Extraction with 5 ml of boiling benzene left a white powdery solid having an ir spectrum now identical with that of **5** but having a low melting point (141–145°); authentic **5**, mp 155–156°. The benzene extract was evaporated to ~2 ml and then diluted to 15 ml with petroleum ether (bp 30–60°) to give a small amount of crude **6**.

**2-Acetoxyiminopiperidine (7).**—2-Hydroximinopiperidine (**6**) (100 mg, 0.87 mmol) dissolved exothermically in 1.0 ml of acetic anhydride. The solution was heated at 50° for 15 min, then cooled, and diluted with 20 ml of ether. A precipitate was removed and discarded. Vacuum-evaporation of the filtrate left a white granular solid which was recrystallized by dissolving it in 20 ml of ether and then diluting the solution to 100 ml with petroleum ether. Crystallization occurred on standing overnight in a freezer. The product (**7**) (51 mg, 38%) sintered at 94° and melted at 97–100°; ir (KBr) 3700–3100 (broad, NH), 1742 (C=O), 1623 $cm^{-1}$ (C=N); nmr ($CDCl_3$), $\delta$ 5.58 (s, broad, 1, NH), 3.30 (m, 2, $NCH_2$), 2.38 (m, 2, $N{=}CCH_2$), 2.12 (s, 3, $CH_3CO$), and 1.77 ppm (m, 4, other $CH_2$ groups).

*Anal.* Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 53.85; H, 7.55; N, 17.88.

**Phenylcarbamoyl Derivative of 2-Hydroximinopiperidine (6).**—To a solution of **6** (200 mg, 1.75 mmol) in 2 ml of chloroform was added phenyl isocyanate (209 mg, 1.75 mmol) dissolved in 2 ml of chloroform. A mild exothermic reaction set in; the mixture was shaken and then allowed to stand for 1 hr. It was diluted with 10 ml of chloroform, heated nearly to boiling on a steam bath, and then diluted with petroleum ether (bp 30–60°) to a volume of 125 ml. Placing the solution in a freezer overnight caused precipitation of a white solid (309 mg, 75.7%), sintering at 134° and melting at 136–138°; uv max (95% EtOH) 237 mμ (ε 22,000); ir (KBr) 3344 and 3184 (NH), 1700 (C=O) and 1621 $cm^{-1}$ (C=N); nmr ($CDCl_3$) $\delta$ 8.67 (broad, 1, CONH), 7.3 (m, 5, phenyl), 5.8 (broad, 1, ring NH), 3.25 (m, 2, $NCH_2$), 2.37 (m, 2, $N{=}CCH_2$), and 1.67 ppm (m, 4, other $CH_2$ groups). An analytical sample was recrystallized from ethanol–water; it sintered at 141–142° and melted at 142–143°.

*Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.44; N, 18.03. Found: C, 61.66; H, 6.46; N, 17.87.

**Registry No.**—THNA, 7032-11-3; hydroxylamine, 7803-49-8; **2**, 25055-43-0; **3**, 25055-44-1; **4**, 25055-45-2; **5**, 660-88-8; **6**, 4515-19-9; **7**, 25055-48-5; **8**, 25055-49-6.

**Acknowledgment.**—Generous support from the American Tobacco Co., Richmond, Va., is gratefully acknowledged.

# Notes

## Pyrazoles from Reaction of 3-Acetyl-1,4,5,6-tetrahydropyridine with Hydrazine and Phenylhydrazine[1]

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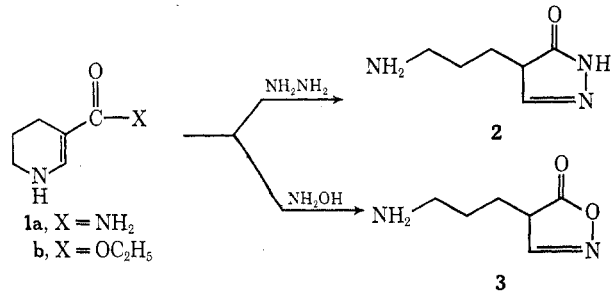
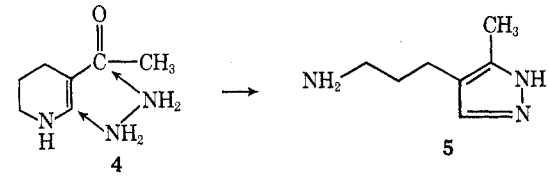
We have previously shown that 1,4,5,6-tetrahydronicotinamide (**1a**) and ethyl 1,4,5,6-tetrahydronicotinate (**1b**), which are readily available from hydrogenation of the corresponding pyridine compounds, react with binucleophiles such as hydrazine[2] and hydroxylamine[3] at both the enamino and carbonyl functions. The original ring is opened and new heterocyclic rings (pyrazolone **2** and isoxazolone **3**, respectively) are formed. In addition to nicotinic acid derivatives,




