Summary

The ultraviolet absorption spectra of a variety of hydroxy- and aminopyrimidines and purines are recorded. These data further substantiate the interpretation that the major chromophore of pyrimidines and purines is the $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=N-$ or $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$ system.

A correlation of the intensities of absorption with the symmetry of substituted pyrimidines has been made.

New methods for the synthesis of 6-hydroxy-, 6-amino-, 2,6-diamino-, 4-amino-6-hydroxy-, and 4,6-diaminopyrimidines are presented.

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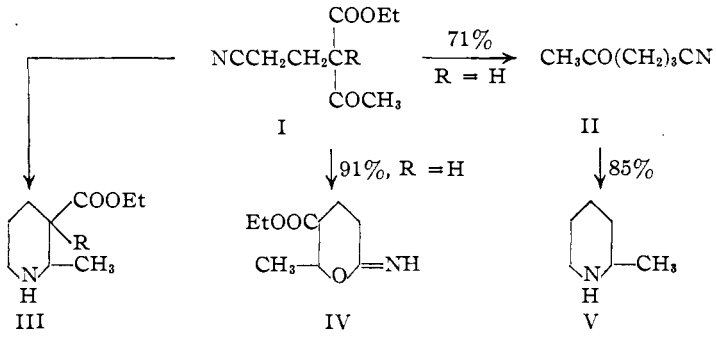
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Piperidines and Azabicyclo Compounds. I. *Via* Michael Condensations

BY NOEL F. ALBERTSON

It has been known for a long time that δ-ketonic nitriles could be reduced to piperidines.[1] Since so many compounds of marked physiological activity contain the piperidine ring, it seemed worthwhile to reinvestigate this method of synthesis of piperidine compounds in light of the recent development of the chemistry of acrylonitrile. Accordingly, such a research program was initiated in this Laboratory a number of years ago. Publication at this time of some of the results of this investigation is prompted by the recent appearance of three papers[2] indicating an overlapping of interest in this and two other laboratories. Reference by Henecka in his *Berichte* article to a French Patent applied for in 1942[3] indicates clearly his priority in this method of synthesis. However, our results (performed independently) differ from those of Henecka in some respects and extend the general method to compounds not prepared by Henecka.



The δ-ketonitriles used in the present work were prepared by Michael condensations between vinyl ketones and cyanoacetic esters, or acrylonitrile and β-ketoesters.

The simplest δ-ketonic nitrile, 5-oxocapronitrile-(II) may be prepared from acetone and acrylonitrile, but the yield is very low,[4] owing to polycyanoethylation. Since β-keto esters give much higher yields of monocyanoethyl derivatives than can be obtained from ketones, a better yield of II was realized by starting with acetoacetic ester. The condensation of acrylonitrile with ethyl acetoacetate gave a 63% yield of ethyl (2-cyanoethyl)-acetoacetate, I (R = H).[5] It was found that aqueous carbonate readily converted I (R = H) to pure II in 71% yield (44% over-all based on acrylonitrile).

Reduction of II with Raney nickel catalyst yielded 2-methylpiperidine (V) in 85% yield. Reduction of I (R = H) may be stopped after the uptake of one mole of hydrogen to give a basic compound the analytical data for which agrees with the formula $C_9H_{15}NO_3$. Since this compound lost nitrogen as ammonium chloride on refluxing with hydrochloric acid, it is most probably 5-carbethoxy-6-methyltetrahydro-2-pyroneimine (IV).[6] This compound is undoubtedly identical with Henecka's compound XX[2c] (1-cyanopentanol-(4)-carbonsäure-(3)-ester) although Henecka gives no properties or experimental details.

Since Koelsch has shown that reduction of γ-cyano esters with Raney nickel catalyst yields piperidones,[7] one might expect that reduction of I would lead to either a piperidine or a piperidone or both. Actually, only piperidines, III, have been isolated, usually in high yield.

Complete reduction of I (R = H) using Raney nickel catalyst gave an 86% yield of 2-methyl-

(1) (a) Wohl and Maag, *Ber.*, **43**, 3280 (1910); (b) Rupe and Heckendorn, *Helv. Chim. Acta*, **9**, 980 (1926); (c) Rupe and Stern, *ibid.*, **10**, 859 (1927).

(2) (a) Henecka, *Angew. Chem.*, **60**, 59 (1948); received Feb. 1949, (b) Boekelheide and Rothchild, THIS JOURNAL, **71**, 879 (1949); (c) Henecka, *Ber.*, **82**, 104 (1949).

(3) French Patent 881,360. To the best of our knowledge the contents of this patent have not yet appeared in the abstract literature.

(4) Shannon, U. S. Patent 2,381,371 (1945). An 8.6% yield of product boiling over a thirty degree range is reported.

(5) (a) Keimatsn and Sugasawa, *J. Pharm. Soc.* (*Japan*), **48**, 755 (1928); (b) Bruson, U. S. Patent 2,394,962 (1946); (c) Wiest and Glaser, U. S. Patent 2,396,626 (1946).

(6) We are indebted to Dr. A. A. Larsen of these laboratories for first suggesting this structure and pointing out the analogy between our compound and the 2-furanoneamine obtained by Schultz, Robb, and Sprague, THIS JOURNAL, **69**, 2454 (1947), and by Easton, Gardner and Stevens, *ibid.*, **69**, 2941 (1947).

