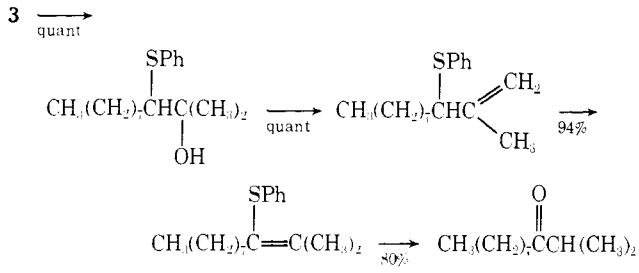
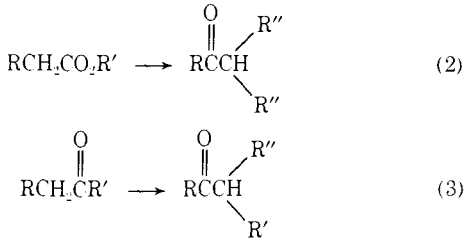
enol thioether.[9] Hydrolysis under the standard conditions ($HgCl_2$, CH_3CN, H_2O, reflux) completes the sequence.



Equations 2 and 3 summarize the transformations achievable by these methods. In addition to effecting a 1,2



shift of the carbonyl group, the method allows for formation of additional carbon–carbon bonds at the former carbonyl group. A novel approach to unsymmetrical ketones from symmetrical ketones is embodied in the approach. Further applications of these methods are in progress.

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A Photolabile Protecting Group for Histidine

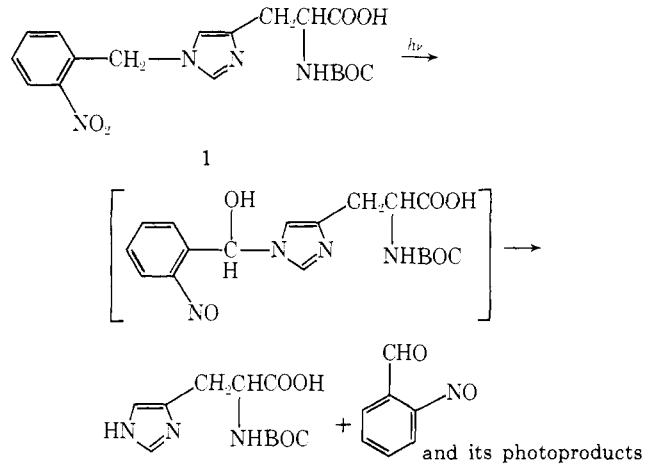
Sir:

We describe a method of introducing the *o*-nitrobenzyl group (ONB) into the imidazole side chain of histidine and its subsequent removal under mild, highly specific conditions by irradiation. This group has been used to block amino and carboxyl groups[1] and is stable under most of the conditions of peptide synthesis. Thus it is unreactive to anhydrous trifluoroacetic acid, anhydrous hydrogen chloride in acetic acid, and sodium hydroxide in methanol but is slowly cleaved by catalytic hydrogenation.

Although *im*-benzyl-L-histidine can be prepared by the reaction of benzyl chloride with the anion of the imidazole side chain, generated by sodium in liquid ammonia,[2] the reaction failed with *o*-nitrobenzyl chloride, resulting instead in the quantitative formation of 2,2′-dinitro-*trans*-stilbene.[3]

The *o*-nitrobenzyl group was introduced instead by reaction of the silver salt of N^{α}-*tert*-butoxycarbonyl-L-histidine methyl ester[4] with *o*-nitrobenzyl bromide in refluxing benzene for 4 hr. After removal of the silver bromide, the crude product was saponified by treatment with 2 equiv of 1 *N* NaOH in MeOH–DMF (3:1) for 2 hr. The solution was diluted with water, adjusted to pH 3.9 with HCl, saturated with NaCl, and extracted with ethyl acetate. N^{α}-Boc-N^{im}-ONB-L-His-OH was crystallized from ethyl acetate–petroleum ether in over-all yields of 60–70% for the three reactions and melted at 90° dec.[5] When the reaction was carried out with *o*-nitrobenzyl chloride in refluxing *p*-xylene, the starting material disappeared in 22 hr (tlc) but the over-all yield of the product was only 40–50%. The same compound was prepared by reaction of N^{α}-Boc-L-His-OMe with *o*-nitrobenzyl halides and dicyclohexylamine in DMF, followed by saponification, in yields of 30 and 45% for the chloride and bromide, respectively.[6]

To remove the *o*-nitrobenzyl group, a solution of **1** (3×10^{-3} *M* in dioxane) was irradiated with a mercury vapor



and its photoproducts

lamp[7] with a Pyrex filter in a quartz immersion well, with stirring by a stream of nitrogen. Photolysis was complete in 1 hr. After evaporation of the dioxane, the residue was dissolved in water and washed with chloroform. The product contained a small amount of a colored water-soluble impurity and was further purified by preparative tlc in silica gel, using $CHCl_3$–MeOH–HOAc (90:30:5). It was precipitated from methanol with ether in nearly quantitative yield, mp 195–200°,[8] $[\alpha]^{27}D$ +18.3 (*c* 1, EtOH).

