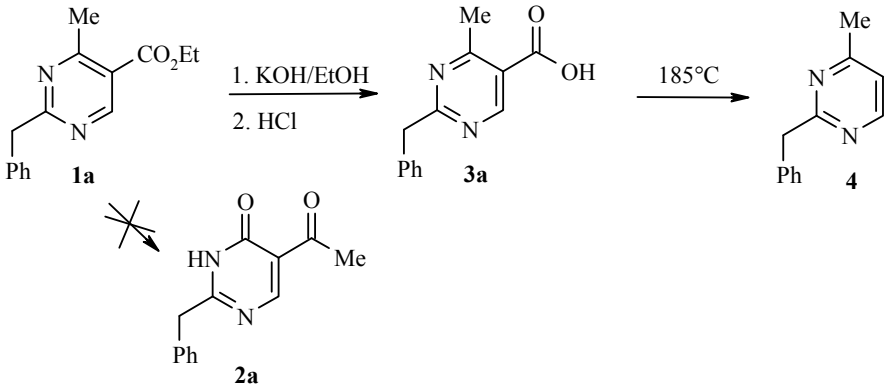
The object of our work was to study the route of hydrolysis of pyrimidine-5-carboxylic acids esters which, according to the various data, can lead either to the corresponding acids as the trivial product or to the 5-acetylpyrimidone rearrangement product. We set out to rationalize these opposing results from the different authors and to show in which of the examples a pyrimidine ring rearrangement can actually occur.

It should be emphasized that the 5-acetylpyrimidone and pyrimidine-5-carboxylic acid reaction products are isomeric. The expected ^{1}H NMR spectra are quite similar and contain the same set of signals which only differ slightly in their chemical shift values.

With the aim of rationalizing this question we have synthesized the esters **1a-d** and studied their behavior under hydrolysis conditions. The hydrolysis of the esters **1** was carried out as reported in the articles [1-5], trying best to reproduce the reaction conditions. At the end of the reaction the ^{1}H NMR spectra of the untreated reaction mixtures were recorded.

The hydrolysis of ester **1a** gave a 76% yield of compound **3a** which had a melting point approximately 10ºC higher than reported in [4].

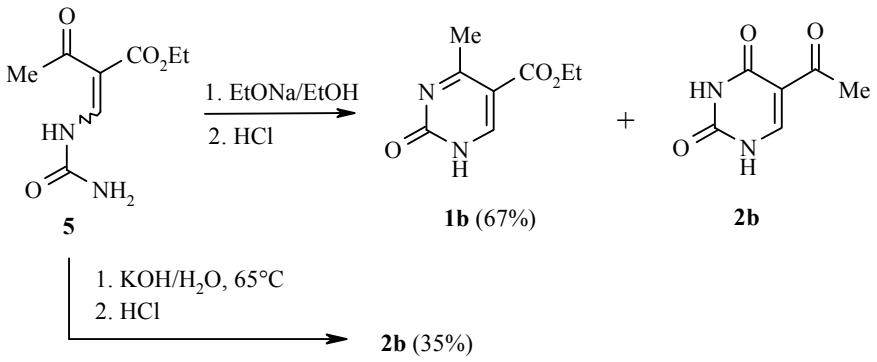


The chemical behavior and the NMR spectra of compound **3a** clearly show that it has the acid structure and it is not the isomeric ketone **2a**. This is supported by the fact that acid **3a** is decarboxylated to the pyrimidine **4**. Its structure results from the ^{1}H NMR spectra in which there are two doublets for the aromatic protons of the pyrimidine ring. The structure of pyrimidine **4** was also confirmed by forming its picrate which had the same melting point as that reported in the literature [8]. A further important pointer to the acid structure **3a** is the chemical shift of the carbonyl carbon atom at 170.7 ppm. This value is typical of carboxylic acids and their esters. In ester **1a** the carbonyl carbon is at 171.9 ppm whereas for a ketone the expected value would be in the range 190-200 ppm. No kind of signals are seen in this region of the spectrum of compound **3a**. Hence hydrolysis of ester **1a** gave only acid **3a** and no traces of ketone **2a** as the rearrangement product were observed.