(7) Koelsch, *ibid.*, **65**, 2458 (1943).

TABLE I

KETONES, $R_1COCR_2R_3CH_2CH_2CN$

R_1	R_2	R_3	Yield, %	B. p., °C.	Mm.	$n^{25}D$	Analyses, % N Calcd.	Obsd.
CH_3	H	COOEt	63[a,5]	121	2	1.4446	7.65	7.53
CH_3	H	H	71[3,4]	86.5	5.2	1.4790	12.61	12.48[a]
CH_3	CH_2CH_2COOMe[b]	COOEt	100	166	1.7	1.4510	5.20	5.27
CH_3	CH_2CH_2COOEt	COOEt	82	168	0.8	1.4578	4.95	5.05
CH_3	$C_6H_5CH_2$	COOEt	85[c]	172	1.5	1.5068	5.13	5.18[d]
CH_3	$C_6H_5CH_2$	COOMe	56	163	0.2	1.5158	5.40	5.33
CH_3	CH_3	COOEt	48	109	0.8	1.4461	7.10	7.03
CH_3	CH_2OH	COOEt	94	...	...	1.4585	6.57	6.38
CH_3	n-C_6H_{13}	COOEt	73	157	2.9	1.4511	5.24	5.08
CH_3	n-C_7H_{15}	COOEt	81	145	0.9	1.4505	4.98	4.91
CH_3	$-CH_2CH_2OCO-$		89	162	1.5	1.4790	7.73	7.78[e]
	$-CH_2CH_2CH_2-$	COOEt	82	145	1.5	1.4663	6.69	6.46[3]
CH_3	$-CH_2C(CH_2Cl)OCO-$		61	199	1.6	1.4982	6.10	5.86
C_6H_5	H	COOEt	86	176	0.7	1.5131	5.71	5.95
C_6H_5	H	H	52[f]	125	.1	1.5326	8.09	7.79
CH_3	Iso-C_3H_7	COOEt	37[g]	121	.1	1.4542	6.22	6.22[h]
CH_3	Iso-C_4H_9	COOEt	60	125	.1	1.4528	5.85	5.62

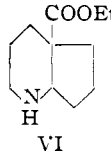
[a] *Anal.* Calcd. for C_6H_9NO: C, 64.86; H, 8.17. Found: C, 64.93; H, 8.34. Dinitrophenylhydrazone, m. p. 154–155°. *Anal.* Calcd. for $C_{12}H_{13}N_5O_4$: N as (NO_2), 9.62. Found: N as (NO_2), 9.57. [b] Some transesterification likely. [c] Based on unrecovered starting material. Direct yield, 68%. [d] *Anal.* Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01. Found: C, 70.25; H, 7.07. [e] M. p. 44–46°, from methanol. *Anal.* Calcd. for $C_9H_{11}NO_3$: C, 59.65; H, 6.12. Found: C, 59.52; H, 6.26 [f] Allen and Ball, THIS JOURNAL, **59**, 686 (1937). [g] Yield based on recovered starting material was 68%. [h] *Anal.* Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50. Found: C, 63.69; H, 8.69.

nipecotic ester. These results are in marked contrast to those obtained by Henecka[2a,c] who states that a piperidine cannot be obtained from I (R = H) by reduction, unless I (R = H) is first converted to the corresponding β-aminocrotonic ester with ammonia.

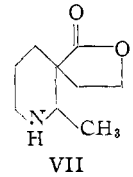
Examples of the use of other R groups such as benzyl, phenyl, isopropyl, etc., are shown in Tables I and II. By replacing ethyl acetoacetate with ethyl benzoylacetate there were prepared compounds analogous to I, II, III, IV and V in which a phenyl group had replaced the methyl group.

By starting with cyclopentanone-2-carboxylic ester and acrylonitrile, the R group of I was made part of a ring joining the acetyl group. Reduction gave 4a-carbethoxy-octahydro-1-pyrindine (VI) a compound also prepared by Henecka.[3]

When acetobutyrolactone was condensed with acrylonitrile the resulting compound had the R group of I part of a ring joining the carbethoxy group. Reduction gave 1-methyl-2-aza-8-oxaspiro[5.4]decan-7-one(VII).

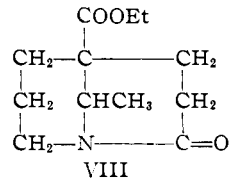


VI

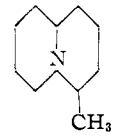


VII

Examination of formula III indicates that there are two reactive groupings present. By proper choice of R it should be possible to form spiro or bicyclo compounds. To examine this possibility, acrylonitrile was condensed with ethyl (2-carbomethoxyethyl)-acetoacetate to give a quantitative yield of I (R = CH_2CH_2COOMe). Upon reduction, this compound gave a 43% yield of piperidine, III (R = CH_2CH_2COOMe) and a 36% yield of the corresponding bicyclo compound, VIII. Like piperidone, this compound



VIII



IX

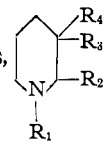
is basic. Upon standing, the piperidine was gradually converted to VIII by loss of methanol. Reduction of I (R = CH_2CH_2COOEt) gave only a 4% yield of VIII, the remainder being the piperidine, III (R = CH_2CH_2COOEt).

