min. Dilution with acetic acid and cooling produced a precipitate which was collected on a filter and extracted with ether. The residue was recrystallized from water yielding 0.45 g (43%) of 2-aminonicotinic acid, **4a**, mp 286–288° dec.

N-Hydroxycinchomeronimide, 14a.—The synthesis paralleled that of **12a**. From 1 g of **2b** and 8 ml of $SOCl_2$ was obtained 0.8 g of crude residue, insoluble in benzene. Crystallization from acetic acid gave 0.72 g (80%) of **14a**: mp 232–233° dec; ir 4.00 (b), 5.55, 5.60, 5.80, 6.20, 11.20, 14.00 μ.

Anal. Calcd for $C_7H_4N_2O_3$: C, 51.22; H, 2.46; N, 17.07. Found: C, 51.10; H, 2.75; N, 16.81.

N-Benzoyloxycinchomeronimide, 14b.—The method described for **12b** was followed; the warm reaction mixture was poured onto ice before collecting the solid product. From 0.3 g of **14a** was obtained 0.3 g (94%) of **14b**; after crystallization from ethanol, the melting point was 191–192°; ir 5.55 (w), 5.65, 5.75, 6.20 (m) μ, and 8 other bands.

Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.00; N, 10.45. Found: C, 62.31; H, 2.94; N, 10.69.

The same compound was obtained in 83% yield from **2c** and thionyl chloride.

Rearrangement of 14b.—**14b** (1 g), insoluble in 10 ml of cold water, was brought into solution by 3 ml of 10% NaOH solution. After heating at 100° for 30 min, it was cooled and acidified (HCl) to pH 5. The precipitate was collected, dried, ether extracted to remove benzoic acid, and crystallized from water to yield 0.28 g (54%) of 3-aminoisonicotinic acid[7] (**15**), mp 299–302° dec (block). After another crystallization the melting point was 307–309° dec; ir 3.00, 3.10, 4.10, 4.70 (b), 6.15, 6.28 μ, and 9 other bands. A mixture of this acid and 4-aminonicotinic acid (mp 340° dec) melted at 265–285° dec.

Registry No.—Sodium 2-(methoxycarbonyl)nicotinate, 23410-97-1; benzyl 3-carboxypicolinate, 23410-98-2; benzyl 2-carboxynicotinate, 23410-99-3; disodium 3-carboxypicolinohydroxamate, 23411-00-9; disodium 3-carboxy-2-pyrazinecarbohydramate, 23411-01-0; disodium 3-carboxy-2-quinoxalinecarbohydroxamate, 23411-02-1; **1b**, 23411-03-2; **1c**, 23411-04-3; **2b**, 23411-05-4; **2c**, 23411-06-5; **3**, 21038-63-1; **4a**, 5345-47-1; **5**, 23411-09-8; **8a**, 23411-10-1; **8b**, 23411-11-2; **9a**, 23411-12-3; **9b**, 23411-13-4; **12a**, 23439-87-4; **12b**, 23411-14-5; **14a**, 23439-88-5; **14b**, 23411-15-6.

Reactions of 2-Acetoacetylaminopyridines with Triethyl Orthoformate and Zinc Chloride

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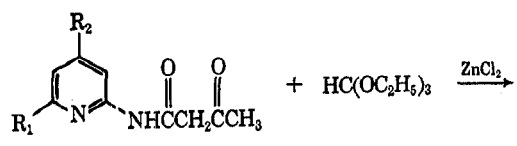
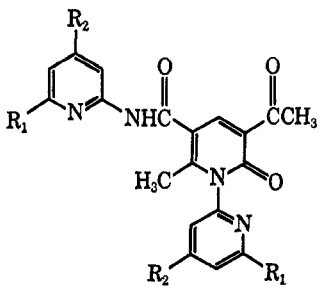
The reaction of 2-acetoacetylaminopyridines with triethyl orthoformate and zinc chloride did not yield the expected ethoxymethylene derivatives, but dimeric products, such as **2**, containing 2 mol of the starting material and one CH moiety. The scope of the reaction was explored. Mixed dimers were obtained upon addition of other acetoacetamides to the reaction mixture. A mechanism explaining these results is proposed.

In an attempt to prepare the ethoxymethylene derivative of 2-acetoacetylaminopyridine (**1**) by reaction with triethyl orthoformate, acetic anhydride, and zinc chloride, the condensation product **2** was obtained in modest yield. The yield could be raised to 69% by the use of ethanol instead of acetic anhydride as solvent; a much higher yield of the analogous product was obtained with the 6-methylpyridine **3**.