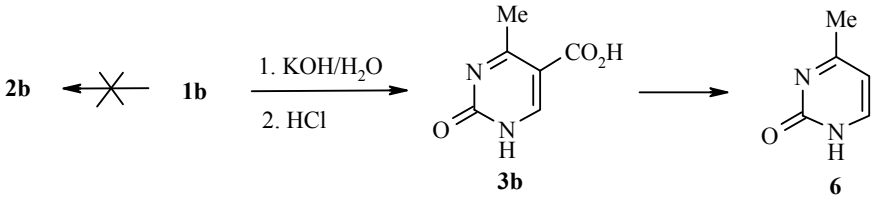
As regards the compound obtained by the authors in the article [4] the following can be stated. It has a melting point somewhat lower than that found by us and has very similar ^{1}H and ^{13}C NMR spectra to ours. The shift of the carbonyl carbon (172.4 ppm) given in [4] shows that the authors were dealing with the acid **3a** which had erroneously been given the structure of ketone **2a**.

In order to synthesize ester **1b** we used the method reported in [9]. Treatment of the ureido compound **5** with sodium ethylate in ethanol at room temperature gave a mixture of ester **1b** and ketone **2b**. According to the original article [9] the authors only obtained ester **1b**. Recrystallization of ester **1b** from water gave it in the pure state in 67% yield.

We also prepared ketone **2b** from the ureido compound **5** in aqueous alkaline medium as described in [10]. It is possible that, under these conditions, a mixture of ester **1b** and ketone **2b** is obtained. Ester **1b** hydrolyses in the presence of the alkali and the acid **3b** formed is more soluble in water than is ketone **2b**. Hence, in this case, we separated only ketone **2b**.



The hydrolysis of ester **1b** gave compound **3b** mixed with potassium chloride. The chemical behavior and NMR spectra of compound **3b** clearly showed that it has the acid structure and that it is not the isomeric ketone **2b**.



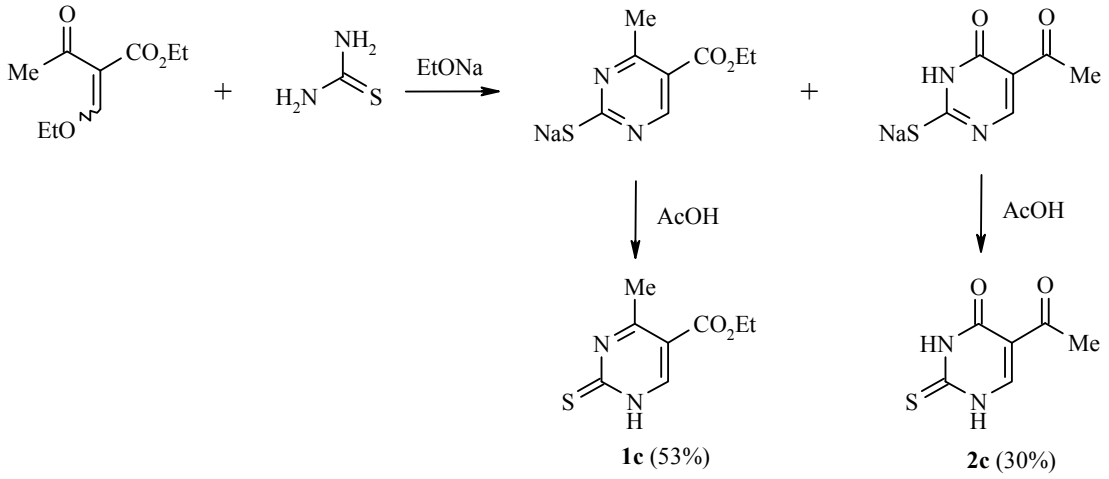
Our attempts to separate acid **3b** in a pure state were unsuccessful. When dissolving acid **3b** in hot acetonitrile or even in cold DMSO very ready decarboxylation occurred to give the 4-methylpyrimidin-2-one **6** with tarring. Pure pyrimidone **6** could not be separated and its formation was identified from the ^{1}H NMR spectrum of the reaction mixture which showed two doublets for the aromatic protons of the pyrimidone ring.

Other important evidence supporting the acid **3b** structure comes from the chemical shift of the carbonyl carbon atom at 172.8 ppm. In ester **1b** the carbonyl carbon is at 165.8 ppm. For ketone **2b** the chemical shift of the carbonyl carbon atom occurs at 194.4 ppm. The spectrum of compound **3** shows no kind of signal in this region. The ^{1}H NMR spectra of the reaction mixtures obtained following hydrolysis of ester **1b** also shows no signals which can be assigned to ketone **2b**.