It seemed probable that some of the reactions shown by acrylonitrile might be duplicated by 2-vinylpyridine since the C=C—C=N grouping is common to both molecules. Such was found to be the case. Reduction of 1-(2-pyridyl)-pentanone-4 (obtained from 2-vinylpyridine and acetoacetic ester by condensation and hydrolysis[8]) gave the expected 4-methylquinolizidine (IX). It is interesting to note that whereas reduction of (cyanoethyl)-acetoacetic esters gave principally piperidines on reduction, reduction of ethyl 2-(2-pyridyl)-ethylacetoacetate in ethanol with Raney nickel at 150° gave a 40% yield of ethyl 4-methylquinolizidine-3-carboxylate and a 45% yield of 3-(1-hydroxyethyl)-4-oxoquinolizidine, the "piperidone" type of ring closure predominat-

(8) Doering and Weil, THIS JOURNAL, **69**, 2461 (1947).

TABLE II

PIPERIDINES,



R_1	R_2	R_3	R_4	Yield, %	B. p., °C.	Mm.	$n^{25}D$	Analyses, % N Calcd.	Obsd.
H	CH_3	H	H	85	117	760	1.4444	[a,3]	
H	CH_3	H	COOEt	86	59	0.5	1.4557	7.94[b,2c]	8.18
CH_3	CH_3	H	COOEt	98	73	.2	1.4557	7.56[c]	7.58
CH_3	CH_3	H	COOH					[d]	
H	CH_3	CH_3	COOEt	89	63	.1	1.4581	7.56[e]	7.58
CH_3	CH_3	CH_3	COOEt	58	67	.9	1.4592	7.03	6.95
H	CH_3	Iso-C_3H_7	COOEt	84	91	.3	1.4666	6.57[f]	6.44
CH_3	CH_3	Iso-C_3H_7	COOEt	82	92	.6	1.4642	6.16	6.07
H	CH_3	Iso-C_4H_9	COOEt	91	98	.3	1.4658	6.16	6.15
CH_3	CH_3	Iso-C_4H_9	COOEt	84	95	.9	1.4612	5.80	5.72
H	CH_3	n-C_6H_{13}	COOEt	85	106	.2	1.4627	5.49	5.49
CH_3	CH_3	n-C_6H_{13}	COOEt	80	130	1.9	1.4609	5.20	5.22
H	CH_3	n-C_7H_{15}	COOEt	63	120	0.7	1.4665	5.20	5.23
CH_3	CH_3	n-C_7H_{15}	COOEt	33	136	1.5	1.4638	4.94	4.42
H	CH_3	$C_6H_5CH_2$	COOEt	85	137	1.4	1.5262	5.36[g]	5.34
CH_3	CH_3	$C_6H_5CH_2$	COOEt	81	134	0.2	1.5110	5.09	4.96
H	CH_3	$C_6H_5CH_2$	COOMe	78	137	.6	1.5335	5.66	5.64
CH_3	CH_3	$C_6H_5CH_2$	COOMe	75	132	.8	1.5223	5.36	5.31
H	CH_3	C_6H_5	COOEt	57	131	.3	1.5323	5.66[h]	5.53
H	CH_3	$-CH_2CH_2OCO-$		30				6.81[i]	6.82
CH_3	CH_3	$-CH_2CH_2OCO-$		70				6.38[j]	6.48
H	$-CH_2CH_2CH_2-$		COOEt	73	87	.6	1.4799	7.10[k,3]	7.00
CH_3	$-CH_2CH_2CH_2-$		COOEt	85	83	1.0	1.4755	6.63[l]	6.37
H	CH_3	CH_2CH_2COOMe	COOEt	43	139	1.4	1.4740	5.44[m]	5.26
H	CH_3	CH_2CH_2COOEt	COOEt	65	133	0.9	1.4740	5.16[n]	5.32
CH_3	CH_3	CH_2CH_2COOEt	COOEt	86	128	1.0	1.4726	4.91[p]	5.16
H	CH_3	$-(CH_2)_3NH_2$	CH_3	77	80	1.2	1.5031	16.45[q]	16.16
H	C_6H_5	H	H	80	80	0.2	1.5232	8.69[r]	8.65
H	C_6H_5	H	COOEt	73	113	0.08	1.5227	6.00[s]	5.78
CH_3	C_6H_5	H	COOEt	94	116	0.1	1.5178	5.66	5.56

