The mass spectra of the methyl 2-, 4-, and 5-pyrimidyl ketones **9**, **10**, and **11** show that loss of ketene (122 → 80) is an important mode of fragmentation in the 2 and 4 isomers **9** and **10** but not in the 5 isomer **11**, where α cleavage (122 → 107) predominates. This suggests that the loss of ketene involves a McLafferty-type rearrangement via a ring nitrogen atom and that the rearrangement can occur by way of a five-membered transition state. Since neither loss of ketene nor type I cleavage is observed photochemically in ketones **9** and **10**,[4a] there appears to be little analogy existing between the mass spectral and photochemical behavior of the methyl pyrimidyl ketones **9–11**.

From the above discussion it is clear that the best correlation of photochemical and mass spectral decomposition of alkyl pyrimidyl ketones exists in the 5-alkyl systems. While the 4-alkyl pyrimidyl ketones show good correlation when the alkyl substituent is ethyl and propyl, they show poorer correlation when it is methyl or butyl. This is in contrast to the 2-alkyl pyrimidyl ketones, which show virtually no correlation at all. The good correlation observed in the 5-alkyl pyrimidyl ketones in comparison to the isomeric 2- and 4-alkyl ketones can best be explained in terms of stereochemical and stereoelectronic factors. In the 5-alkyl ketone systems the geometrical features of the ketones ensure little to no involvement of a ring nitrogen atom in both photochemical and electron impact induced reactions. This leads to behavior in these ketones which is similar to that reported[3,5] for butyrophenone, valerophenone, and the 3- and 4-butyryl and valeryl pyridines. In the case of the 2- and 4-alkyl pyrimidyl ketones the close proximity of a ring nitrogen atom to the reaction center necessitates its involvement. The degree of involvement, however, will depend to a great extent on the relative electron densities of the nitrogen atoms in the excited ketones. When the nature of the electron densities of these atoms in the electronically excited state differ substantially from their relative charge densities in the corresponding ionized state, the photochemical and mass spectral behavior of the ketones will show poor correlation. This appears to be the case for the 4-butyl pyrimidyl ketone **7**, where exclusive type II reaction occurs photochemically and competitive nitrogen and oxygen hydrogen atom abstraction occurs in the mass spectrometer. This is also apparently true of the 2-propyl and 2-butyl pyrimidyl ketones **1** and **6** and of the 2-butyryl and 2-valeryl pyridines,[3,5] where exclusive type II cleavage occurs photochemically and a McLafferty-type rearrangement via a ring nitrogen atom predominates upon electron impact.

Experimental Section

The recorded mass spectra were obtained with an LKB 9000 mass spectrometer at a nominal ionizing voltage of 70 eV.

The alkyl pyrimidyl ketones were prepared as previously described[2] and were purified by gas chromatography.

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A Method for Cleaving 2,4-Dinitrophenylhydrazones to Ketones

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2,4-Dinitrophenylhydrazone (2,4-DNP) derivatives of ketones and aldehydes are important, both because of their use in purifying and characterizing the parent compounds, and because of their occasional use in synthesis.[1] Regeneration of the parent carbonyl compound from a 2,4-DNP can present severe problems, however. The major difficulty is that 2,4-DNP's are stable to acid hydrolysis. A variety of methods have been devised to overcome this problem.

The most common method of cleaving a 2,4-DNP is to effect an exchange reaction with another carbonyl compound such as pyruvic acid[2,3] or levulinic acid.[4] Yields are often unacceptable in these reactions, however. A second method is to ozonize the C=N double bond at low temperatures.[1,5] The reaction works moderately well, but is clearly incompatible with the presence of unsaturation within the molecule. A third general method is to activate the 2,4-DNP toward hydrolysis. This is usually done by reducing the nitro groups to amines with either stannous ion,[6,7] lithium aluminum hydride,[8] or chromous ion.[9] The resulting 2,4-diaminophenylhydrazone then hydrolyzes. Yields are generally acceptable if there are no other reactive functional groups present, but acidic conditions are necessary.