Hence the hydrolysis of ester **1b** gave only the acid **3b** in our hands and we did not observe formation of the ketone **2b** rearrangement product.

The article [5] reported the rearrangement of ester **1b** to ketone **2b**. At this point the following observations can be made. The authors [5] apparently actually separated ketone **2b**. This was indicated by the authors report of the melting point and ability of this compound to give a hydrazone. However, the generation of ketone **2b** as the rearrangement product of ester **1b** was not proved and raises strong doubts. The synthesis of ester **1b** in article [5] is not reported and there is given only a mistaken reference to work in which ester **1b** is not mentioned overall. The characteristics of the starting ester **1b** are also not given by the authors [5]. Bearing in mind the formation of ketone **2b** in the course of cyclocondensation it can be suggested that the authors undertook the hydrolysis of a mixture of ester **1b** and ketone **2b**. As a result, they separated ketone **2b** in a formal yield of 49% and the acid **3b** was readily soluble in water and was lost.

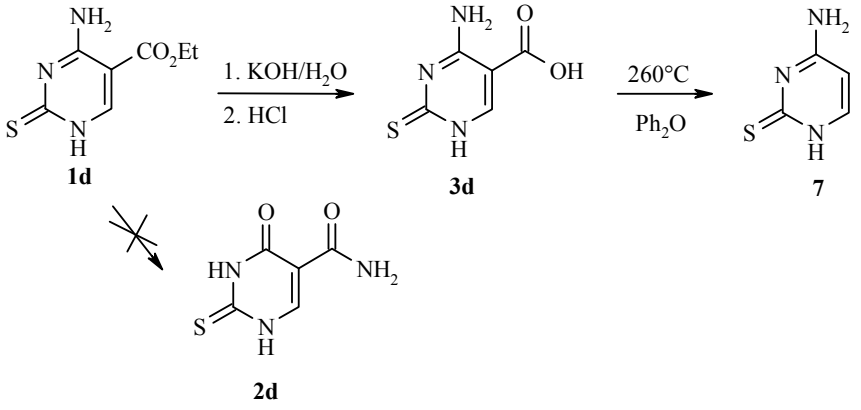
Ester **1c** was obtained using the method reported in [5]. Carrying out the reaction of ethoxymethylene-acetoacetate with thiourea in sodium ethylate solution gave a mixture of ester **1c** and ketone **2c**. In this case ketone **2c** is also very likely formed indirectly as a result of the cyclocondensation and not *via* a rearrangement. In the original article [5], the authors only obtained ester **1c**. We have isolated both materials in a pure state. They were separated at a stage of formation of the sodium salts.



The hydrolysis of ester **1c** gave a complex mixture which could not be separated or identified. Comparative data for the ^{1}H NMR spectra of ketone **2c** and the mixture obtained allowed us to state confidently that ketone **2c** is not formed in the conditions of hydrolysis of ester **1c**.

Similarly the hydrolysis of ester **1c** by us and the authors of [5] gave fundamentally different results. In [5] a pure substance was reported which was unprovenly assigned the ketone **2c** structure. In our opinion this substance is most likely not the ketone since it differs markedly from that obtained by us in both melting point and ^{1}H NMR spectrum. We are unable to explain the result reported in [5].

Hydrolysis of ester **1d** gave an 80% yield of compound **3d**. In this case the NMR spectra do not allow a distinction between the acid **3d** and amide **2d**.



The chemical behavior of compound **3d** clearly shows that it has an acid structure and is not the isomeric amide **2d**. The acid **3d** decarboxylates to pyrimidine **7**. That structure was proved by ^{1}H NMR spectroscopy in which there are two doublets for the aromatic protons of a pyrimidine ring. The molecular weight of the pyrimidine **7** is confirmed by the mass spectrum. Decarboxylation of acid **3d** is accompanied by strong tarring, the yield of the pyrimidine **7** is small, and it cannot be separated in a pure state. However, the fact that it is formed is not in doubt. Thus the hydrolysis of ester **1d** gave only acid **3d** and we were unable to observe formation of amide **2d** as the rearrangement product. With the agreement of the ^{1}H NMR spectra for the hydrolysis product of ester **1d** in our case and for that reported in [5] and the fact that the hydrolysis was carried out under identical conditions in mind it is established that rearrangement does not occur in this case even though the authors of [5] report it without proof.