[a] Identity confirmed by mixed m. p. of the hydrochloride with an authentic specimen. [b] 1-Carbanilino derivative, m. p. 134.6–136.0° cor. *Anal.* Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.17; H, 7.64; N, 9.65. Found: C, 66.26; H, 7.38; N, 9.57. [c] Methiodide, m. p. 185.0–186.4° cor. *Anal.* Calcd. for $C_{11}H_{22}INO_2$: C, 40.39; H, 6.78; I, 38.80. Found: C, 40.44; H, 6.70; I, 38.40. [d] Hydrochloride, m. p. 185.8–188.0° cor. *Anal.* Calcd. for $C_8H_{15}NO_2$·HCl: C, 49.60; H, 8.33; Cl, 18.30. Found: C, 49.62, 49.33; H, 7.86, 7.97; Cl, 18.22. [e] Hydrochloride, m. p. 164.4–165.0° cor. *Anal.* Calcd. for $C_{10}H_{19}NO_2$·HCl: C, 54.17; H, 9.09; Cl, 15.99. Found: C, 53.95; H, 8.75; Cl, 15.79. [f] *Anal.* Calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.86. Found: C, 67.68; H, 10.64. [g] *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.87. Found: C, 73.33; H, 9.02. [h] *Anal.* Calcd. for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.56. Found: C, 72.78; H, 8.46. A small amount of water-soluble neutral by-product (b. p. 210° at 0.1 mm.; m. p. 166–167° from isopropyl alcohol) had an observed nitrogen value of 7.64%. [i] Isolated as the hydrochloride, m. p. 265–266°. *Anal.* Calcd. for $C_9H_{15}NO_2$·HCl: Cl, 17.24. Found: Cl, 17.10. [j] Isolated as hydrochloride, m. p. 72–75°. *Anal.* Calcd. for $C_{10}H_{17}NO_2$·HCl: C, 54.66; H, 8.25. Found: C, 54.88; H, 8.21. [k] *Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.96; H, 9.71. Found: C, 66.98; H, 9.89. [l] *Anal.* Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02. Found: C, 67.97; H, 9.73. [m] *Anal.* Calcd. for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01. Found: C, 60.40; H, 8.41. [n] *Anal.* Calcd. for $C_{14}H_{25}NO_2$: C, 61.98; H, 9.29. Found: C, 61.96; H, 9.04. [p] *Anal.* Calcd. for $C_{15}H_{27}NO_4$: C, 63.12; H, 9.54. Found: C, 63.19; H, 9.31. [q] B. p. 250–255° at atm. press. Dihydrochloride, m. p. 243–246°. *Anal.* Calcd. for $C_{10}H_{22}N_2$·2HCl: C, 49.38; H, 9.12; Cl, 29.16. Found: C, 49.40; H, 8.87; Cl, 29.18. Monopicrate, m. p. 194–195°. *Anal.* Calcd. for $C_{10}H_{22}N_2$·$(NO_2)_3C_6H_2OH$: N (AP), 7.00. Found: N (AP), 6.61. [r] Gabriel, *Ber.*, **41**, 2013 (1908). This compound readily formed the crystalline hydrate on shaking with water. [s] Hydrochloride, m. p. 202.2–203.4° cor. *Anal.* Calcd. for $C_{14}H_9NO_2$·HCl: C, 62.32; H, 7.47; Cl, 13.14. Found: C, 62.36; H, 7.31; Cl, 13.02. Phosphate, m. p. 183.3–184.9° cor. *Anal.* Calcd. for $C_{14}H_{19}NO_2$·H_3PO_4: N, 4.23; H_3PO_4, 29.61. Found: N, 4.19; H_3PO_4, 29.60.

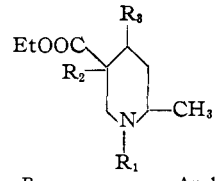
ing. These, and a number of other quinolizidines which were independently prepared in this Laboratory, have recently been described in an excellent paper by Boekelheide and Rothchild.[2b]

Although some of the molecules so far described have more than one asymmetric carbon atom, only a single *dl*-modification is usually obtained on reduction.

Rupe and Heckendorn[1b] prepared a δ-ketonitrile by addition of cyanoacetic ester to benzalacetophenone. Reduction of the condensation product gave ethyl 4,6-diphenylnipecotate. By

TABLE III

PIPERIDINES



R_1	R_2	R_3	B. p. °C.	Mm.	$n^{25}D$	Analyses, % N Calcd.	Obsd.
H	H	C_6H_5	130	1.0	1.5172	5.66	5.76[a,2c,3]
CH_3	H	C_6H_5	127	1.5	1.5104	5.36	5.13[b,2c,3]
H	Et	C_6H_5	131	1.6	1.5148	5.08	4.96[a]
CH_3	Et	C_6H_5	118	0.6	1.5105	4.84	4.66[c]
H	Et	2,3-$(MeO)_2C_6H_3$	158	.8	1.5194	4.18	4.13[a]
CH_3	Et	2,3-$(MeO)_2C_6H_3$	153	.9	1.5152	4.01	3.91

[a] Basic nitrogen by titration with perchloric acid in acetic acid. [b] *Anal.* Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.62; H, 8.82. [c] *Anal.* Calcd. for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40. Found: C, 74.51; H, 9.08.

analogous reaction we have prepared ethyl 1,6-dimethyl-4-phenylnipecotate, ethyl 3-ethyl-1,6-dimethyl-4-phenylnipecotate and ethyl 3-ethyl-4-(2,3-dimethoxyphenyl)-1,6-dimethyl nipecotate.

It will be noted that nearly all of the piperidines and bicyclo compounds reported in this paper have been prepared in only three steps from readily available and cheap materials. Some of the compounds show mild analgesic activity.