**1a**, X = $NH_2$
**b**, X = $OC_2H_5$

3-acylpyridines are cleanly reduced to the tetrahydro stage.[2,4] The reaction of hydrazine with such a keto compound should yield a pyrazole, and in this paper the formation of 3(5)-methyl-4-(3-aminopropyl)pyrazole (**5**) from 3-acetyl-1,4,5,6-tetrahydropyridine (**4**) is described.

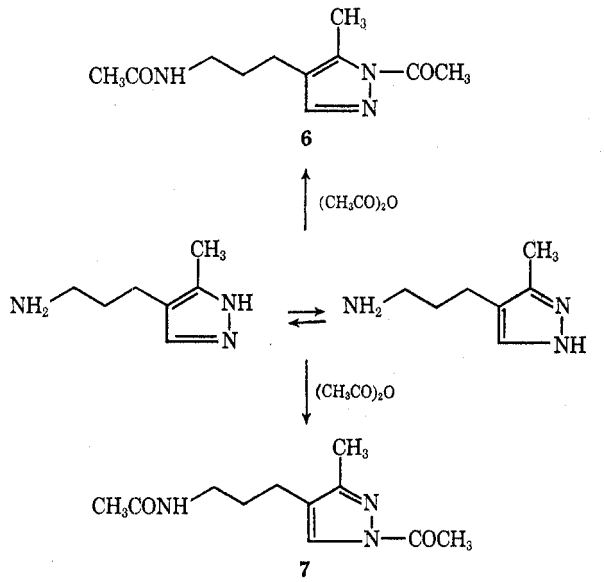



The reaction was brought about by refluxing the reactants in aqueous alcohol. The course of the reaction was easily followed by uv spectroscopy; **4** has a strong maximum at 300 mμ, which gradually diminished as the maximum for **5** (220 mμ) developed. The product was a distillable liquid, obtained in 68% yield.

The ir spectrum of **5** contained the expected pyrazole features.[5] The terminal amino group was suggested to be strongly associated from its broad band at 3600–2400 $cm^{-1}$. The nmr spectrum ($CDCl_3$) had C–H signals in agreement with structure **5**. Pyrazoles generally have NH signals around 11 ppm;[5] compound **5** had only one signal ($\delta$ 5.59) other than those for C–H. The integration was not conclusive, giving a value of 2.5 H. Nevertheless, it appears that the signal is derived from protons of the amino group as well as the ring NH, presumably undergoing rapid exchange. The signal disappeared on deuteration; no other changes occurred in the spectrum.

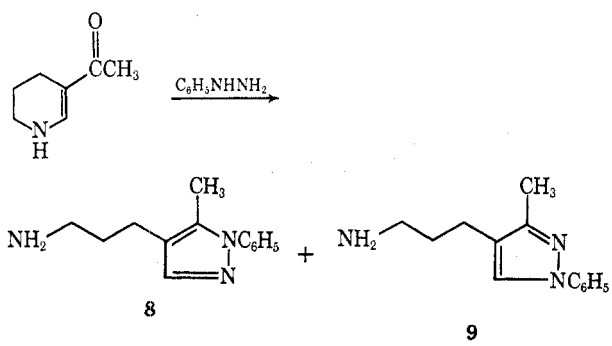
(1) From the Ph.D. Dissertation of D. O. Pinion, Duke University, 1969.
(2) P. M. Quan and L. D. Quin, *J. Org. Chem.*, **31**, 2487 (1966).
(3) L. D. Quin and D. O. Pinion, *ibid.*, **35**, 3130 (1970).
(4) M. Freifelder, *ibid.*, **29**, 2895 (1964).
(5) G. Zerbi and C. Alberti, *Spectrochim. Acta*, **18**, 407 (1962); **19**, 1261 (1963).