In summary we can state that recyclization of the ethyl pyrimidine-5-carboxylates **1-d** to the corresponding 5-acetylpyrimidines **2a-c** and amide **2d** in the presence of alkali does not occur. Alkaline hydrolysis of these esters gives only the corresponding acids.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument (300 and 75 MHz respectively) using DMSO-d_6 with the residual signals of DMSO-d_5 (δ 2.50 ppm) for ^{1}H and DMSO-d_6 (δ 39.7 ppm) for ^{13}C as internal standards. Spin-spin couplings in the ^{1}H NMR spectra were measured in first order approximation. Elemental analysis was carried out on a Hewlett-Packard HP-185B CHN-analyzer.

Hydrolysis of Ethyl 2-Benzyl-4-methylpyrimidine-5-carboxylate (1a). Ester **1a** (3.0 g, 12 mmol) was added with stirring to a solution of potassium hydroxide (1.96 g, 35 mmol) in ethanol (39 ml). The product was stirred at room temperature for 10 min, ethanol was evaporated off, and the residue was dissolved in a minimum amount of water. Hydrochloric acid was added to the solution to pH 3-4. The precipitate formed was filtered off and dried. Yield of 2-benzyl-4-methylpyrimidine-5-carboxylic acid (**3a**) 2.03 g (76%); mp 173-174ºC. ^{1}H NMR spectrum, δ, ppm: 10.18 (1H, br. s, OH); 9.27 (1H, s, H-6); 7.42-7.25 (5H, m, C_6H_5); 4.37 (2H, s, CH_2); 2.89 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 170.7 (CO); 168.1 (C-2); 166.2 (C-4); 158.9 (C-6); 137.9 (*ipso*-C_6H_5); 129.1, 128.4 (*o*- and *m*-C_6H_5); 126.5 (*p*-C_6H_5); 121.6 (C-5); 45.1 (CH_2); 24.1 (CH_3); Mass spectrum, *m/z* (I_{rel}, %): 228 $[M]^+$ (48), 227 (100), 121 (8), 91 (23). Found, %: C 68.36, 68.20; H 5.21, 5.21; N 11.90, 11.85. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.41; H 5.30; N 12.27.

Decarboxylation of Acid 3a. Acid **3a** (1.96 g, 8.6 mmol) was heated at 180-185ºC for 6 h. After cooling, methyl *tert*-butyl ether was added. The organic phase was washed with a solution of potassium carbonate, saturated sodium chloride solution, dried over sodium sulfate, and the solvent was removed. The residue was purified by flash chromatography eluting with methyl *tert*-butyl ether. Solvent was evaporated. The yield of 2-benzyl-4-methylpyrimidine (**4**) as a colorless, mobile oil was 1.27 g (33%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.52 (1H, d, *J* = 5.1, H-6); 7.39-7.22 (5H, m, C_6H_5); 6.99 (1H, d, *J* = 5.1, H-5); 4.27 (2H, s, CH_2); 2.52 (3H, s, CH_3).

2-Benzyl-4-methylpyrimidine 4 Picrate. A solution of picric acid (238 mg, 1 mmol) in a minimum amount of alcohol was added to the pyrimidine **4** (242 mg, 1.3 mmol) and refluxed for 2-3 min. The product was cooled and the ethanol evaporated. The crystals formed were washed with ether, filtered, dissolved in a minimum amount of acetonitrile, and reprecipitated using ether. Mp 125-126ºC (mp 126ºC [8]).

