1-Phenyl-2-acyl-3-amino-2-pyrazolin-5-ones from 1-Phenyl-3-azidocarbonyl-2-pyrazolin-5-ones[1]

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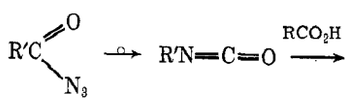
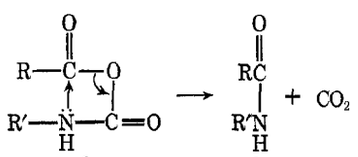
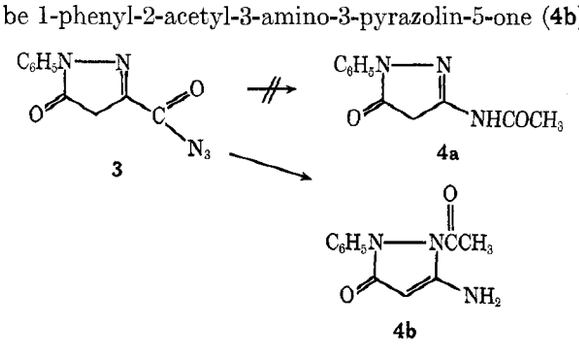
The Curtius reaction of 1-phenyl-3-azidocarbonyl-2-pyrazolin-5-one (**3**) in glacial acetic acid leads to 1-phenyl-2-acetyl-3-amino-3-pyrazolin-5-one (**4b**) rather than the expected 1-phenyl-3-acetamido-2-pyrazolin-5-one.

The Curtius reaction, the conversion of a carboxylic acid to an amine *via* the acid azide and isocyanate, has been used extensively in synthetic organic chemistry. When an acylamine is the desired product, this frequently may be obtained directly by rearranging the azide in an anhydrous acid.[2] It has been proposed[2] that this rearrangement proceeds *via* the mixed anhydride **1** which forms the acylamine **2** with loss of carbon dioxide.



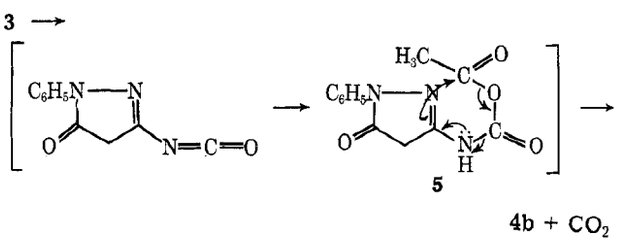


However, when this reaction sequence was attempted with 1-phenyl-3-azidocarbonyl-2-pyrazolin-5-one (**3**) in glacial acetic acid, 1-phenyl-3-acetamido-2-pyrazolin-5-one (**4a**),[3] which would be expected by analogy to the conversion of **1** to **2**, was not obtained. The major product of the reaction of **3** with glacial acetic acid is a new monoacetyl derivative, which I have shown to be 1-phenyl-2-acetyl-3-amino-3-pyrazolin-5-one (**4b**).



Comparison with authentic samples by thin layer chromatography (silica gel with ethyl acetate as eluent) showed the presence of small amounts of 1-phenyl-3-acetamido-2-pyrazolin-5-one (**4a**) and 1-phenyl-3-amino-2-pyrazolin-5-one.

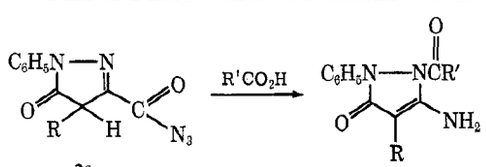
Apparently, in the proposed intermediate mixed anhydride[4] **5**, two nitrogen atoms are capable of nucleophilic attack on the acid carbonyl—the exocyclic nitrogen at position 3 and the 2 nitrogen of the ring. Attack by the exocyclic nitrogen to give compound **4a** would require a four-membered ring in the transition state (as in **1**). Attack by the ring nitrogen involves a six-membered ring, and would lead directly to the observed product **4b**.



Other pyrazolone–acid combinations gave products which were assigned analogous structures (Table I)

TABLE I

1-PHENYL-2-ACYL-3-AMINO-3-PYRAZOLIN-5-ONES



R	R′	Registry no. of product	Mp, °C	Acid
H	H	34804-11-0	185 dec	Formic
H	CH_3	34804-12-1	188–190	Acetic
H	CH_2CH_3	34804-13-2	200–203	Propionic
OC_6H_5	CH_3	34804-14-3	209–211	Acetic
p-$OC_6H_4CH_3$	CH_3	34804-15-4	185–187	Acetic

[a] Registry numbers: 34804-09-6 (R = OC_6H_5), 34804-10-9 (R = *p*-$OC_6H_4CH_3$).

on the basis of the similarity of their nmr and infrared spectra to those of **4b**.