Experimental[9]

Ethyl (2-Cyanoethyl)-acetoacetate.[5]—To a solution of 3 g. of sodium in 400 ml. of alcohol was added 600 ml. of acetoacetic ester. With stirring, 246 ml. of acrylonitrile was added at such a rate that the temperature did not exceed 45°. The alcohol was distilled off and the residue washed with water containing 10 ml. of acetic acid. Distillation gave acetoacetic ester and then the product (Table I). The residue, ethyl bis-(2-cyanoethyl)-acetoacetate, may be recrystallized from alcohol.[10]

5-Oxocapronitrile (II).[4]—To a solution of 200 g. of sodium carbonate in 1800 ml. of water was added 200 g. of I (R = H). The mixture was refluxed for four hours during which time the upper layer disappeared. The product was salted out with potassium carbonate and extracted with ether (see Table I).

Ethyl Benzyl-(2-cyanoethyl)-acetoacetate.—To 0.5 g. of sodium in 200 ml. of 95% alcohol was added 168 g. of benzylacetoacetic ester. With stirring, 53 ml. of acrylonitrile was added at such a rate that the temperature remained at 25–35°. One-half hour after the addition of the nitrile, alcoholic hydrogen chloride was added to make the solution acid. Distillation gave 35 g. of benzyl acetoacetic ester and 141 g. of ethyl benzyl-(2-cyanoethyl)-acetoacetate (Table I).

In earlier experiments commercial absolute alcohol was used with the result that there was some loss of the acetyl group so that ethyl 2-(2-cyanoethyl)-3-phenylpropionate was sometimes the major or sole product; b. p. 152° at 2.0 mm., $n^{25}D$ 1.5002.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.41; N, 6.05. Found: C, 72.52; H, 7.41; N, 6.03.

Dr. C. F. Koelsch suggested the addition of water to the reaction medium to avoid deacetylation.

2-Aceto-2-(2-cyanoethyl)-butyrolactone.—To a solution of 2 g. of sodium in 300 ml. of ethanol was added 512 g. of acetobutyrolactone. With stirring 290 ml. of acrylonitrile was added. (The product may separate as a second layer.) After one hour the mixture was acidified with alcoholic hydrogen chloride, and either distilled or allowed to stand. The distilled product has remained liquid for several years, whereas when the reaction mixture was allowed to stand the product crystallized in a day or two. The product, obtained in yields of 86–92%, slowly developed a pale color with alcoholic ferric chloride. It gave a negative iodoform test.

Refluxing the product for six hours with 10% aqueous sodium carbonate solution, salting out with potassium carbonate, extracting with isopropyl alcohol and distilling gave a poor yield of yellow oil, boiling at 115–146° at 3.5 mm. Presumably the oil is 4-(2-hydroxyethyl)-5-oxocapronitrile. It gave a 2,4-dinitrophenylhydrazone, m. p. 159° from ethyl acetate.

Anal. Calcd. for $C_{14}H_{17}N_5O_5$: $TiCl_3$ equiv., 14.00. Found: $TiCl_3$ equiv., 14.12 (based on 335.3 molecular weight).

2-(2-Hydroxyethyl)-glutaric Acid Lactone.—Hydrolysis of 40 g. of 2-aceto-2-(2-cyanoethyl)-butyrolactone with 80 g. of potassium hydroxide in aqueous methanol gave, on acidification, extraction with ethyl acetate and concentration, 22 g. (part was accidentally spilled) of oil, b. p. 165–188° at 1.0 mm. Upon redistillation it boiled at 163–166 at 1.0 mm.

Anal. Calcd. for $C_7H_{10}O_4$: neut. equiv. (hot), 79.1; neut. equiv. (cold), 158.2. Found: neut. equiv. (hot), 78.5; neut. equiv. (cold), 153.2.

4-Benzoylbutyronitrile.[11]—This compound was prepared by refluxing 100 g. of ethyl (2-cyanoethyl)-benzoylacetate with 100 g. of sodium carbonate and 900 ml. of water for ten hours. The oil was extracted with ether, dried and distilled to give 37.0 g. of product (Table I) and about 4 g. of residue which readily crystallized. This was recrystallized from water, m. p. 140–141°. Though not further investigated, this is undoubtedly 4-benzoylbutyramide.[11]

4-Benzoylbutyronitrile was also prepared by condensing acrylonitrile with ethyl benzoylacetoacetate and hydrolyzing the crude condensation product with sodium carbonate solution.

Ethyl (2-Cyanoethyl)-methylacetoacetate.—To 15.3 g. of sodium in 300 ml. of dry ethanol was added 122 g. of I (R = H) and 50 ml. of methyl iodide. The mixture was allowed to stand two days and then worked up in the usual manner. Distillation gave 35.6 g. of 4-cyano-2-methylbutyrate, boiling at 74–80° at 0.8 mm.; $n^{25}D$ 1.4270.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.57; H, 8.71; N, 8.76.

There was also obtained 63.3 g. of product boiling at 108–110° at 0.8 mm. (Table I). When the reaction mixture was allowed to stand only sixteen hours, the yield of product increased to 77%.

Ethyl (2-Cyanoethyl)-phenylacetoacetate.—This compound was prepared according to directions received in a personal communication from Dr. Koelsch [see Koelsch and Walker, THIS JOURNAL, **72**, 346 (1950)].