Pyrazole **5** was acetylated readily. Two isomers (**6** and **7**) are possible from this reaction, but the product appeared to be homogeneous since the nmr spectrum contained only one ring-$CH_3$ signal ($\delta$ 2.25 ppm). It seems likely that the compound has structure **7**



since steric hindrance with the methyl group can be expected to direct acylation to the remote nitrogen. Thus, acetylation of 3(5)-methylpyrazole occurs at this nitrogen.[6] The chemical shift of the ring $CH_3$ is in accord with this assignment; it compares with the value ($\delta$ 2.22) reported for the 3-methyl of 1-acetyl-3,5-dimethylpyrazole rather than for the 5-methyl ($\delta$ 2.52).[7] Uv spectroscopy provides further support. The maximum is at rather long wavelength (252 m$\mu$), compared to 1-acetyl-3,5-dimethylpyrazole (241 m$\mu$[8]). This may be taken to mean that the acetyl can better stabilize the excited state in **7**, suggesting its location where maximum resonance interaction (coplanarity of ring and carbonyl) can occur. In the dimethylpyrazole, steric interaction of acetyl with methyl on the adjacent carbon could hinder this resonance effect.

Phenylhydrazine on refluxing with **4** in a slightly acidic aqueous medium gave a 1:1 mixture of isomeric pyrazoles **8** and **9**. The isomer ratio was evident from



the nmr spectrum, which contained two ring-$CH_3$ singlets of equal area at $\delta$ 2.19 and 2.31 ppm. The isomer mixture has not yet been separated. The isomer with $CH_3$ singlet at 2.19 ppm was made to predominate (7:3 by nmr analysis) by conducting the reaction at 145–150° in ethylene glycol. It is likely, but not conclusively established, that the major isomer is the 5-methyl derivative **8**; this is suggested by the upfield position of the ring-$CH_3$ signal, an effect attributable to shielding by an adjacent phenyl group. Also the uv spectrum of the 7:3 mixture had a maximum at 252 m$\mu$; a fraction enriched in the other isomer by ether–water partitioning of the 1:1 mixture had a maximum at 260 m$\mu$. Adjacent phenyl can again account for this difference; in **8**, steric hindrance prevents maximum resonance stabilization of the excited state, accounting for absorption at lower wave length. This effect has been observed for a simpler isomer pair: 1-phenyl-5-methylpyrazole, $\lambda_{max}$ 240 m$\mu$; 1-phenyl-3-methylpyrazole, $\lambda_{max}$ 256 m$\mu$.[9]

(6) K. V. Auwers and W. Daniel, *J. Prakt. Chem.*, **110**, 153 (1925).
(7) L. G. Tensmeyer and C. Ainsworth, *ibid.*, **31**, 1878 (1966).
(8) W. Otling and H. A. Staab, *Justus Liebigs Ann. Chem.*, **622**, 23 (1959).

### Experimental Section[10]

**3-Acetyl-1,4,5,6-tetrahydropyridine** (**4**).—The procedure of Freifelder[4] was used. 3-Acetylpyridine (45 g) in 250 ml of ethanol was hydrogenated at 3 atm over 2.5 g of 10% palladium on charcoal. The product (27.1 g, 58.2%) was recovered by distillation at 130–135° (0.2 mm), lit.[4] bp 175° (10 mm); uv max (95% EtOH) 300 m$\mu$ ($\epsilon$ 21,000), lit.[4] 301 m$\mu$ ($\epsilon$ 21,150).

**3(5)-Methyl-4-(3-aminopropyl)pyrazole** (**5**).—A mixture of 5.0 g (0.04 mol) of **4** and 10 ml of 64% aqueous hydrazine in 10 ml of 95% ethanol was refluxed for 4.5 hr. The uv maximum of **4** had disappeared, and a peak at 220 m$\mu$ for **5** developed. Solvent was stripped from the solution and the residue distilled; **5** was received at 123–124° (0.08 mm). The yield was 3.8 g (68%): uv max (95% EtOH) 220 m$\mu$ ($\epsilon$ 2800); ir (neat) 3135 (broad, NH), 1572, 1481, and 1308 cm$^{-1}$; nmr ($CDCl_3$) $\delta$ 7.41 (s, 1, ring proton), 5.59 (s, 2.5, $NH_2$ and NH), 2.70 (t, 2, $NCH_2$), 2.43 (t, 2, $NCH_2CH_2CH_2$), 2.21 (s, 3, $CH_3$), and 1.63 (m, 2, $CH_2CH_2CH_2$) ppm. By titration with perchloric acid in acetic acid, the equivalent weight was found to be 69.7 (calcd 69.5).

*Anal.* Calcd for $C_7H_{13}N_3$: C, 60.43; H, 9.35; N, 30.22. Found: C, 60.82; H, 9.51; N, 29.78.