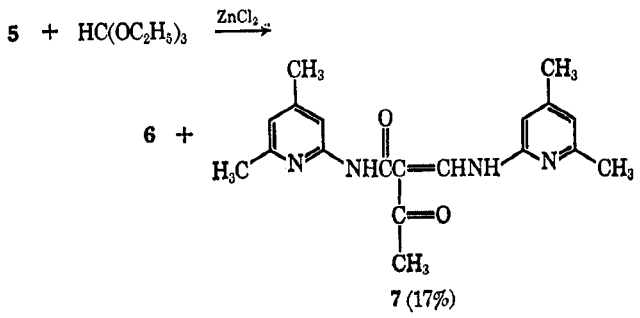


1, $R_1 = R_2 = H$
3, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = R_2 = CH_3$



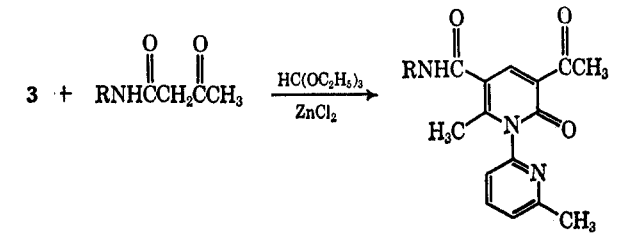
2, $R_1 = R_2 = H$ (69%)
4, $R_1 = CH_3$; $R_2 = H$ (91%)
6, $R_1 = R_2 = CH_3$ (12%)

Several 2-acetoacetylaminopyridines were used in this reaction (see Table I for details); 2-acetoacetylaminothiazole gave an analogous product. 2-Acetoacetylamino-4,6-dimethylpyridine was the only compound giving two isolable products. In addition to **6** (12%) a 17% yield of **7** was isolated.



7 (17%)

Addition of 2 mol of *p*-chloroacetoacetanilide to the reaction mixture gave rise to a mixed dimer. Compound **8** crystallized from the reaction mixture and was uncontaminated with a possible isomer or with **4**.



8, R = *p*-ClC_6H_4 (59%)
9, R = *n*-C_3H_7 (12%)
12, R = *t*-C_4H_9 (70%)

TABLE I
2-ACETOACETYLAMINOPYRIDINES

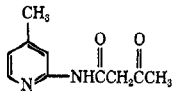
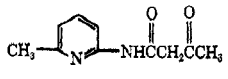
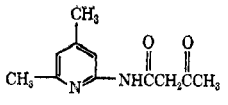
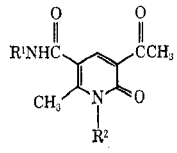
Compound	Structural formula	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
28		$C_{10}H_{12}N_2O_2$	57	121–123°	62.48	6.30	14.58	62.78	6.28	14.59
3		$C_{10}H_{12}N_2O_2$	77	100.5–102.5	62.48	6.30	14.58	62.62	6.41	14.61
5		$C_{11}H_{14}N_2O_2$	98	Oil	64.07	6.84	13.59	64.11	7.16	14.19

TABLE II
3-ACETYL-6-METHYL-2-PYRIDONE-5-CARBOXYLIC ACID 2-PYRIDYLAMIDES



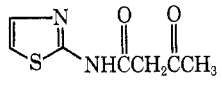
Compound	R^1	R^2	A^a	Empirical formula	Yield, %	Mp, °C	Calcd, % C	H	N	Other	Mol wt	Found, % C	H	N	Other	Mol wt
2	2-Pyridyl	2-Pyridyl	8.32	$C_{19}H_{16}N_4O_3$	69	228–229	65.51	4.63	16.05	O, 13.78	348	65.70	4.57	16.01	O, 13.75	357 ± 6[b]
29	5-Chloro-2-pyridyl	5-Chloro-2-pyridyl	8.63	$C_{19}H_{14}Cl_2N_4O_3$	79	216–219	54.69	3.38	13.43		417	54.45	3.20	13.57		400 ± 4[b]
30	4-Methyl-2-pyridyl	4-Methyl-2-pyridyl		$C_{21}H_{20}N_4O_3$	30	235–236.5	67.01	5.36	14.89			67.10	5.20	14.61		
4	6-Methyl-2-pyridyl	6-Methyl-2-pyridyl	8.38	$C_{21}H_{20}N_4O_3$	91	252.5–253	67.01	5.36	14.89		376	67.11	5.37	14.94		377 ± 7[b]
31	2-Thiazolyl	2-Thiazolyl	8.87	$C_{15}H_{12}N_4O_3S_2$	76	259.5–260.5	49.98	3.36	15.55	S, 17.80	360	50.11	3.42	15.54	S, 17.49	373 ± 2[b]
6	4,6-Dimethyl-2-pyridyl	4,6-Dimethyl-2-pyridyl	8.28	$C_{23}H_{24}N_4O_3$	12	253–255	68.30	5.98	13.85			68.15	6.09	13.67		
8	4-Chlorophenyl	6-Methyl-2-pyridyl	8.30	$C_{21}H_{18}ClN_3O_3$	59	231–233	63.72	4.57	10.62	Cl, 8.96		63.74	4.69	10.66	Cl, 9.07	
19	6-Methyl-2-pyridyl	4-Chlorophenyl	8.5	$C_{21}H_{18}ClN_3O_3$	25	215–218	63.72	4.57	10.62			63.70	4.58	10.39		
12	*t*-Butyl	6-Methyl-2-pyridyl		$C_{19}H_{23}N_3O_3$	70	243.5–245.5	66.84	6.79	12.31			66.79	7.07	12.30		
9	*n*-Propyl	6-Methyl-2-pyridyl		$C_{18}H_{21}N_3O_3$	12	215.7	65.88	6.47	12.84			66.06	6.70	12.77		
32	Phenyl	2-Pyridyl		$C_{20}H_{17}N_3O_3$	40	230–232	69.15	4.93	12.10			69.54	4.87	12.12		
33	Phenyl	6-Methyl-2-pyridyl		$C_{21}H_{19}N_3O_3$	57	210–212	69.79	5.30	11.63			69.53	5.37	11.70		