The assignment of structure **4b** to the reaction product is based on chemical properties, infrared and nuclear magnetic resonance spectroscopy, and high-resolution mass spectrometry.

Of the four possible structures for the monoacetyl compound (**4a**, **4b**, **4c**, and **4d**), only the 3-acetyl derivative, **4a**, is known.[3] Synthetic routes to **4c** and **4d** could not be devised, nor could an alternative route to **4b**. Comparison with a sample of **4a**, prepared by the literature method,[3] ruled out this structure.

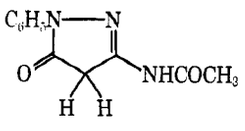
The presence of the 1-phenyl-3-amino-2-pyrazolin-5-one[3] nucleus was confirmed by hydrolysis of **4b** to this compound. The ease of hydrolysis of **4b** (2% aqueous sodium hydroxide, 10 min at room temperature) is consistent with a compound containing a 2-acetyl or 5-*O*-acetyl group (**4b** or **4d**) rather than a

(1) R. W. Hendess, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, No. 89.

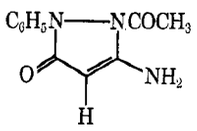
(2) P. A. S. Smith, *Org. React.*, **3**, 377 (1946).

(3) A. Weissberger and H. D. Porter, *J. Amer. Chem. Soc.*, **64**, 2133 (1942).

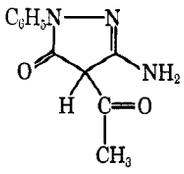
(4) The proposed intermediate isocyanate could not be isolated or synthesized independently.



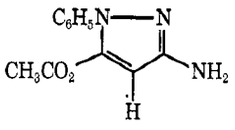
4a



4b



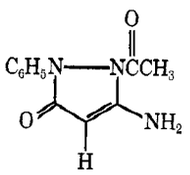
4c



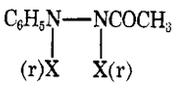
4d

3-*N*- or 4-acetyl group (**4a** or **4c**). (For example, 1-phenyl-3-acetamido-5-acetoxypyrazole[3] is hydrolyzed only as far as **4a**, and 1-phenyl-3-methyl-4-acetyl-2-pyrazolin-5-one[5,6] is stable under similar conditions.)

High-resolution mass spectrometry provided the most conclusive evidence for acetylation of **4b** (M = $C_{11}H_{11}N_3O_2$, mol wt 217) in the 2 position.[7] A strong peak at *m/e* 150.0794 (M − C_3HNO), which corresponds to fragment **6a**, is most significant. The gen-



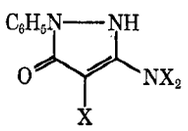
4b



6a, X = H
b, X = D

eration of this fragment from **4b** can be envisioned as arising from cleavage of the 2–3 and 1–5 bonds of the pyrazolone with rearrangement (indicated by r) of hydrogen (or deuterium, see below). This fragment **6** would be difficult to rationalize if the pyrazolone were acylated at a position other than the 2 nitrogen.

Among the other fragments observed in the mass spectrum of **4b** was a parent molecular ion and a fragment peak at *m/e* 175.0748 (M − C_2H_2O). This peak is attributed to fragment **7a** formed by loss of $COCH_2$



7a, X = H
b, X = D

from **4b** with rearrangement of a hydrogen from the acetyl to the ring nitrogen. The loss of the acetyl group is consistent with the presence of $NCOCH_3$, but not with $CCOCH_3$.

When the sample was allowed to exchange with deuterium oxide in the heated inlet system,[7] three deuterium atoms were introduced into the parent molecular ion (see also the discussion of the nmr spectrum, below). This sample gave deuterated fragments corresponding to those above; the M − C_3HNO fragment **6** contained two deuterium atoms and the M − C_2H_2O fragment **7** three deuterium atoms.

(5) F. Stoltz, *J. Prakt. Chem.*, **55**, 145 (1897).
(6) A. Weissberger and H. D. Porter, *J. Amer. Chem. Soc.*, **65**, 1495 (1943).
(7) G. P. Happ and D. P. Maier, personal communication.

The nmr spectrum of **4b** exhibited a singlet at τ 8.00, corresponding to the methyl of the acetyl group, and a singlet at τ 5.47 assigned to the single hydrogen at C-4 on the basis of its slow exchange with deuterium oxide. The resonance peak of the two amino protons (which also exchanged with deuterium oxide) was located under those of the aromatic protons centered at τ 2.67.

Experimental Section

Diethyl α-(*p*-Tolyloxy)oxalacetate.—The preparation of this compound was analogous to that of α-phenoxyoxalacetate,[8] precaution being taken to prevent contact of the compound with ground glass[9] during distillation.

