an oily semisolid product (33 g.) which was collected at the vacuum filter. Recrystallization from hexane (Skellysolve B) gave 12.3 g. of first crop, m.p. 83–85° and 6.1 g. of second, m.p. 82–84° (18.4 g. = 46% of theory, based on unrecovered carbinol). Several more recrystallizations for analysis raised the melting point to 84–86°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75; O, 30.73. Found: C, 61.68; H, 7.97; O, 30.80.

The infrared spectrum was consistent with the assigned structure.

Methyl dicyclopropylglycolate (II). To a solution of 6 g. of diazomethane in 100 ml. of ether was added a solution of 8 g. (0.051 mole) of dicyclopropylglycolic acid (I) in 50 ml. of ether. After standing at room temperature in the dark for 24 hr., the ether was removed by distillation and the residual oil was distilled under reduced pressure. After a forerun, 2.1 g., b.p. 30–124° (60 mm.), the methyl ester II distilled at 124° (60 mm.); yield, 6.2 g. (71%), n_D^{23} 1.4535.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.18; H, 8.51.

The infrared spectrum, including a band at 1.63 μ in the near infrared, characteristic of the cyclopropane ring,[6] was consistent with the assigned structure.

β-Diethylaminoethyl dicyclopropyglycolate hydrochloride (III). A solution of 7.8 g. (0.05 mole) of dicyclopropylglycolic acid (I) and 7.5 g. (0.055 mole) of β-diethylaminoethyl chloride in 60 ml. of isopropanol was refluxed with stirring for 18 hr. On cooling, the product crystallized. It was collected by vacuum filtration and dissolved in 50 ml. of cold water. Addition of excess cold 40% sodium hydroxide solution precipitated an oil (free ester base) which was taken up in ether, washed with water and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, a slight excess of ethereal hydrogen chloride solution was added and the precipitated hydrochloride was collected. Three recrystallizations from ethanol gave 6.5 g. (45%) of the ester hydrochloride III, m.p. 152–154°.

Anal. Calcd. for $C_{14}H_{26}ClNO_3$: C, 57.62; H, 8.98; N, 4.80; Cl, 12.15. Found: C, 57.77; H, 8.98; N, 4.82; Cl, 12.17.

(6) W. H. Washburn and M. J. Mahoney, *J. Am. Chem. Soc.*, **80**, 504 (1958).

Acknowledgments. The authors are indebted to Mr. E. F. Shelberg and Mr. W. H. Washburn and their associates for the microanalyses and infrared spectra, respectively.

ORGANIC RESEARCH DEPARTMENT
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Synthesis of 3-Hydroxypyridines. I. Condensation of Aromatic Aldehydes with Ethyl Cyanoacetate

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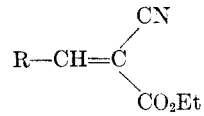
Received October 1, 1959

In the course of investigations of methods of syntheses of 3-hydroxypyridines in progress in this laboratory, it was necessary to prepare a series of compounds of type I.



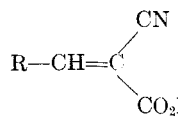
The α,β-unsaturated cyanoesters, I, in which R is an aromatic group, were prepared by condensation of the appropriate aromatic aldehyde with ethyl cyanoacetate by the general Knoevenagel[1] reaction using piperidine as a catalyst.[2] In this

(1) J. Scheiber and F. Meisel, *Ber.*, **48**, 257 (1915).

(2) See for example P. D. Gardner and R. I. Brandon, *J. Org. Chem.*, **22**, 1704 (1957).

TABLE I

CONDENSATION OF ALDEHYDES WITH ETHYL CYANOACETATE



R	Yield, %	M.P.[a]	Calcd. Carbon	Calcd. Hydrogen	Calcd. Nitrogen	Found[b] Carbon	Found[b] Hydrogen	Found[b] Nitrogen
o-ClC_6H_4—	61	54–55[c,d]	61.16	4.28	5.95	61.11	4.03	5.97
3,4-$(C_2H_5O)_2C_6H_3$—	86	126–127[c]	66.42	6.62	4.84	66.40	6.64	4.95
p-$(ClCH_2CH_2)_2NC_6H_4$—	89	174–175[e]	56.31	5.32	8.21	56.38	5.54	7.93
3,4-$(CH_2O_2)C_6H_3$—	77	106–107[c,f]	63.67	4.52	5.71	63.70	4.63	5.47
o-$O_2NC_6H_4$—	68	101–103[c,g]	58.53	4.09	11.38	58.82	4.16	11.60
3-CH_3O-4-HOC_6H_3—	92	108–109[c,h]	63.15	5.30	5.67	63.13	5.39	5.90
p-HOC_6H_4—	58	173–174[c,i]	66.35	5.11	6.45	66.69	5.05	6.23
p-$(CH_3CH_2)_2NC_6H_4$—	81	95–96[c]	70.56	7.40	10.29	70.42	7.49	10.09
o-$O_2NC_6H_4CH{=}CH$—	83	141–142[c]	61.76	4.44	10.29	62.21	4.42	10.42

[a] All melting points are uncorrected. [b] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Straus, Oxford, Eng. [c] Recrystallized from 95% ethanol. [d] Reported m.p. 53° (from esterification of acid), J. A. McRae and C. Y. Hopkins, *Can. J. Res.*, **7**, 248 (1932). [e] Recrystallized from chloroform. [f] Reported m.p. 104° (from esterification of acid), C. H. Clarke and F. Francis, *Ber.*, **44**, 273 (1911). [g] Reported m.p. 96° (from condensation reaction), F. Reidel, *J. prakt. Chem.*, (2), **54**, 533 (1896). [h] Reported m.p. 111° (from esterification of acid), reference as footnote f. [i] Reported m.p. 162–163° (from condensation reaction), reference as footnote g.

manner, the compounds shown in Table I were prepared.

