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Synthesis of the Isomers of 3-Butyl-5-methyloctahydroindolizine, a Trail Pheromone of Pharaoh Ant

Summary: The four stereoisomers of 3-methyl-5-butyloctahydroindolizine, a trail pheromone of the Pharaoh ant, have been synthesized by methods that unambiguously defined their stereochemistry.

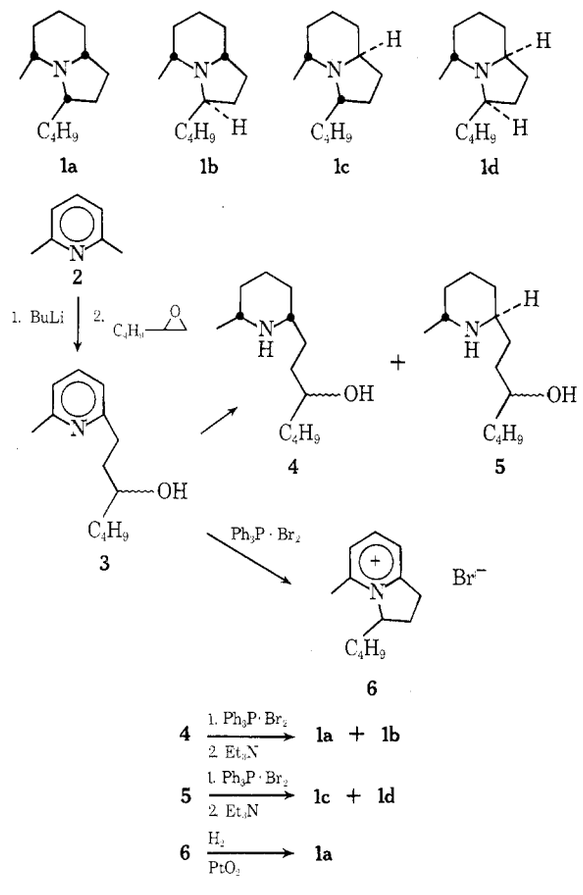
Sir: Ritter, *et al.*,[1] recently described the isolation and identification of a 3-butyl-5-methyloctahydroindolizine as a trail pheromone of the Pharaoh ant, *Monomorium pharaonis* (L.). Which of the four possible geometrical isomers (**1a–d**) of this structure was the active pheromone was not determined. Because of our interest in the synthesis of pheromones of potential utility for pest control,[2] and because the reported[1] synthesis of **1a–d** would not be practical for preparation of the individual isomers, we undertook syntheses of each of the isomers by routes that would define their stereochemistry and allow their isolation. We here report successful preparations of each of the isomers from 2,6-lutidine (**2**) (Scheme I).

Sequential treatment of **2** with *n*-butyllithium and hexene 1-oxide gave the alcohol **3** [bp 92° (0.06 mm), n^{27}D 1.5022].[3] Cyclization of **3** with triphenylphosphine dibromide ($Ph_3P{\cdot}Br_2$) provided the dihydroindolizinium bromide **6** (characterized as the iodide, mp 126–127°) which was hydrogenated over PtO_2 to give the *all-cis*[4]-3,5-dialkyloctahydroindolizine **1a** [bp 119° (27 mm), n^{25}D 1.4669].

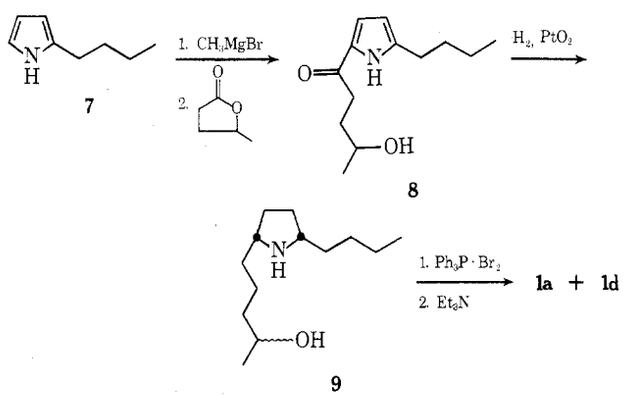
Hydrogenation of **3** gave the *cis*[5]-piperidyl alcohols **4** (mp 55–63°). Cyclization of **4** with $Ph_3P{\cdot}Br_2$ followed by triethylamine gave a mixture (separated by spinning-band distillation) of **1a** and **1b** [bp 125° (27 mm), n^{25}D 1.4704].

The final two isomers, **1c** and **1d,** whose substituents on the piperidine ring bear a trans relationship, were prepared analogously. Reduction of **3** with sodium and ethanol gave an 80:20 mixture of **4** and its trans isomer **5,** respectively. Seeding an acetonitrile solution of the crude mixture with **4** initiated crystallization of that isomer; the mother liquor contained approximately equal parts of **4** and **5.** Spinning band distillation achieved final separation of the *trans*-piperidyl alcohol **5** [bp 77° (0.005 mm), n^{25}D 1.4732]. Cyclization of **5** with $Ph_3P{\cdot}Br_2$ then gave **1c** [bp 121° (27 mm), n^{25}D 1.4699] and **1d** [bp 125° (27 mm), n^{25}D 1.4695]; these were also separated by spinning-band distillation. A variety of packed glc columns (Carbowax 20M, SE-30, others) served to distinguish the indolizidines and to monitor the