1-Phenyl-3-ethoxycarbonyl-4-(*p*-tolyloxy)-2-pyrazolin-5-one.—To a solution of 596.6 g of diethyl α-(*p*-tolyloxy)oxalacetate in 600 ml of dimethylformamide was added a solution of 216.3 g of phenylhydrazine in 400 ml of dimethylformamide. After the solution had been heated on a steam bath for 2 hr, it was cooled and 4 l. of water was added. The syrup which formed solidified on standing overnight. The solid was washed with water in a Waring Blendor and dried. After repeated washings of this yellow solid with warm methylcyclohexane in a Waring Blendor, 300 g (44%) of the product was obtained as a tan powder. A portion was recrystallized from acetonitrile to give a white solid: mp 145–146°; nmr ($CDCl_3$) τ 9.08 (t, J = 7 Hz, 3 H) and 6.03 (q, J = 7 Hz, 2 H), ethyl group, 7.82 (s, 3 H), methyl of the tolyl group, a complex multiplet centered at 2.92 of the nine aromatic protons, and the acidic H at −0.40 (s).

Similarly prepared was 1-phenyl-3-ethoxycarbonyl-4-phenoxy-2-pyrazolin-5-one, mp 169–171°.

1-Phenyl-3-azidocarbonyl-2-pyrazolin-5-one (**3**).—This compound was prepared from 1-phenyl-3-ethoxycarbonyl-2-pyrazolin-5-one *via* the carboxhydrazide according to the procedure of Weissberger and Porter.[3]

A similar procedure was used to prepare 1-phenyl-3-azidocarbonyl-4-(*p*-tolyloxy)-2-pyrazolin-5-one, decomposing at 127°, and 1-phenyl-3-azidocarbonyl-4-phenoxy-2-pyrazolin-5-one, decomposing at 125°, both showing absorption due to the azide at 2160 cm^{-1}.

1-Phenyl-2-acetyl-3-amino-3-pyrazolin-5-one (**4b**).—A stirred suspension of 11.5 g of **3** in 100 ml of glacial acetic acid was warmed slowly on a steam bath. Evolution of gas began at *ca.* 70°. After being heated for 1.5 hr, the solution was cooled and diluted with 400 ml of water. A small amount of tar which separated was removed and discarded. After dilution of the filtrate to 1 l. with water, the product was extracted with 3 × 250 ml of ethyl acetate. The extracts were combined, washed with water, and evaporated to a syrup, which was crystallized from 30 ml of acetonitrile to give 3.2 g (29%) of 1-phenyl-2-acetyl-3-amino-3-pyrazolin-5-one. Recrystallization from acetonitrile (charcoal) gave an analytical sample, mp 188–190°. The properties and spectra of this compound are discussed above.

Anal. Calcd for $C_{11}H_{11}N_3O_2$ (217.23): C, 60.8; H, 5.4; N, 19.4. Found: C, 60.8; H, 5.1; N, 19.6.

Similarly prepared were 1-phenyl-2-propionyl-3-amino-3-pyrazolin-5-one (16%), mp 200–203°, nmr (DMSO-d_6) τ 9.13 (t, J = 7 Hz, 3 H) and 7.70 (q, J = 7 Hz, 2 H), ethyl group, 5.46 (s, 1 H), hydrogen on C-4, 2.66 (m, 5 H), phenyl group, and 2.27 (s) of the amine; 1-phenyl-2-acetyl-3-amino-4-(*p*-tolyloxy)-3-pyrazolin-5-one (57%), mp 185–187°, nmr ($CDCl_3$) τ 7.98 (s, 3 H), methyl group of the acetyl, 7.76 (s, 3 H), methyl of the tolyl group, and a multiplet of 11 H due to the nine aromatic and two amino hydrogens; 1-phenyl-2-formyl-3-amino-3-pyrazolin-5-one (10%), mp 185° dec; and 1-phenyl-2-acetyl-3-amino-4-phenoxy-3-pyrazolin-5-one (29%), mp 209–211°.

Elemental analyses of all compounds were satisfactory.

Registry No.—**3**, 34804-05-2; **4a**, 2311-90-2; **4b**, 34804-07-4; 1-phenyl-3-ethoxycarbonyl-4-(*p*-tolyloxy)-2-pyrazolin-5-one, 34804-16-5; 1-phenyl-3-ethoxycarbonyl-4-phenoxy-2-pyrazolin-5-one, 34804-17-6.

(8) E. H. Huntress and R. T. Olson, *J. Amer. Chem. Soc.*, **70**, 2856 (1948).
(9) W. E. Bachmann, W. Cole, and A. L. Wilds, *ibid.*, **62**, 824 (1940).