binations,[6] and the sodium naphthalene procedure is clearly more convenient for most cases. As in the case of alkali metal–ammonia cleavages, easily reduced functional groups, *e.g.*, halogen and cyano, do not survive, but the limitations this imposes on this new procedure have not yet been established.

The only organic products other than the amine formed in the cleavage reaction appear to be the corresponding sulfinate salt and desulfonated hydrocarbon, *e.g.*, toluene from toluenesulfonamides. No thiol product has been observed in any of the reactions, and both benzenethiol and *p*-toluenethiol were shown to be stable to the reaction conditions. Toluenesulfinate ion (from the sodium salt dihydrate) is slowly converted to toluene by excess sodium naphthalene in dimethoxyethane,[7] but this process does not seem to be fast enough to account for all the toluene produced in a typical cleavage reaction. More likely, there are two distinct cleavage processes involved, one yielding toluene directly and one producing sulfinate anion, similar to those postulated by Kovacs and Ghatak for sodium–liquid ammonia cleavage of tosylamides[8] but with the pathway for reduction of sulfinate to thiol being unavailable in the anion radical reaction.

One further interesting point is the lack of proton abstraction from the highly acidic sulfonamides of primary amines. Quenching in air (which does not affect dihydronaphthalenes already present) of the reaction mixture from *p*-toluidinetosylamide and sodium naphthalene yields no dihydronaphthalene, implying that only electron transfer from naphthalene occurs during the reaction. The sodium salt of this sulfonamide, which could also be produced by reaction of the amide anion with unreacted tosylamide, *is* cleaved in respectable yield (see Table I).

(6) V. du Vigneaud and O. K. Behrens, *J. Biol. Chem.*, 117 27 (1937); A. J. Birch and H. Smith, *Quart. Rev.* London), 12 17 (1958).

(7) This is contrary to the observed inertness of this salt in THF solutions,[2] but this difference in behavior may simply be due to differing solubilities of the salt in the different ether solvents. It is not very soluble in either.

(8) J. Kovacs and U. R. Ghatak, *J. Org. Chem.*, 31, 119 (1966).

(9) On leave from the Department of Chemistry, Brooklyn College, 1965–1966.

(10) National Science Foundation Undergraduate Research Participant, 1966.

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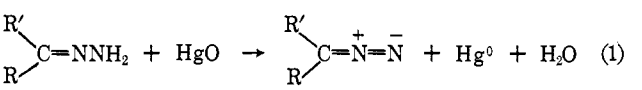
Diazoalkanes from Hydrazone Anions. A Novel Oxidation Reaction

Sir:

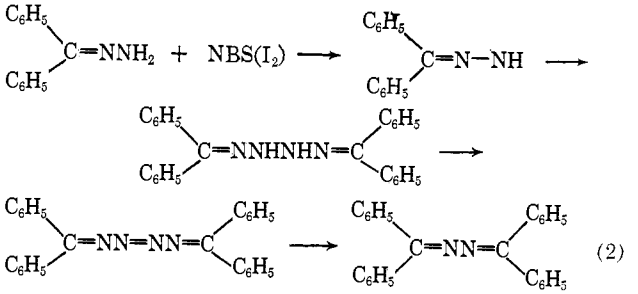
The oxidation of hydrazones with metal oxides such as those of mercury, silver, and manganese has long been a very useful method for the preparation of diazoalkanes.[1]

(1) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 258–259; C. G. Overberger, J.-P. Anselme, and J. G. Lombardino, "Organic Compounds with Nitrogen–Nitrogen Bonds," The Ronald Press Co., New York, N. Y., 1966, p 49.



(1)

Although not well understood, the mechanism is probably not radical in nature since, under conditions in which radicals are involved, the corresponding azines are obtained directly *without* the intervention of diazoalkanes. For example, the oxidation of benzophenone hydrazone with N-bromosuccinimide[2] or iodine[3] gives benzophenone azine, possibly *via* the following sequence of reactions.



(2)

During the course of our investigations of the chemistry of anions of nitrogen derivatives, we have discovered a remarkable oxidation. To a solution of benzophenone hydrazone in tetrahydrofuran at room temperature was added through a rubber septum an equimolar solution of methyllithium in tetrahydrofuran. The evolution of methane began immediately and a yellow solution of benzophenone hydrazone anion was obtained. Upon being stirred, the solution began to assume a reddish coloration and within 60 min became deep wine-red in color. The solution was shaken with water and the organic phase separated and dried. Upon evaporation of the solvent, a red oil was obtained. It was identified as diphenyldiazomethane by comparison of its infrared spectrum with that of an authentic sample and by its conversion to benzhydryl 3,5-dinitrobenzoate.

If the solution of the anion was stirred under *nitrogen*, the characteristic red color failed to appear even after 2 hr. However, when oxygen was bubbled through the yellow solution, and immediate and rapid change to red was observed, and the formation of diphenyldiazomethane was essentially completed in 15 min. The aqueous phase gave a positive test for peroxide. In a quantitative run, the yield of diphenyldiazomethane was 37%, calculated from the weight of the 3,5-dinitrobenzoate ester. Titration of the acidified aqueous phase with permanganate indicated a 30% yield of peroxide. Benzophenone hydrazone was recovered in 44% yield. The corresponding diazoalkanes were obtained from the anions of fluorenone, acetophenone, and benzil hydrazones.[3a]

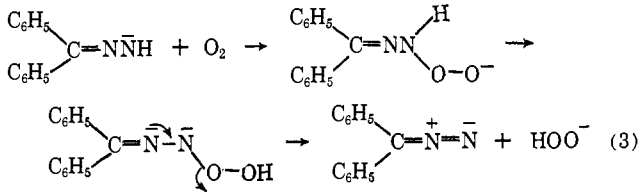
The oxidation of the hydrazone anions may be viewed as proceeding *via* the formation of peroxy anions followed by a prototropic shift and the elimination of

(2) M. Z. Barakat, M. F. A. El-Wahab, and M. M. El-Sadr, *J. Am. Chem. Soc.*, 77, 1670 (1955).