[a] *A*, nmr absorption of lone hydrogen in pyridone ring (in parts per million). [b] Ebullioscopic determination in acetone.

Mixed dimers **32** and **33** were obtained using **1** and **3** with acetoacetanilide (see Table II).

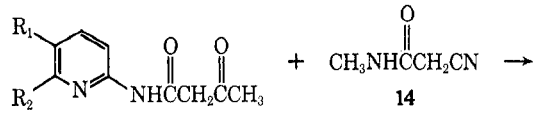
When **3** was treated with triethyl orthoformate and $ZnCl_2$ in the presence of a fourfold excess of N-*n*-propylacetoacetamide, **4** was isolated in 21% yield together with 12% **9**; when a twofold excess was used, a 15% yield of **10** was the only product isolated. Using a fourfold excess of N-*t*-butylacetoacetamide, a 70% yield of a product could be isolated which by tlc was pure **12**.

Other active methylene compounds were added to the reaction mixture of substituted 2-acetoacetylaminopyridine, triethyl orthoformate, and zinc chloride in ethanol. The results were threefold: either (a) the added compound did not influence the normal reaction at all, or (b) it interfered in the reaction without showing up in the end product, or, in one case, (c) a mixed compound was formed. (a) When cyanoacetamide or ethyl acetoacetate was added in a twofold excess, **1** and 2-acetoacetylaminothiazole (**13**) gave rise



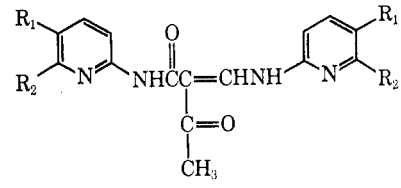
13

to undiminished yields of the normal 1:1 products, the added compounds not influencing the reaction at all. (b) Another type of result was obtained when a twofold excess of N-methylcyanoacetamide (**14**) was added.



14

3, $R_1 = H; R_2 = CH_3$
15, $R_1 = Cl; R_2 = H$



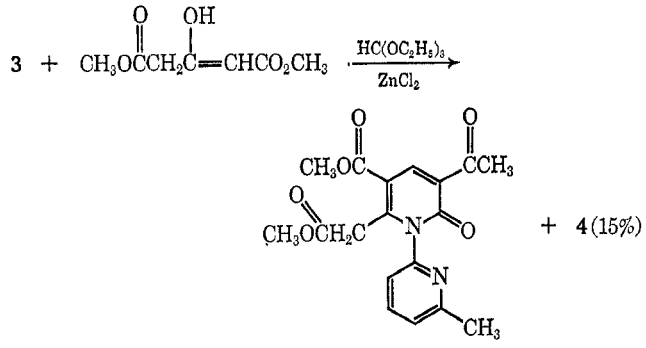
10, $R_1 = H; R_2 = CH_3$ (95%)
16, $R_1 = Cl; R_2 = H$ (68%)

The N-methylcyanoacetamide did not show up in the product but, obviously, it had profoundly influenced the reaction. (c) The reaction of **3** with triethyl ortho-

TABLE III
2-ACETYL-3-PYRIDYLAMINOACRYL-2-PYRIDYLAMIDES

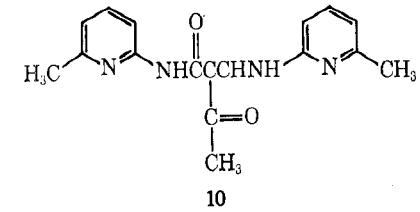
Compound	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7	$C_{19}H_{22}N_4O_2$	17	226–228	67.44	6.55	16.56	67.40	6.55	16.58
10	$C_{17}H_{18}N_4O_2$	15, 91	187.5–189	65.79	5.85	18.05	65.87	5.86	18.11
16	$C_{15}H_{12}Cl_2N_4O_2$	68	235–237	51.28	3.42	15.91	51.55	3.60	15.77

formate in the presence of dimethyl acetonedicarboxylate gave rise to the ring closed compound **17**.