Ethyl (2-Cyanoethyl)-isopropylacetoacetate.—This was prepared in 37% yield using the same procedure employed for the phenyl compound above. It was also prepared in poorer yield from ethyl (2-cyanoethyl)-acetoacetate, isopropyl ether and boron trifluoride by the method used by Hauser and Breslow[12] to alkylate acetoacetic ester. Other ketonitriles of Table I were prepared in a manner similar to I (R = H), except ethyl (2-cyanoethyl)-hydroxymethylacetoacetate which was prepared from II and formalin.

Hydrolysis of Ethyl 2-(2-Cyanoethyl)-cyclopentanone-2-carboxylate.—A mixture of 38.2 g. of ketonitrile was refluxed for six hours with a solution of 40 g. of sodium car-

(9) N(AP) refers to nitrogen determined by titration with perchloric acid in acetic acid; N(K) refers to Kjeldahl nitrogen; and N(D) refers to Dumas nitrogen.

(10) Bruson and Riener, THIS JOURNAL, **64**, 2850 (1942). See also reference 5. It is interesting to note that 5c has a new product claim to ethyl bis-(2-cyanoethyl)-acetoacetate in spite of the fact that it is clearly indexed in *C. A.*, **23**, 834 (1929).

(11) Allen and Ball, THIS JOURNAL, **59**, 686 (1937).

(12) Hauser and Breslow, *ibid.*, **62**, 2389 (1940).

bonate in 350 ml. of water during which time the second phase disappeared. Nothing could be salted from the resulting solution by the addition of potassium carbonate, or extracted with chloroform, ether or isopropyl alcohol. Accordingly the solution was acidified with hydrochloric acid and extracted with ethyl acetate. Concentration gave 20.7 g. of orange oil, most of which distilled at 210–231° at 2.0 mm. and solidified in the receiver. Recrystallization from water gave needles, m. p. 149–151°, soluble in ammonium hydroxide. This compound gave ammonia on further hydrolysis.

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.57; N, 7.03. Found: C, 54.39; H, 6.39; N (K), 7.33; neut. equiv., 209 and 214.

The analytical results suggest that the compound might be 2-(2-carbamylethyl)-cyclopentanone-2-carboxylic acid, but the stability (b. p.) precludes this possibility. Furthermore, cyclization with loss of water between the amide and ketone functions would be expected.[13]

Ethyl 3-(2-Carbomethoxyethyl)-2-methylnipecotate and 5-Carbethoxy-9-methyl-2-oxo-1-azabicyclo(3.3.1)nonane (VIII).—A solution of 93 g. of ethyl (2-carbomethoxyethyl)-(2-cyanoethyl)-acetoacetate in 400 ml. of ethanol was reduced at 100° at 500 pounds initial hydrogen pressure in the presence of Raney nickel. Reduction took six hours. The alcohol was removed *in vacuo*, and the residue was diluted with ether and filtered to give 26.1 g. of VIII, m. p. 162–164°. Concentration of the ether solution gave 50.9 g. of oil which on distillation gave 37.9 g. of ethyl 3-(2-carbomethoxyethyl)-2-methylnipecotate (Table II). (Upon standing five months, the analytical sample crystallized with formation of VIII.) The distillation residue, when triturated with ether, gave more VIII, m. p. 158–163°. Recrystallization of the solid from alcohol gave a 36% yield of 5-carbethoxy-9-methyl-2-oxo-1-azabicyclo(3.3.1)nonane (VIII) m. p. 170.4–171.3° cor.

Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22; mol. wt., 225. Found: C, 63.57; H, 7.59; N (AP), 6.27; mol. wt., 229 (cryoscopic).

Ethyl 3-Benzyl-2-methylnipecotate.—Reduction of 140 g. of ethyl benzyl-(2-cyanoethyl)-acetoacetate in 460 ml. of ethanol in the presence of Raney nickel at 80° and 500 lb. hydrogen pressure required five hours. Concentration gave 131 g. of basic oil, 114 g. of which distilled at 134–140° at 1.4 mm. (see Table II).

4a-Carbethoxyoctahydro-1-pyrindine (VI).[8]—A solution of 115 g. of ethyl 2-(2-cyanoethyl)-cyclopentanone-2-carboxylate in 400 ml. of alcohol was reduced in the presence of Raney nickel at 120° and 400 lb. hydrogen pressure in seven hours. Distillation gave 79 g. of product (Table II) and 14.7 g. of yellow oil, b. p. 153–209 at 0.4 mm. Upon redistillation, the yellow oil boiled at 150–212° at 0.9 mm., and the refractive index varied from $n^{25}D$ 1.4858 to 1.4852 (supercooled). The sample solidified and was recrystallized from ether, m. p. 52.9–54.8 cor.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.52; H, 8.11; N, 6.63. Found: C, 62.05; H, 8.29; N (K), 6.35, 6.45.

This by-product may be the alcohol obtained by reduction of the carbonyl. Upon standing overnight with dilute sulfuric acid and then making basic no ammonia is evolved, so that a tetrahydropyroneimine structure seems improbable.