(3) D. H. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962).

(3a) NOTE ADDED in PROOF. H. Staudinger and A. Gaule (*Ber.*, **49**, 1951 (1916)) reported the preparation of diazofluorene by the action of oxygen on fluorenone hydrazone in the presence of base. However, other hydrazones subjected to the same conditions failed to give the corresponding diazoalkanes except in the case of benzil monohydrazone where the orange color of the diazo compound was observed.

hydroperoxide anion[4] as shown in eq 3. The initial



attack is similar to that suggested for the oxidation of Grignard reagents by oxygen.[5]

(4) H. E. Zimmerman and D. H. Paskovich, *J. Am. Chem. Soc.*, **86**, 2149 (1964), footnote 12.
(5) C. Walling and S. A. Buckler, *ibid.*, **75**, 4372 (1953).

The interesting possibilities suggested by this novel reaction are under active investigation in our laboratories.

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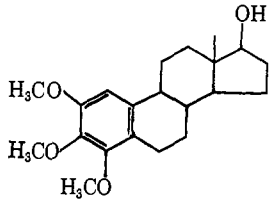
Additions and Corrections

A Steroidal Analgesic [*J. Am. Chem. Soc.*, **88**, 856 (1966)]. By LEONARD R. AXELROD and P. NARASIMHA RAO, Southwest Foundation for Research and Education, San Antonio, Texas, and DAVID H. BAEDER, Mallinckrodt Chemical Works, St. Louis, Missouri.

In the above publication, the synthesis of a new class of compounds having poly(lower alkoxy)estrane structures was reported. In a subsequent publication [L. R. Axelrod and D. H. Baeder, *Proc. Soc. Exptl. Biol. Med.*, **121**, 1184 (1966)], analgesic activity of one of these compounds was compared with that of some clinically active standard analgesics. Based on the findings of this investigation, the compound, MP-2001, *d*-2,3,4-trimethoxyestra-1,3,5(10)-trien-17β-ol



was reported to be more potent than morphine. More recently, laboratory testing of poly(alkoxy)estratrienes yielded results which indicated that the compounds were devoid of pharmacologic activity [D. R. Van Deripe, G. B. Hoey, W. R. Teeters, and T. W. Tusing, *J. Am. Chem. Soc.*, **88**, 5365 (1966)].

Since the pharmacologic evaluation of these compounds for the above-cited studies was not conducted in our laboratories, it was decided to reevaluate MP-2001 for analgesic activity using morphine and meperidine as comparison standards.

The procedures used were the tail-flick test in rats [F. E. D'Amour and D. L. Smith, *J. Pharmacol.*, **72**, 74 (1941)] and a variation of the titration method [B. Weiss and V. G. Laties, *Science*, **125**, 1575 (1958)] in a cynomolgous monkey. Our experience with the tail-flick technique revealed the necessity for rigid control of several critical variables to prevent false positives in the use of this test. We have discussed this elsewhere in detail [I. Geller and L. R. Axelrod, presented at the International Symposium on Pain, Paris, France, April 11–13, 1967]. These variables include ambient temperature, pretraining of animals, and sudden changes in exteroceptive stimuli. The titration method involves the periodic delivery to an animal of electric shocks of successively increasing intensities. In our procedure, the monkey was able to reduce the shock intensity to zero by pressing a lever. After a period of training, resets to zero generally occurred at the same shock level throughout a 6-hr experimental session.

Morphine and meperidine were prepared in water and MP-2001 was prepared in propylene glycol. The drugs were administered intraabdominally to the rats and intravenously to the monkey. Morphine and meperidine were both active in the tail-flick test, yielding AD_{50} values of 3.5 and 10.6 mg/kg, respectively. MP-2001, in a dose range of 1.0 and 16.0 mg/kg, showed no activity in this test. In the titration test, following intravenous administrations of morphine at 2.0 and 3.0 mg/kg and meperidine at 12.5 mg/kg, resets of shock levels to zero occurred at intensities above control values. The monkey tolerated higher shock intensities under morphine and meperidine. Intravenous administrations of MP-2001 at 5 and 10 mg/kg were ineffective in this test.

Electron Spin Resonance Studies of Substituent Effects. Correlations with σ Constants [*J. Am. Chem. Soc.*, **88**, 2065 (1966)]. By E. THOMAS STROM, Mobil Research and Development Corp., Field Research Laboratory, Dallas, Texas 75221.

In calculating the ρ values given in the communication, the coordinates were inadvertently reversed so the values cited are really the reciprocals of the slopes. Even if the ρ values had been calculated correctly, they would have units of gauss and would be meaningless in comparing the sensitivity of the hyperfine splitting constants to substituent. If the ratio $A^{H}_{sub}/A^{H}_{unsub}$ is plotted *vs.* σ, however, the slope will be unitless and its value will be a measure of the sensitivity of the system