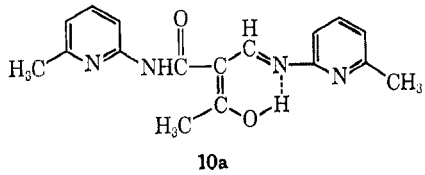


17 (45%)

Confirmation of Structural Assignments. 1. Compound 10.—The ir spectrum of this compound displays an "insufficient amount" of carbonyl absorption, one band at 6.05 and a small shoulder at 5.95 μ. It may therefore, exist mainly in the form **10a**. Supporting this is the presence of three strong bands at 6.25, 6.40, and 6.55 μ.

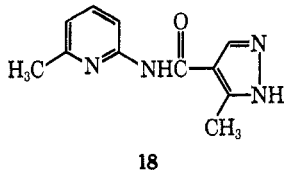


10



10a

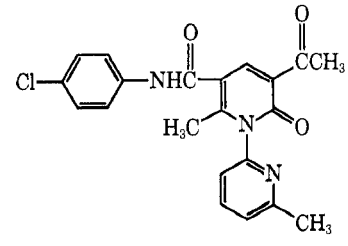
The structure of **10** was also supported by the reaction with hydrazine which resulted in the formation of **18** in 62% yield.



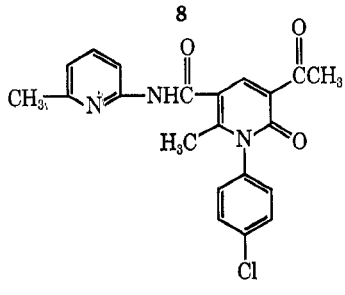
18

The structures of **7** and **16** (see Table III) were assigned by analogy to **10**.

2. Compound 8.—The question here is whether the compound obtained by reaction of **3** with *p*-chloroacetoacetanilide in triethyl orthoformate has structure **8** or **19**.

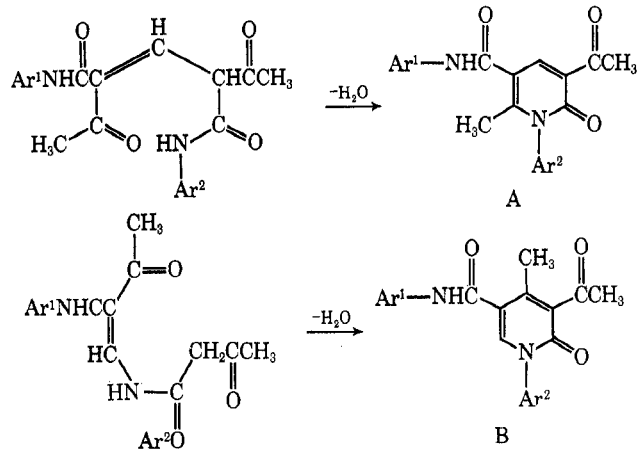


8

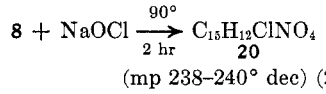


19

The methyl group on the pyridone ring could be in the 6 position as shown in **8** and **19**, or in the 4 position. Ring closure could occur in two ways, one leading to A (**8** or **19**) and the other leading to B.



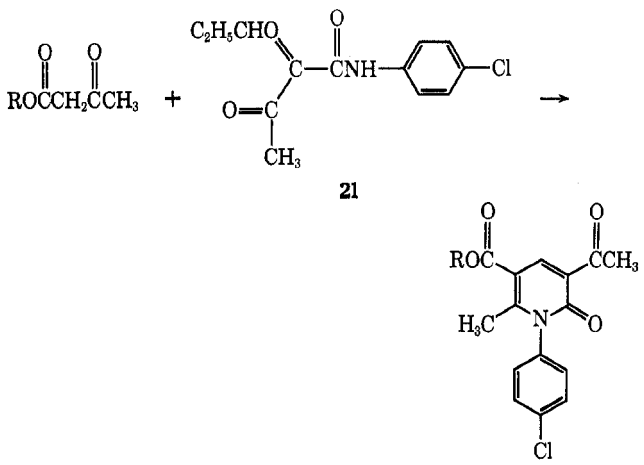
Hydrolysis with either strong aqueous base or acid led to destruction of the compound. Treatment with aqueous sodium hypochlorite in basic solution led to a new compound having lost the amino pyridine part of the molecule.