To confirm further that no racemization occurred in any of the reactions, we esterified N^{α}-Boc-N^{im}-(ONB)-His with CH_2N_2, removed the ONB group by irradiation, and separated the reaction products by preparative tlc. An almost quantitative yield of N^{α}-Boc-L-histidine methyl ester was obtained, mp 124–125.5° (EtOAc–petroleum ether). The ORD spectrum of this sample was identical with that of an authentic sample synthesized from histidine methyl ester hydrochloride, with $[\alpha]_{290}$ −50.7.

Work is in progress on the synthesis of peptides using this protecting group.

Acknowledgment. This work was supported by grants from the National Science Foundation and from Eli Lilly and Company. We thank Dr. Robert Archer, Dr. Bruce H. Frank, and Mr. Allen Pekar of the Lilly Research Laboratories for the use of the equipment needed in the photolysis experiments and for the ORD data.

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(5) N^{α}-Boc-N^{im}-ONB-His, Calcd for $C_{18}H_{22}O_6N_2 \cdot H_2O$: C, 52.93; H, 5.92; N, 13.72. Found: C, 52.98; H, 5.68; N, 13.75, $[\alpha]D^{27}$ +12.9 (*c* 2, MeOH). Satisfactory nmr and ir spectra were obtained.
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5-Thiomethylpentane-2,3-dione. A Unique Natural Product from the Striped Hyena

Sir:

Ruzicka's isolation of civetone and muskone in 1926[1] opened the area of mammalian scent materials.[2] Only recently have compounds of further chemical interest[3] been identified. We now report the isolation of 5-thiomethylpentane-2,3-dione from the anal scent gland of the striped hyena (*Hyaena hyaena*), the first α-diketone thioether from a natural source.

Analysis (gc–mass spectral) of a chloroform extract of waxy material deposited by either sex[4] indicated two volatile components, representing 2% of the total material. The more volatile of these, mol wt 146, appeared to contain sulfur. In addition to the parent, P + 1, and P + 2, large peaks were observed at *m/e* 118, 103, 90, 75, 61, and 43. The second less volatile compound exhibited *m/e* 224 and did not contain sulfur. Material of mol wt 146 was collected by vacuum distillation of crude, waxy material at 55° (2 mm) into cold traps, followed by preparative glc, giving a light yellow odoriferous oil[5] which exhibited the following pmr spectrum: δ 2.03, s, 3 H; 2.30, s, 3 H; 2.63, t, 2 H, J = 5.5 Hz; 2.95, t, 2 H, J = 5.5 Hz. The two methylene groups are adjacent, indicated by their coupling, and the presence of only ten protons shows that other groups must be present to achieve a mol wt of 146. The ir spectrum confirmed this, showing a single carbonyl absorption at 5.82 μ. Further confirmation was achieved by preparation of a dimethoxime[6] which exhibited *m/e* 204, 173, 157, 142, 127, 126, 125, 95, and 61 and a substituted quinoxaline[7] which indicates that the two carbonyl groups are adjacent to each other in the original molecule: *m/e* 218, 203, 190, 171, 143, 108, 76, and 61.[8] On the basis of these derivatives, and the pmr and ir spectra, the structure of the 146 material is CH_3CO-$COCH_2CH_2SCH_3$ (I).

Synthesis of I was achieved from biacetyl, sodium hydride, and chloromethyl methyl sulfide as well as by mixing equimolar amounts of biacetyl, formaldehyde, methanethiol, and a catalytic amount of diethylamine[9] at 0° followed by distillation at 70°. The residue of this distillation was distilled, bp 72° (3 mm), giving 30% of I; as bissemicarbazone, mp 234.0–234.5° dec, mmp 234.0–235.0° dec. *Anal.* Bissemicarbazone, $C_8H_{16}N_6O_2S$, calcd: C, 36.90; H, 6.19; N, 32.29; S, 12.31. Found: C, 37.08; H, 5.98; N, 32.59; S, 12.31. The mass spectrum, retention times, and ir and pmr spectra of synthetic I purified by preparative glc[5] were identical with those of the natural material.

Although *n*-butyl mercaptan and dicrotyl sulfide have been identified as odorous components of skunk[10] and di- and trisulfides have been found in ponerine ants,[11] this thioether containing an α-dicarbonyl represents a unique natural product. The nature of the mol wt 224 compound, its relationship to I, and scent-marking behavior are under investigation.

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