**Acetylation of 5.** A solution of 250 mg (1.8 mmol) of **5** in 1 ml of chloroform was treated with 1 ml of acetic anhydride. After the exothermic reaction subsided, the mixture was allowed to stand for 4 hr and then stripped of solvent. The oily residue was dissolved in 100 ml of ether; on chilling, the product crystallized. After recrystallization from ether, the yield of **7** was 328 mg (82%): mp 92–94°; uv max (95% EtOH) 252 m$\mu$ ($\epsilon$ 8680); ir (KBr) 3322 (NH), 1724 (C=O of ring acetyl), 1634 cm$^{-1}$ (C=O of terminal acetyl); nmr ($CDCl_3$) $\delta$ 8.05 (s, 1, ring proton), 6.96 (broad s, 1, NH), 3.38 (apparent q, becoming t on adding $D_2O$, 2, $NCH_2$), 2.62 (s, 3, ring $CH_3CO$), 2.49 (m, 2, $NCH_2CH_2CH_2$), 2.25 (s, 3, 3-$CH_3$), 2.00 (s, 3, $CH_3CONH$), and 1.86 (m, 2, $NCH_2CH_2CH_2$) ppm.

*Anal.* Calcd for $C_{11}H_{12}N_3O_2$: C, 59.19; H, 7.62; N, 18.83. Found: C, 59.51; H, 7.78; N, 19.12.

**Reaction of 4 with Phenylhydrazine.**—A solution of **4** (3.00 g, 0.024 mol) and phenylhydrazine (2.59 g, 0.024 mol) in 12 ml of ethylene glycol containing 0.25 ml of concentrated hydrochloric acid was heated in an oil bath at 145–150° for 4 hr. Gas chromatography showed negligible amounts of starting materials. After adding 0.5 ml of 6 *N* sodium hydroxide, ethylene glycol was removed by distillation under reduced pressure; the product, an oil, had bp 134–144° (0.07–0.14 mm), 3.15 g (61.0%). Redistillation gave bp 137–138° (0.14 mm): uv max (95% EtOH) 252 m$\mu$ ($\epsilon$ 10,000); ir (neat) 3311 (NH), 1602, 1567, 1499 cm$^{-1}$; nmr ($CDCl_3$) $\delta$ 8.05–7.22 (m, 6, phenyl and C-3(5) ring protons), 2.73 (t, 2, $NCH_2CH_2$), 2.50 (t, 2, $NCH_2CH_2CH_2$), 2.31 and 2.19 [both s, 3 H total for 3-$CH_3$ (28.1%) and 5-$CH_3$ (71.9%)], 1.72

(9) S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Tetrahedron*, **22**, 2703 (1966).
(10) Melting points are corrected. Infrared spectra were obtained with Perkin-Elmer Model 137 or 237 spectrophotometers, uv spectra with a Beckman Model DB-G spectrophotometer, and nmr spectra with a Varian A-60 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(m, 2, $CH_2CH_2CH_2$) and 1.35 (s, 2, NH; disappears with $D_2O$) ppm.

Titration with perchloric acid in glacial acetic acid gave equiv wt 107.7 (calcd 107.5).

*Anal.* Calcd for $C_{13}H_{17}N_3$: C, 72.51; H, 7.96; N, 19.53. Found: C, 72.05; H, 8.11; N, 19.67.

**Registry No.**—**4**, 7032-12-4; hydrazine, 302-01-2; phenylhydrazine, 100-63-0; **5**, 24978-50-5; **7**, 24978-51-6; **8**, 24978-52-7; **9**, 25080-59-5.

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## Reduction of 2-(2-Imidazolin-2-yl)benzophenone

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In the course of the structural investigation of compounds obtained by the condensation of *o*-benzoylbenzaldehyde with aliphatic diamines,[2] we decided to study the reduction of these products. The equilibrium between the two tautomeric forms of the imidazoline derivatives **1a** and **1b** has been previously discussed.[2] Reduction with borohydride gave a nearly quantitative yield of the tautomeric dihydro compound **3a–b**.