(mp 238–240° dec) (29%)

The compound was acidic, phenolic (positive $FeCl_3$ test) but could not be methylated with either diazomethane or dimethyl sulfate. The ir spectrum showed the typical features of a six-membered enol chelate ring. The nmr spectrum showed the presence of two equivalent acetyl groups.

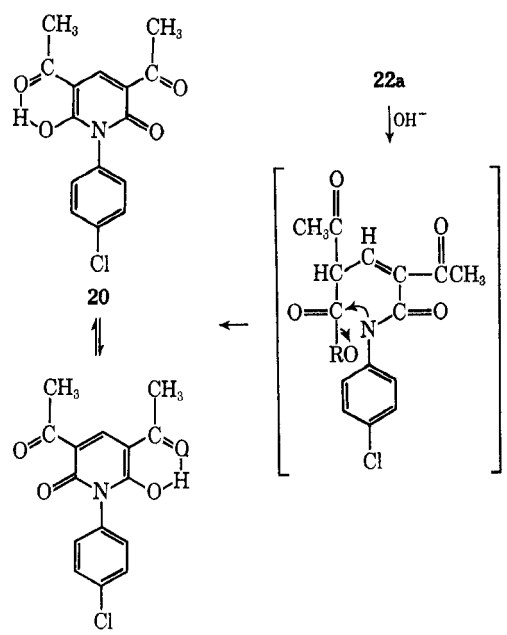
Several acetoacetic esters were condensed with **21** to form the esters **22a–22c** (listed in Table IV).



22a, R = C_2H_5-
b, R = *t*-C_4H_9-
c, R = CH_3
d, R = H

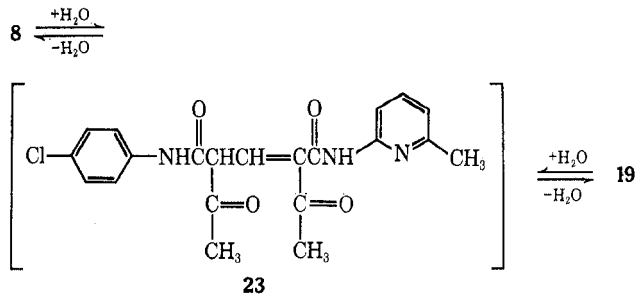
When **22a** was treated with methanolic NaOH and then acidified, a compound identical with **20** was isolated in 82% yield. The fact that it was not identical with the expected acid, **22d**, was shown by preparing **22d** *via* acid hydrolysis of **22b**. The acid **22d** had a melting point of 272.5–274.5° dec and gave **22c** on treatment with diazomethane.

The formation of **20** involved a base-catalyzed rearrangement of the pyridone ring in **22a** and **8**.



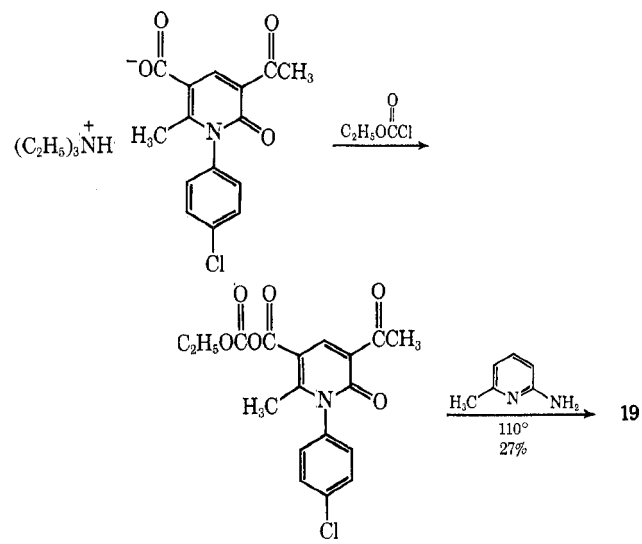
The same compound, **20**, is formed by the action of basic NaOCl on **8**. Attachment of a positive chlorine on the pyridine ring labilizes the amide linkage to the point where, after base-catalyzed ring opening, an analogous displacement can occur, leading to **20**. The identity of the products from the two sources established the position of the methyl group on the pyridone ring in **8**.

At this point, it would appear that formula **19** is the correct one for the triethyl orthoformate derived compound since in the formation of **20** the 6-methyl-2-aminopyridine group was lost, but, after base-catalyzed ring opening, both **8** and **19** can be expected to give tautomeric forms of the same intermediate **23**. The



intermediate **23** could obviously ring close in two directions to give either starting material.

In order to pin down the structure of **19**, it was made from the acid **22d** by using a mixed anhydride method.