Ethyl 4-Methyl-2-oxo-1H-pyrimidine-5-carboxylate (1b). Solutions of the ureidomethyleneaceto-acetate ester **5** [9] (9.3 g, 43 mmol) in absolute ethanol (60 ml) and sodium ethylate (sodium (1.3 g) in absolute ethanol (50 ml)) were mixed. The reaction product was held for 3 days at room temperature, ethanol was evaporated off, and the residue was dissolved in a minimum amount of water and acidified using hydrochloric acid to pH 3-4. The precipitate was filtered off and recrystallized from water. Yield 5.25 g (67%); mp 248-249ºC (mp 248-250ºC [1]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.4 (1H, s, NH); 8.72 (1H, s, H-6); 4.23 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 2.55 (3H, s, CH_3); 1.27 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 165.8 (CO); 164.3 (C-4); 156.4 (C-6); 153.4 (C-2); 106.9 (C-5); 61.3 ($O\underline{C}H_2CH_3$); 18.7 (CH_3); 14.9 ($OCH_2\underline{C}H_3$). Mass spectrum, *m/z* (I_{rel}, %): 183 (5), 182 $[M]^+$ (43), 181 (5), 154 (40), 137 (100), 110 (24), 96 (35), 82 (18), 67 (19).

5-Acetyluracil (2b). The ureidomethyleneacetoacetate ester **5** (7.0 g, 35 mmol) at 65ºC was added portionwise with stirring to an aqueous solution of potassium hydroxide (7.5%, 70 ml). After 1 min the reaction mixture was acidified to pH 5 using hydrochloric acid, cooled, the precipitate was filtered off and recrystallized from water. Yield 1.89 g (35%); mp 293-295ºC (mp 293-294ºC [10]). ^{1}H NMR spectrum, δ, ppm: 11.37 (1H, s,

NH), 8.05 (1H, s, H-6); 2.42 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 194.4 (CO); 163.1 (C-4); 151.5, 149.4 (C-6 + C-2); 111.9 (C-5); 30.9 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 155 (7), 154 $[M]^+$ (76), 139 (100), 91 (29), 69 (51).

Hydrolysis of Ethyl 4-Methyl-2-oxo-1H-pyrimidine-5-carboxylate (1b). Ester **1b** (1.5 g, 8.3 mmol) was added to a solution of potassium hydroxide (10%, 33 ml) and refluxed for 1 h. Conc. HCl (8 ml) was added. Water was evaporated and the residue was dried in air to give a mixture of 4-methyl-2-oxo-1H-pyrimi-dine-5-carboxylic acid (**3b**) and potassium chloride (5.2 g). ^1H NMR spectrum, δ, ppm: 8.85 (1H, s, H-6); 2.62 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 172.8 (CO); 164.6 (C-6); 160.9 (C-4); 151.3 (C-2); 108.5 (C-5), 21.5 (CH_3). Attempts to prepare acid **3b** in a pure state led to its decomposition, the only identified product being the 4-methylpyrimidin-2-one (**6**) formed *via* decarboxylation. Its formation was judged from the following signals in the ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.61 (1H, d, *J* = 6.3, H-6); 6.85 (1H, d, *J* = 6.3, H-5).

Ethyl 4-Methyl-2-thioxo-1H-pyrimidine-5-carboxylate (1c) and 5-Acetylthiouracil (2c). Thiourea (7.6 g, 100 mmol) was added to a solution of sodium ethylate (sodium (2.3 g, 100 mmol) in absolute ethanol (150 ml)). Following solution, ethoxymethyleneacetoacetate (18.6 g, 100 mmol) was added portionwise and the product was refluxed with stirring for 8 h.

The sodium salt of ketone **2c** was insoluble in sodium ethylate solution and was filtered off and dissolved in water. The solution was acidified with acetic acid and the precipitated ketone was filtered off. The ketone **2c** was recrystallized from alcohol to give 5-acetylthiouracil (**2c**) (5.15 g, 30%); mp 270-271ºC. ^1H NMR spectrum, δ, ppm: 12.82 (2H, s, NH); 7.88 (1H, s, H-6); 2.44 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 194.4 (CO); 177.3 (C-2); 160.2 (C-4); 147.0 (C-6); 115.4 (C-5); 31.1 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 172 (6), 171 (9), 170 $[M]^+$ (100), 155 (35), 96 (12), 87 (8), 83 (15). Found, %: C 42.35, 42.31; H 3.71; 3.73; N 16.18, 16.21. $C_6H_6N_2O_2S$. Calculated, %: C 42.34; H 3.55; N 16.46.