The uv absorption of **3** is similar to that of **4** and different from that of **6** (Table I). This is probably due to steric hindrance in compounds **3** and **4**. These results indicate the presence of $C_6H_5C{=}N$ moiety in **3**, but do not allow a quantitative estimate of the equilibrium **3a** ⇌ **3b**. The near ir spectrum of **3** was recorded in $CHCl_3$ at three different concentrations. All spectra exhibit a band at 1.494 $\mu$ ($\epsilon$ 0.8) (NH of **3a**), a broad small band at 153 $\mu$ (NH of **3b**), and a very broad band at 1.4 $\mu$ area (strongly bonded OH of **3a**). This gives an approximate ratio for **3a**:**3b** of 9:1. For comparison, the near ir spectrum of salicylideneaniline (Frinton Laboratories) was recorded. With this compound the OH also forms a very strong intramolecular bonding and no absorption for nonbonded OH was detected. Compounds **4** and **6** exhibit only one kind of NH and no OH. Polarograms of **3** and **6** were recorded in 0.1 *N* KOH. The half-wave potential $E^{1/2}$ (reduction of $-C{=}N-$) of both compounds is similar (−1.755 and −1.730 V, respectively, *vs.* Ag|AgCl electrode) but the intensity of the molar diffusion currents ($I_d$) is different ($I_d \times 10^{-3}$ for **3** = 9.38 $\mu$A; and $I_d \times 10^{-3}$ for **6** = 12.72 $\mu$A), indicating the presence of some **3b** in 0.1 *N* KOH. On the assumption that reduction at the mercury dropping electrode is faster than the tautomeric equilibrium rate and that the diffusion coefficients are essentially the same for compounds **3** and **6**, these data also suggest a predominance of **3a**.

As expected, the results of chemical reactions were compatible with either structural possibility. Thus, hydrolysis gave 3-phenylphthalide and treatment of **3** with an acidic catalyst gave the imidazoisoindoline **2**.

Reduction of compound **2** with lithium aluminum hydride in boiling tetrahydrofuran yielded the 2-benzylphenylimidazoline **4** as the major product. The same product was obtained by heating the amide **8**, a compound which in turn was obtained either from the reaction of *o*-benzyl benzoate and ethylenediamine or by the reduction of compound **3** with zinc in acetic acid (Scheme I).

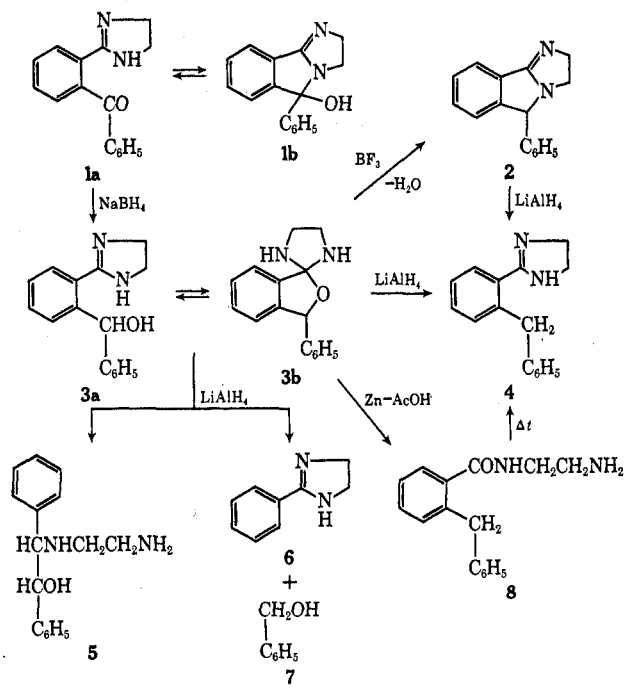
TABLE I

ULTRAVIOLET ABSORPTION DATA

| Compd | Solvent | $\lambda_{max}$, m$\mu$[a] | $\epsilon \times 10^{-3}$ |
|---|---|---|---|
| **3** | 2-Propanol | 260 (s), 275 (i), 284 (i) | 2.52, 2.20, 1.65 |
| | $CHCl_3$ | 260 (i), 275 (i), 283 (s) | 3.00, 2.28, 1.68 |
| | 0.1 *N* HCl | 235 (i), 273 (i) | 7.60, 1.40 |
| | 0.1 *N* KOH | 265 (i), 283 (i) | 2.10, 0.95 |
| **6** | 2-Propanol | 230, 270 (i) | 12.50, 3.80 |
| | 0.1 *N* HCl | 236, 270 (i) | 16.65, 3.30 |
| | 0.1 *N* KOH | 266, 265 | 13.25, 3.90 |
| **4** | 0.1 *N* HCl | 235 (i), 262 (i), 269 (i) | 7.30, 2.0, 1.60 |
| | 0.1 *N* KOH | 263 (i), 269 (i) | 2.20, 1.72 |

[a] s, shoulder; i, inflection.

SCHEME I




On prolonged treatment (>60 hr) of compound **3** with lithium aluminum hydride in boiling tetrahydrofuran a mixture of products was obtained which consisted of compounds **4**, **5**, **6**, and **7** in a molar ratio of 1:9:13:12. Compound **5** could be isolated directly from the reaction mixture in 24% yield as the least ether soluble product. Compound **6** was obtained

(1) To whom inquiries should be addressed.

(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).