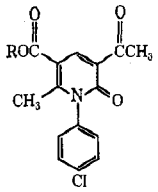


The compound melted at 216–218°, and it depressed the melting point of **8**. Once **19** was available the mother liquors from the preparation of **8** were worked up on an effort to find traces of **19**. Using tlc, no such traces could be found.

In the acidic reaction medium of the triethyl orthoformate reaction, then, no **19** is formed. Base, however, should transform **8** into **19** and *vice versa*, if **23** is formed under these conditions. Using NaOH in ethanol, at room temperature, **8** was partially isomerized into **19**. The compound dissolved rapidly upon addition of the base and the product isolated on acidification after 2 hr was largely **19** (by tlc). After two recrystallizations, a 30% yield of pure **19** was obtained.

Mechanism of Formation of 2 and 8, and Their Analogs.—The zinc chloride catalyzed reaction between 2-acetoacetylaminopyridines and triethyl orthoformate yielding dimeric pyridones of type **2** is unexpected.

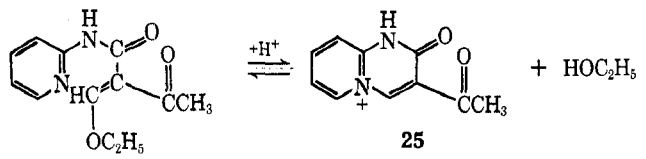
TABLE IV
3-ACETYL-6-METHYL-2-PYRIDONE-5-CARBOXYLIC ACID DERIVATIVES



Compound	R	A[a]	Empirical formula	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
22a	Ethyl	8.34	$C_{17}H_{16}ClNO_4$	42	185–186.5	61.17	4.83	4.20	61.37	4.70	4.13
22b	*t*-Butyl		$C_{19}H_{20}ClNO_4$	69	228 dec	63.07	5.57	3.87	63.40	5.44	3.68
22d	H	8.26	$C_{15}H_{12}ClNO_4$	83	272.5–274.5	58.93	3.96	4.58	59.04	4.25	4.45
22c	Methyl		$C_{16}H_{14}ClNO_4$	85	207.4	60.10	4.41	4.38	60.03	4.23	4.18

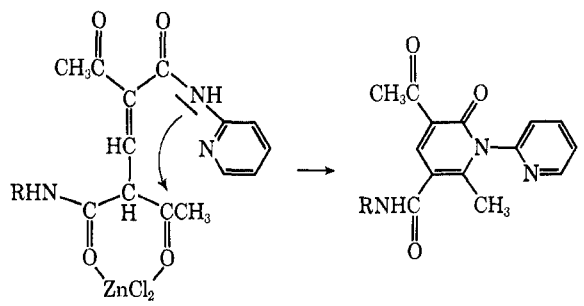
[a] *A*, nmr absorption of lone hydrogen on pyridone ring in parts per million.

It is reasonable to assume that an ethoxymethylene derivative **24** is formed initially. The favorable



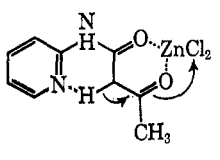
24 **25**

steric arrangement of **24**, however, makes the ethoxy group labile and acid-catalyzed removal of ethanol should give **25**. These reactions should be reversible under the reaction conditions. When **25** reacts with another mole of starting material instead of ethanol, dimeric products can be formed. If the methylene carbon of **1** condenses with **25** to give **26**, ring closure to the observed products can occur.



26

An interesting phenomenon concerns the preference of the acetoacetylaminopyridine to react with itself instead of reacting with other acetoacetamides. Only an excess of *p*-chloroacetoacetanilide gives rise to **8** as the sole product. Only an excess of *t*-butylacetoamide prevents completely the formation of **4**. This may be due to assistance by the pyridine ring nitrogen, facilitating the reaction of the reactant with **25**. This assistance would be removal or partial removal of a proton from the methylene group as shown in **27**.



27

Compounds such as **7**, **10**, and **16** probably are formed when the starting 2-acetoacetylamino pyridine partially solvolyzes and the free 2-aminopyridine reacts with **25**.

Experimental Section

All melting points are uncorrected. The microanalyses were carried out by Mr. C. W. Nash and his associates.

Acetoacetamides.—The acetoacetamides used as starting materials were prepared by reaction of the appropriate amine with diketene in toluene. N-*n*-propylacetoacetamide,[1] **1**,[2] 2-acetoacetylamino-5-chloropyridine,[3] **11**,[4] and **13**[5] have already been described.

The properties were in accord with those described in the literature. Other acetoacetamides are listed in Table I.