1-Methyl-2-aza-8-oxaspiro(5,4)-decan-7-one Hydrochloride (VII).—One mole of 2-aceto-2-(2-cyanoethyl)-butyrolactone in 400 ml. of methanol was reduced at 90° in the presence of Raney nickel at 500 lb. initial hydrogen pressure in six hours. The reaction product was treated with alcoholic hydrogen chloride to precipitate 62 g. of hydrochloride, m. p. 252–255°. Recrystallization of an analytical sample from ethanol gave crystals, m. p. 265–266.4° cor. (see Table II).

Ethyl 1,2-Dimethylnipecotate.—A solution of 116.2 g. of 2-methylnipecotic ester in 400 ml. of ethanol and 68 ml. of 37% formalin solution was hydrogenated at room temperature and 400 lb. pressure with a buffered palladium–carbon catalyst. Reduction took less than forty-five minutes. Distillation gave 122.2 g. of colorless product (Table II).

Other 1-Methylpiperidines of Table II.—These were prepared in a manner similar to the above, except that 1-methyl-2-aza-8-oxaspiro(5.4)decan-7-one hydrochloride was converted to the acetate before being reductively methylated.

5-Carbethoxy-6-methyltetrahydro-2-pyroneimine (IV).—Reduction of 90 g. of I (R = H) in 400 ml. of alcohol at 60° and 600 lb. hydrogen pressure using Raney nickel catalyst required one to three hours for one mole of hydrogen. The product was obtained in yields of 89–93%, b. p. 103–106° at 0.9 mm.; $n^{25}D$ 1.5350 (supercooled). The product solidified at room temperature.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.37; H, 8.16; N, 7.56. Found: C, 58.90; H, 7.86; N, 7.58.

Ethyl 2-Phenylnipecotate and 5-Carbethoxy-6-phenyltetrahydro-2-pyroneimine.—Reduction of 165 g. of ethyl (2-cyanoethyl)-benzoylacetate in 335 ml. of ethanol with Raney nickel catalyst required one hour at 115° and 700 lb. hydrogen pressure. Distillation gave 113.1 g. of ethyl 2-phenylnipecotate (Table II), and 10.3 g. of oil boiling at 123–164° at 0.3 to 1.8 mm. with decomposition. This fraction contained some benzaldehyde recognized by odor and by the preparation of the 2,4-dinitrophenylhydrazone. An additional 9.0 g. was obtained boiling up to 226° at 1.8 mm. after removal of the fractionating column. The lower boiling by-product deposited crystals in several hours, but the higher boiling fraction partially crystallized only after several days. By trituration with petroleum ether and recrystallization from ethyl acetate and then from isopropyl alcohol, crystals melting at 106.2–108.4° cor. were obtained. These readily dissolved in dilute hydrochloric acid, and were shown by analysis to be 5-carbethoxy-6-phenyltetrahydro-2-pyroneimine.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.87; H, 6.89; N (K), 5.64.

4-(2,3-Dimethoxyphenyl)-3-buten-2-one.—This compound was prepared in 70% yield from 2,3-dimethoxybenzaldehyde and acetone in the usual manner; b. p. 135–139° at 1.1 mm., n^{25} 1.5810.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.34; H, 6.55.

Ethyl 2-Cyano-5-oxo-3-phenylhexanoate.[20,8]—Prepared in the usual manner; b. p. 160–165° at 0.8 mm., $n^{25}D$ 1.5102.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.70; H, 6.49; N, 5.26.

Ethyl 2-Cyano-2-ethyl-5-oxo-3-phenylhexanoate.—Addition of ethyl ethylcyanoacetate to benzalacetone gave 23% yield of product, the remainder of the reaction mixture being mainly starting material. The product boiled at 153–161° at 1.4 mm. with slight decomposition; $n^{25}D$ 1.5050.

Anal. Calcd. for $C_{17}H_{21}NO_3$: N, 4.87. Found: N, 4.82.

Ethyl 2-Cyano-2-ethyl-3-(2,3-dimethoxyphenyl)-5-oxohexanoate.—A solution of 103 g. of 4-(2,3-dimethoxyphenyl)-3-buten-2-one and 71 g. of ethyl ethylcyanoacetate in 100 ml. of ethanol was made just basic by the addition of sodium ethylate. The solution was warmed on the steam-bath for two and one-half hours, made acid with alcoholic hydrogen chloride, concentrated and distilled. There was obtained 129 g., b. p. 55–151° at 1.5 mm., and 38.2 g. of product, b. p. 151–187° at 1.5 mm. This product was used directly for reduction. The 129 g. of forerun was retreated with sodium ethylate and allowed to stand three days at room temperature. It was then worked up as before to give 29.4 g. of forerun and 95.6 g. of product; b. p. 160–197° at 1.5 to 2.4 mm., $n^{25}D$ 1.5168 (supercooled); m. p. 91–94° (from alcohol).

Anal. Calcd. for $C_{19}H_{25}NO_5$: N, 4.03. Found: N, 3.94.

(13) Dr. Koelsch proposed that cyclization may have occurred without loss of water to give 7a-hydroxy-2-oxo-octahydro-1-pyrindine-4a-carboxylic acid.