All of the compounds reported had infrared spectra which exhibited a nitrile band at 2195 ± 10 cm.$^{-1}$ and an ester band at 1700 ± 10 cm.$^{-1}$

EXPERIMENTAL

Reagents. The author thanks Kay-Fries Chemicals, Inc. for a generous gift of ethyl cyanoacetate. The aldehydes used were obtained from commercial sources and used without further purification or were prepared by standard literature methods. Thanks go to the Antara Chemicals Division of General Aniline and Film Corp. for a sample of *p*-diethylaminobenzaldehyde.

Typical condensation. To a mixture of 22.6 g. (0.2 mole) of ethyl cyanoacetate and 0.2 mole of aldehyde in about 60 ml. of dry dioxane at 0° was added dropwise 0.8 ml. of piperidine. After standing overnight at room temperature, crystals had formed (in a few cases cooling was needed to promote crystallization). The solids were filtered, washed, dried, and recrystallized several times from an appropriate solvent.

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Preparation of Various Substituted Pyrimidines[1]

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Received October 29, 1959

During the last decade, numerous pyrimidines and purines have been investigated which might be useful in human cancer chemotherapy, and several have been found to possess tumor-inhibiting properties.[3,4] The pharmacological activity of these compounds has prompted the preparation of various substituted pyrimidines.

The substituted pyrimidines synthesized during the course of this investigation have incorporated the physiologically active ring systems of pyridine and thiophene and were prepared in hopes that some of them would exhibit physiological activity of some type, since they are related to a number of the biological and medicinal agents, such as nucleic acids, several vitamins and enzymes, uric acid, and sulfadiazine.

Pharmacological tests of these substituted pyrimidines are being made.

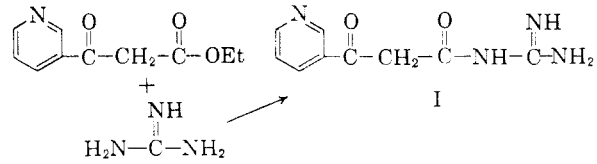
The substituted pyrimidines synthesized are listed in Table I and Table II and were prepared by condensing the appropriate β-diketone or β-keto ester with guanidine carbonate. The general procedure is given in the experimental section.

The 2-amino-4-alkyl-6-(α-thienyl)pyrimidines were prepared by condensing the appropriate acyl-2-thenoylmethane with guanidine carbonate.

The 2-amino-4-alkyl-6-(β-pyridyl)pyrimidines were prepared by the same method, but the appropriate nicotinylacylmethane was employed.

In the case of 2-amino-4-hydroxy-6-(α-thienyl)-pyrimidines, ethyl β-keto-(α-thienyl)propionate was condensed with guanidine carbonate.

In the attempted preparation of 2-amino-4-hydroxy-6-(β-pyridyl)pyrimidine, ethyl nicotinoylacetate was treated with guanidine carbonate, but ring closure did not occur as the intermediate product (I) was obtained instead.



The infrared spectra of these pyrimidines have been recorded and showed prominent peaks near 3200–3100 cm.$^{-1}$ due to CH stretching vibrations. In addition, strong peaks were noted in the region near 1665 cm.$^{-1}$, 1600–1565 cm.$^{-1}$ and 1555–1540 cm.$^{-1}$ which are due to C=C and C=N vibrations, respectively, in this aromatic system. There is some belief that the higher frequency bands are due to NH_2 deformations modes rather than C=C and C=N vibrations themselves.[5] There is also a strong band near 3320 cm.$^{-1}$ and this is assigned to the NH_2 group.

EXPERIMENTAL

Preparation of substituted pyrimidines. The substituted pyrimidines were prepared by heating 3.5 g. of the appropriate β-diketone or β-keto ester with 1.5 g. of guanidine carbonate at 130–140° for 3–4 hr. according to the method of Evans.[6] The molten mass was allowed to cool and then dissolved in hydrochloric acid. The substituted pyrimidine was then precipitated upon the addition of dilute ammonium hydroxide.

The substituted pyrimidine was recrystallized three times from absolute alcohol, and white crystals were obtained. The average yield was 20%.

The respective picrates were prepared by dissolving 0.1 g. of the pyrimidine in 5 ml. of absolute alcohol and adding a saturated solution of picric acid dissolved in absolute alcohol. Upon standing, the picrate settled out and was recrystallized from absolute alcohol.

In the case of the 2-amino-4-hydroxy-6-(α-thienyl)pyrimidine, the acid-base technique was not employed, but the pyrimidine was recrystallized from 80% alcohol.

(1) This work is based on a thesis submitted by James J. Zelko in partial fulfillment for the degree of Master of Science at Loyola University, Chicago, Ill.

(2) Cooperative National Science Foundation Fellow, Summer 1959.

(3) C. Heidelberger, N. C. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, **179**, 663 (1957).

(4) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Amer. Chem. Soc.*, **79**, 4559 (1957)

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Second Edition, John Wiley and Sons, (New York, 1956), p. 282.

(6) P. N. Evans, *J. prakt. Chem.* [2] **48**, 513 (1893).