General Procedure for the Reaction of Acetoacetylaminopyridines with Triethyl Orthoformate. 5-Acetyl-2-methyl-1-(6-methyl-2-pyridyl)-N-(6-methyl-2-pyridyl)-6-(1H)-oxonicotinamide (4) (Table II).—A solution of 58 g (0.3 mol) of 2-acetoacetylamino-6-methyl pyridine (**3**), 1 g of $ZnCl_2$ in 180 ml of absolute ethanol, and 70 ml of triethyl orthoformate was refluxed for 4 hr, then cooled, and filtered. The product was recrystallized from Methyl Cellosolve, yield 51 g.

5-Acetyl-1-(*p*-chlorophenyl)-2-methyl-N-(6-methyl-2-pyridyl)-6-(1H)-oxonicotinamide (19) (Table II).—To a slurry of 12.5 g (0.04 mol) or **22d** in 200 ml of toluene, 4.1 (0.04 mol) of triethylamine was added. Ethyl chloroformate (4.5 g, 0.04 mol) was added to the solution. The resultant mixture was left standing for 1 hr. Then 4.5 g (0.04 mol) of 2-amino-6-methylpyridine was added and the mixture was refluxed for 2 hr, whereupon excess water was added and ice cooling was applied. The product was filtered off and recrystallized from ethanol, yield 6 g.

Methyl 5-Acetyl-2-carbomethoxymethyl-1-(6-methyl-2-pyridyl)-6(1H)-oxonicotinate (17).—A solution of 19.2 g (0.1 mol) of 2-acetoacetylamino-6-methylpyridine (**3**), 34 g (0.2 mol) of dimethylacetone dicarboxylate, and 1 g of $ZnCl_2$ in 150 ml of abolute ethanol and 60 ml of triethyl orthoformate was refluxed for 4 hr. After the mixture cooled in the refrigerator overnight, 11.5 g of **4** was isolated by filtration. The filtrate was evaporated and the residue was taken up in a small amount of ethanol. The precipitated product was recrystallized from ethanol, yield 32 g (45%), mp 171.7°.

Anal. Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.62; H, 5.06; N, 7.72.

1-Acetyl-2-ethoxy-(*p*-chloro)acrylanilide (21).—A solution of 30 g (0.124 mol) of 2-carbethoxy-(*p*-chloro)acetanilide,[6] 30 ml each of triethyl orthoformate and acetic anhydride, and 2 g of $ZnCl_2$ was refluxed for 3 hr. The product crystallized on cooling overnight in the refrigerator and was recrystallized from methanol yield 23 g of **21** (61%), mp 130–132°.

(1) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 225 (1961).
(2) Beilsteins Handbuch, Vol. 22, p I 630.
(3) V. F. Kucherov, *J. Gen. Chem. USSR*, **20**, 1890 (1950); *Chem. Abstr.*, **45**, 2951*h* (1951).
(4) C. H. Eugster, L. Leichner, and E. Jenny, *Helv. Chim. Acta*, **46**, 543 (1963).
(5) I. G. Farbenindustrie A.-G., German Patent 607,623 (Jan 3, 1935).
(6) F. D. Chattaway and F. A. Mason, *J. Chem. Soc.*, **97**, 339 (1910).

Anal. Calcd for $C_{13}H_{14}ClNO_3$: C, 56.47; H, 5.42; N, 4.70. Found: C, 56.74; H, 5.41; N, 4.79.

3-Methyl-4-(6-methyl-2-pyridyl)carbamoylpyrazole (18).—A solution of 9.5 g (0.03 mol) of **10** and 5 g (0.1 mol) of hydrazine hydrate in 100 ml of ethanol was refluxed for 3 hr. It was then poured into water and the solution was acidified with acetic acid. The precipitated crystals were recrystallized from ethanol, 4 g (62%), mp 236–239°.

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.60; N, 25.91. Found: C, 61.33; H, 5.57; N, 25.75.

3-Acetyl-5-carbo-*t*-butoxy-1-(*p*-chlorophenyl)-6-methyl-2-pyridone (22b) (Table IV).—To a slurry of 26.7 g (0.1 mol) of **21** and 25 g (0.158 mol) of *t*-butyl acetoacetate in ice-cooled ethanol (150 ml), 6 g of $NaOCH_3$ (0.11 mol) was added. The solution became almost clear before the product crystallized. After 2 hr in an ice bath, the mixture was filtered and the product was washed with ethanol, yield 25 g.

3-Acetyl-5-carboxy-1-(*p*-chlorophenyl)-6-methyl-2-pyridione (22d) (Table IV).—Compound **22b** (20 g, 0.055 mol) was dissolved in 100 ml of concentrated H_2SO_4 by heating the mixture to 60°, whereupon it was left to stand at room temperature for 30 min. The solution was poured into ice water and filtered. The product was recrystallized from methanol–water, yield 14 g.