The filtrate after separation of the salt of ketone **2c** was evaporated to dryness. The sodium salt of ester **1c** was dissolved in water and acidified with acetic acid. The precipitate was filtered off and recrystallized from alcohol to give ester **1c** (10.4 g, 53%); mp 186-187ºC (mp 188-189ºC [5]). ^1H NMR spectrum, δ, ppm (*J*, Hz): 14.05 (1H, s, NH); 8.56 (1H, s, H-6); 4.26 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 2.58 (3H, s, CH_3); 1.29 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 182.9 (C-2); 165.5 (CO); 163.5 (C-6); 156.4 (C-4); 111.7 (C-5); 61.1 ($O\underline{C}H_2CH_3$); 21.3 (CH_3); 14.3 ($OCH_2\underline{C}H_3$). Mass spectrum, *m/z* (I_{rel}, %): 200 (6), 199 (11), 198 $[M]^+$ (100), 153 (44), 112 (28), 68 (31).

Hydrolysis of Ethyl 4-Methyl-2-thioxo-1H-pyrimidine-5-carboxylate (1c). Ester **1c** (2 g, 10 mmol) was added to potassium hydroxide solution (10%, 40 ml) and refluxed for 10 min. Conc. HCl (10 ml) was added, the product was cooled, and the precipitated solid was filtered off to give a mixture of compounds which we were unable to separate or identify.

Ethyl 4-Amino-2-thioxo-1H-pyrimidine-5-carboxylate (1d). Thiourea (15 g, 200 mmol) was added to a solution of sodium ethylate (sodium (4.6 g, 200 mmol) in absolute ethanol (125 ml)). The solution obtained was stirred and ethyl ethoxymethylenecyanoacetate (33.8 g, 200 mmol) was added portionwise and refluxed for 6 h. The cooled product was treated with water (350 ml), acidified with acetic acid (30 ml), and taken to reflux with stirring. The solution was cooled and the precipitate formed was filtered off, washed with water, and dried. Yield 27.8 g (76%); mp 258-259ºC (mp 260-262ºC [11]). ^1H NMR spectrum, δ, ppm (*J*, Hz): 12.46 (1H, s, NH); 8.48, 7.87 (2H, s, NH_2); 8.05 (1H, s, H-6); 4.23 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 1.27 (3H, t, *J* = 7.0; $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 181.2 (C-2); 165.2 (CO); 160.4 (C-4); 148.7 (C-6); 97.6 (C-5); 61.7 ($O\underline{C}H_2CH_3$); 14.9 ($OCH_2\underline{C}H_3$). Mass spectrum, *m/z* (I_{rel}, %): 201 (6), 200 (10), 199 $[M]^+$ (100), 171 (9), 154 (9), 141 (10), 127 (13), 113 (28), 95 (38), 68 (22).

Hydrolysis of Ethyl 4-Amino-2-thioxo-1H-pyrimidine-5-carboxylate (1d). A mixture of aqueous potassium hydroxide (10%, 100 ml) and ester **1d** (4.58 g, 25 mmol) was refluxed for 10 min. Hydrochloric acid (25 ml) was added and the precipitated solid was filtered off, washed with water, and dried. Yield of compound **3d** 3.08 g (80%). Decomposition point 261-262ºC (decomposition point 253-263ºC [12]). ^1H NMR spectrum, δ,

ppm: 12.57 (1H, s, OH); 8.44, 8.02 (2H, s, NH_2); 7.99 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 180.9 (C-2); 167.1 (CO); 160.9 (C-4); 148.5 (C-6); 98.2 (C-5). Mass spectrum, *m/z* (I_{rel}, %): 173 (7), 172 (10), 171 $[M]^+$ (100), 127 (26), 113 (14), 95 (13), 85 (17).

Decarboxylation of Acid 3d. A mixture of biphenyl (1.8 g), diphenyl ether (18.6 g) and acid **3d** (0.437 g, 2.5 mmol) was refluxed for 15 min and cooled. The precipitate filtered off was washed with hexane and recrystallized from ethanol. The yield of compound **7** was 58 mg (18%); mp 260-262ºC. ^1H NMR spectrum, δ, ppm (*J*, Hz): 11.97 (1H, s, NH); 7.60, 7.52 (2H, s, NH_2); 7.39 (1H, d, *J* = 7.0, H-5); 5.92 (1H, d, *J* = 7.0, H-6). Mass spectrum, *m/z* (I_{rel}, %): 129 (6), 128 (8), 127 $[M]^+$ (100), 111 (28), 95 (44).

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