4-Methylquinolizidine.—This compound, together with 1-(2′-piperidyl)-4-pentanol, was obtained by reduction of 1-(2-pyridyl)-pentanone-4 in the presence of Raney nickel catalyst at 150° and 250 lb. hydrogen pressure. Results were substantially the same as those recently reported by Boekelheide and Rothchild.[2b]

The hydrochloride of 4-methylquinolizidine melted above 360°.[14]

Anal. Calcd. for $C_{10}H_9N\cdot HCl$: C, 63.27; H, 10.62; Cl, 18.68. Found: C, 63.27; H, 10.57; Cl, 18.70.

3-Acetyl-1-(2′-pyridyl)-4-pentanone.[15]—A mixture of 50 g. of acetylacetone, 1.5 g. of sodium and 108 g. of 2-vinylpyridine was refluxed for seven hours. Distillation gave 57.1 g. of yellow oil boiling at 90–127° at 1.1 mm. and 50.7 g. of red glassy residue. Redistillation of the oil gave 14.1 g. of 1-(2′-pyridyl)-4-pentanone boiling at 84–118° at 1 mm. and 37.4 g. of 3-acetyl-1-(2′-pyridyl)-4-pentanone boiling at 118–119° at 1.0 mm.

The product gives a red color with alcoholic ferric chloride and reacts exothermically with phenylhydrazine.

Piperidines of Table III.—These were prepared by Raney nickel reduction of the ketonitriles in ethanol or by reductive methylation of the piperidine with formalin and a palladium–carbon catalyst in the manner previously described for compounds of Table II.

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Summary

δ-Ketonitriles have been prepared by Michael condensations involving (a) the reaction of acrylonitriles with β-ketoesters, or (b) the reaction of vinyl ketones with cyanoacetic esters.

Catalytic reduction of these ketonitriles has led to the formation of piperidines and bicyclo nitrogen compounds.

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(14) Lukes and Sorm, *Coll. Czech. Chem. Comm.*, **12**, 356 (1947).

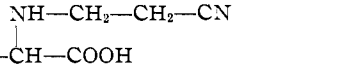
(15) Although the preparation of this compound in 16% yield was recently reported by Boekelheide and Rothchild,[2b] they stated that only a small amount of 1-(2′-pyridyl)-4-pentanone and none of the required product was obtained when an attempt was made to effect condensation according to the method used by Doering and Weil[3] to condense 2-vinylpyridine and acetoacetic ester. Since we independently found that this latter method, when applied to acetylacetone, gives 39% of 3-acetyl-1-(2′-pyridyl)-4-pentanone, the procedure for the preparation of this compound is included.

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY,[1] PEORIA, ILLINOIS]

Cyanoethylation of Alpha Amino Acids. I. Monocyanoethyl Derivatives[2]

BY L. L. MCKINNEY, E. H. UHING, E. A. SETZKORN AND J. C. COWAN

The condensation of acrylonitrile with alpha amino acids offers a possibility for increasing their functionality by yielding monocyanoethyl derivatives of the type



Compounds of this type have not been described. However, the patent literature[3] indicates that acrylonitrile reacts with glycine in aqueous solution in the presence of acidic catalysts such as copper acetate or mineral acids. By employing the methods prescribed, no reaction was observed between glycine hydrochloride and acrylonitrile in aqueous solution. Upon refluxing glycine for five hours with excess acrylonitrile and 0.01 equivalent of copper acetate, we observed that 0.4 equivalent of acrylonitrile reacted. The reaction products proved difficult to isolate and this line of attack was dropped.

Preliminary experiments were then conducted to determine optimum conditions for obtaining the N^{α}-cyanoethyl derivatives of amino acids by condensing with acrylonitrile. In the preliminary work, the reactions were followed by observing the depression of the basicity of the amino group as indicated by comparing titration curves of the reaction mixtures with those for the amino acids. This procedure was chosen because the literature[4] indicates that some question exists as to the reliability of Kjeldahl determinations for nitrile nitrogen and because the similar solubility of alpha amino acids and their monocyanoethyl derivatives make separation difficult when both are present in the reaction mixture. These titrations indicated that no reaction occurred when glycine was refluxed with excess acrylonitrile in the presence of catalytic amounts of sodium methoxide, or when aqueous solutions were refluxed with or without hydrochloric acid. When sodium hydroxide was added to aqueous solutions of glycine containing one equivalent of acrylonitrile and the mixture was allowed to stand for twenty-four hours at room temperature, the depression of the basic portion of the titration curve was directly proportional to the amount of sodium hydroxide used, up to one equivalent.

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Presented before the Division of Biological Chemistry at the 116th meeting of The American Chemical Society, Atlantic City, New Jersey, September 18–23, 1949.

(3) (a) U. Hoffmann and B. Jacobi, U. S. Patent 1,992,615, Feb. 2, 1935; (b) J. Y. Johnson, British Patent 404,744, July 27, 1933.

(4) (a) E. L. Rose and H. Ziliollo, *Ind. Eng. Chem., Anal. Ed.*, **17**, 211 (1945); (b) H. S. Davis and O. F. Wiedeman, *Ind. Eng. Chem.*, **37**, 482 (1945); (c) A. Friedrich, E. Kühass and R. Schurch, *Z. physik. Chem.*, **216**, 68 (1933); (d) P. Fleury and H. Levaltier, *Bull. soc. chim.*, **37**, 330 (1925).