1-(*p*-Chlorophenyl)-3,5-diacetyl-6-hydroxy-2-pyridone (20). 1.—A slurry of 44 g (0.112 mol) of **8** in 400 ml of Clorox and 80 g of 50% aqueous NaOH was heated on a steam bath for 2 hr. Most of the starting material dissolved. The mixture was then cooled by addition of ice and acidified with concentrated HCl. The product was filtered off and recrystallized from ethanol, yield 10 g (29%), mp 238–240° dec.

2.—Compound **22a** (20 g, 0.06 mol) was added to a solution of 70 ml of methanol, 50 ml of water, and 30 g of 50% aqueous NaOH. The mixture was heated gently until the solid was dissolved and then left standing overnight. The product was filtered after acidification with concentrated HCl and recrystallized from ethanol, yield 15 g (82%).

Anal. Calcd for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; N, 4.56. Found: C, 58.68; H, 4.10; N, 4.40.

Registry No.—**2**, 23600-24-0; **3**, 16867-47-3; **4**, 23646-59-5; **5**, 23600-26-2; **6**, 23600-27-3; **7**, 23600-28-4; **8**, 23646-60-8; **9**, 23600-29-5; **10**, 23600-30-8; **12**, 23646-61-9; **16**, 23600-31-9; **17**, 23600-32-0; **18**, 23600-33-1; **19**, 23646-64-2; **20**, 23600-34-2; **21**, 23600-35-3; **22a**, 23600-36-4; **22b**, 23600-37-5; **22c**, 23600-38-6; **22d**, 23600-39-7; **28**, 23600-40-0; **29**, 23646-62-0; **30**, 23646-63-1; **31**, 23674-48-8; **32**, 23600-41-1; **33**, 23600-42-2.

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Fluorinated Aminoimidazolines. Synthesis and Determination of Tautomeric Structure

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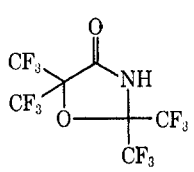
Hexafluoroacetone imine reacts with sodium cyanide to give 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**), a compound that possesses pronounced pharmacological activity as a central nervous system depressant and muscle relaxant. This imidazoline has unexpected chemical and thermal stability. The ^1H nmr spectrum of ^{15}N-labeled **2** shows that it exists primarily as the amino tautomer, and not as the imino tautomer **16**, and indicates restricted rotation for the amino group because of the contribution of ionic resonance form **17** or solvent complexing. The preparation of several analogs, including 4-amino-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (**9**), 4-amino-2,2,5,5-tetramethyl-3-imidazoline (**12**), and 2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (**13**), is also described.

In earlier studies aimed at the synthesis of heterocyclic compounds highly substituted with fluoroalkyl groups, it was found that sodium cyanide reacts with 2 equiv of hexafluoroacetone to yield the sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidinone



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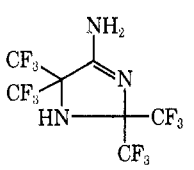

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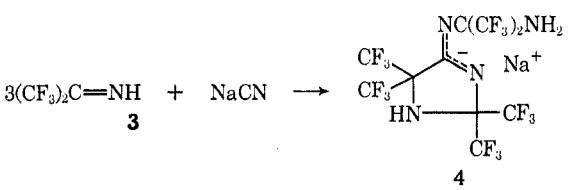
(**1**).[1] In continuing these studies, we have investigated the related reactions of cyanide with imines of fluoro ketones in attempts to prepare analogous heterocyclic compounds containing more nitrogen. One of the compounds that resulted from this study, 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**), has been shown in laboratory and clinical studies to possess pronounced pharmacological activity as a central nervous system depressant and muscle relaxant.[2]

(1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **32**, 951 (1967).

Reactions of Cyanide with Fluoro Ketone Imines.—Hexafluoroacetone imine (**3**) reacts readily and exothermally with a suspension of sodium cyanide in a polar solvent such as dimethyl sulfoxide, dimethylformamide, or acetonitrile at temperatures as low as −30° to give the 3:1 adduct **4**. Regardless of which reagent is in excess or the mode of addition, the 3:1 adduct is always formed.



3 **4**

This behavior is in contrast to the reaction of hexafluoroacetone with sodium cyanide, which could be stopped at either a 1:1 adduct or a 2:1 adduct and which never formed a 3:1 adduct.[1] Acidification of **4**

(2) J. L. Claghorn and J. D. Schoolar, *Current Therap. Res.*, **10**, 279 (1968); I. M. Levine, P. B. Jossmann, D. F. Friend, and J. DeAngelis, *Clin. Pharmacol. Therap.*, **9**, 448 (1968); R. Clark, T. E. Lynes, W. A. Price, J. P. Marvel, D. H. Smith, and V. G. Vernier, *The Pharmacologist*, **10**, 197 (1968).