Scheme I



Scheme II



distillations. Although **1b** and **1d** could not be separated by gas chromotography, the synthetic routes chosen circumvented the necessity for separation. The production of *cis*-dialkylpiperidines by catalytic hydrogenation of the corresponding pyridines provided the basis for assigning the stereochemistry at positions 6 and 9 of **1a–d;**[6] the stereochemistry at position 3 of **6** (and therefore of **7**) was established by the alternate preparation of **1a** from **6.** To assign the stereochemistry at position 3 of **1c** and **1d,** we again turned to the principle of cis hydrogenation, in this case to produce the cis-2,5-disubstituted pyrrolidine **9** (Scheme II). γ-Valerolactone was added to the Grignard reagent from 2-butylpyrrole (**7**) to give **8** (mp 63–64°). Hydrogenation (PtO_2, 50 psi) of **8** gave the pyrrolidinyl alcohol **9** which was not purified but instead was cyclized directly with $Ph_3{\cdot}Br_2$ to a mixture consisting mainly of **1a** and **1d,** thereby establishing **1d** as the isomer with hydrogens at positions 3 and 9 situated cis to each other. Small amounts of

1b and 1c (total ~15%) were also detected in the reaction mixture, indicating that the hydrogenation of 8 must have provided a small amount of the trans isomer of 9.[7] However, the fact that 1a (all-cis) was one of the major products from this cyclization requires that the substituents on the pyrrolidine ring of the other major product must also have been cis.

Experimental details and additional work on this system will be reported at a later date.

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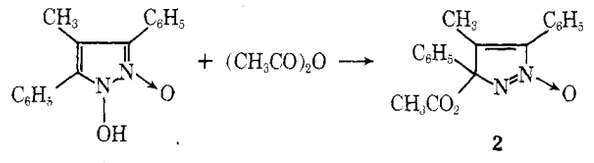
Molecular Rearrangements of *N*-Hydroxypyrazole Derivatives[1]

Summary: The tosylates of *N*-hydroxypyrazoles are hydrolyzed quantitatively to 5-pyrazolones, a reaction involving 1,2 migration in which anti-aromatic diazacyclopentadienyl cations are possible intermediates.

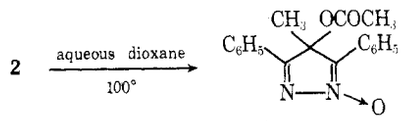
Sir: In an earlier investigation it was observed that acetylation of 1-hydroxy-3,5-diphenyl-4-methylpyrazole 2-oxide (**1**) yielded a *C*-acetoxy compound (**2**) rather than an *N*-



1 2

acetoxy compound.[2] Recently others have reported analogous rearrangements in this heterocyclic series.[3] In many respects these reactions resemble some of those reported in the indole[4] and purine[5] series. In each instance the driving force appears to be the exchange of the weak N–O bond for a stronger C–O bond.

Some additional rearrangements have now been observed. Upon heating in aqueous dioxane, acetate **2** further rearranges to acetate **3**. The structure of **3** rests upon its el-



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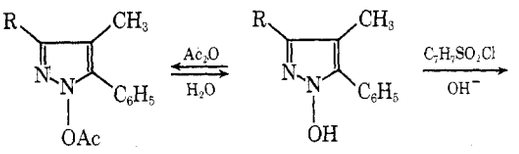
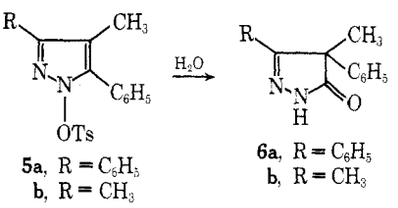
ementary analysis and the similarity of its infrared and nmr spectra to that of the corresponding dioxide.[2,6] Similar sequential 1,2 rearrangements of *N*-methoxypyrazole oxides[3] and *N*-nitropyrazoles[8] have been observed.

Acetylation of *N*-hydroxy-3,5-diphenyl-4-methylpyrazole (**4a**) produced the *N*-acetoxy derivative which did not rearrange after prolonged heating in boiling xylene. Hydrolysis regenerated the *N*-hydroxypyrazole. However, the corresponding *N*-tosyloxy compound (**5a**) was converted quantitatively, upon heating in aqueous dioxane, to 3,4-diphenyl-4-methyl-5-pyrazolone (**6a**). This transformation



4a, R = C_6H_5
b, R = CH_3



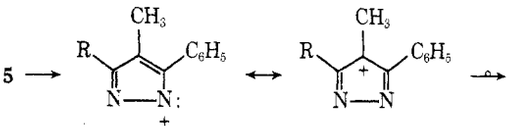
5a, R = C_6H_5
b, R = CH_3

6a, R = C_6H_5
b, R = CH_3

resembles the conversion of indoles into oxindoles by hypochlorite, a sequence which may begin by N-chlorination[4] yielding an intermediate analogous to the *N*-tosylate **5**.[9]

When 3(5)-phenyl-4,5(3)-dimethyl-1-hydroxypyrazole was similarly tosylated and heated in water, the product was again that of phenyl migration, 3,4-dimethyl-4-phenyl-5-pyrazolone (**6b**).

A possible mechanism analogous to those proposed for the indoles[4] involves ionization of **5** to ion **7**, a heterolog of the anti-aromatic cyclopentadiene cation.[10] Isomerization



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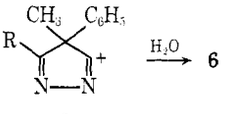

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to ion **8** would lead to the product.[11-13] In an effort to determine the chemistry of possible precursors of ions like **7**, the electrophilic substitution reactions of the hydroxypyrazoles are being investigated as sources of such compounds. Treatment of **4a** with *tert*-butyl hypochlorite yields 4-chloro-4-methyl-3,5-diphenylpyrazolenine 1-oxide (**9**). While the *N*-oxide function may strongly influence the reactivity of **9** so that it is a poor model[14] for precursors of ion **7**, it was found that **9** reacts readily with silver acetate to yield acetate **3**. Thus, in this case at least, a reaction which most likely involves a carbonium ion intermediate proceeds