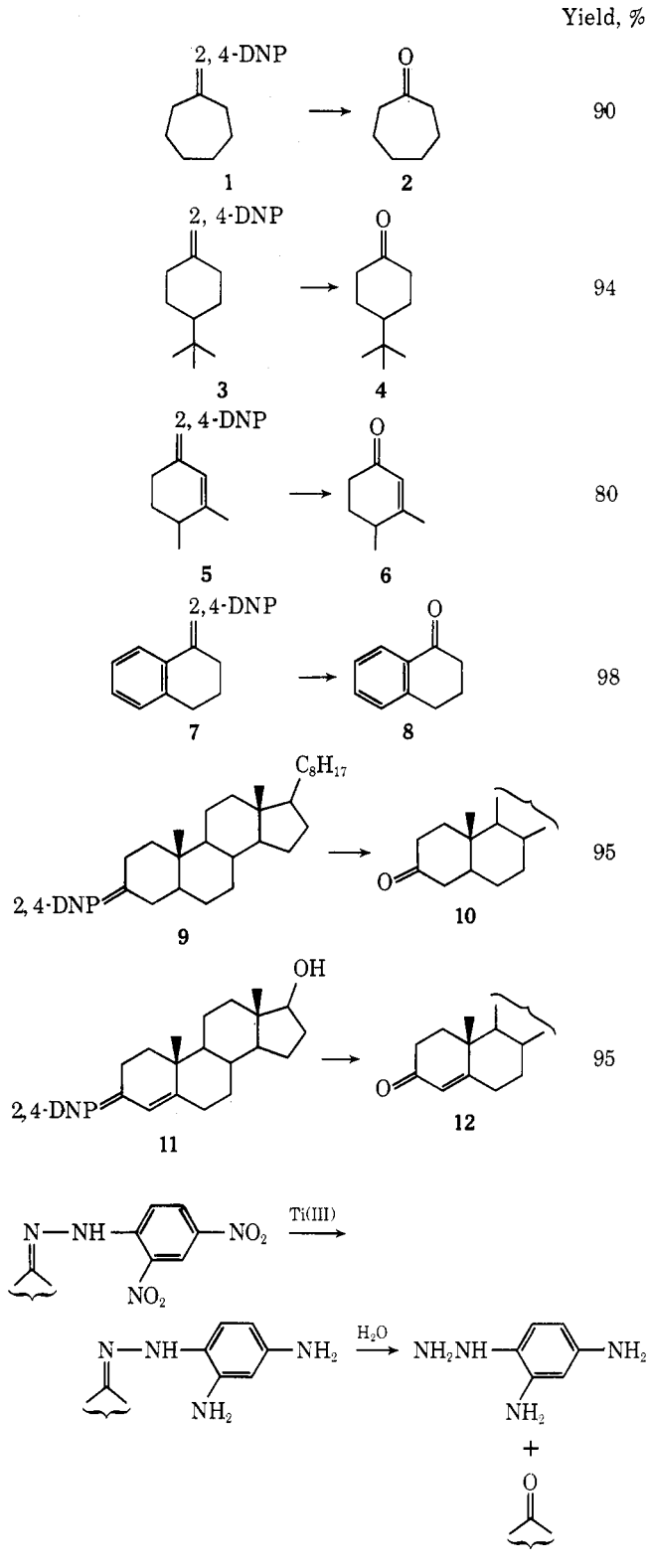
We have had several occasions in our own laboratory to regenerate the parent carbonyl compounds from their 2,4-DNP's, and we have found aqueous titanous ion to be an excellent and convenient new reagent for effecting this transformation.[10] Some of our results are given in Chart I.

We believe that this method has several advantages over presently known ones. The reaction works for a variety of cases, both saturated and unsaturated, and has given high yields of carbonyl products in all examples tested. Further, titanous ion is inexpensive and commercially available as a stable 20% aqueous solution.[11] It thus does not have to be prepared freshly before use as does chromous ion. Most important, however, is the fact that the reaction can be carried out under neutral conditions whereas other methods require acidic conditions.

Mechanistically, there are two obvious possibilities for the course of the cleavage reaction. The simplest possibility is to assume that titanous ion acts by reducing the nitro groups to amino groups in a manner similar to that of stannous or chromous ion, and that the resulting 2,4-diaminophenylhydrazone then undergoes hydrolysis.

It is well known that titanous ion can rapidly reduce nitroarenes to aminoarenes,[12] and thus we cannot completely rule out this mechanism. We nevertheless feel that it is unlikely because, as we have demonstrated, the cleavage reaction works equally well under buffered conditions, and we consider it surprising that a 2,4-diaminophenylhydrazone would hydrolyze so readily at neutral pH.

Chart I
Reaction of 2,4-Dinitrophenylhydrazones with Titanous Ion



A second possibility, and one which we favor, is that titanous ion acts by first reducing the nitro groups, and then by cleaving the hydrazone N–N bond to generate an imine. The imine should then hydrolyze readily to a carbonyl compound.

Titanous ion is well known for its ability to cleave the N–O bond of oximes[13] and nitro compounds,[14] and the S–O bond of sulfoxides.[15] We consider the cleavage of the N–N hydrazone bond to be exactly analogous. Good evidence for this hypothesis comes from the fact that when we examined the basic reaction products from the titanous ion cleavage of 2,3-dimethylcyclohexenone 2,4-DNP, we isolated 1,2,4-triaminobenzene rather than 2,4-diaminohydrazine. Clearly, titanous ion is capable of cleaving a N–N bond, and we feel that this supports our hypothesis.

In summary, we have developed a mild, new method for the regeneration of carbonyl compounds from their 2,4-dinitrophenylhydrazones. The process proceeds in high yield, and has considerable advantage over other known procedures.

Experimental Section

General Reaction Procedure for the Reductive Cleavage of 2,4-Dinitrophenylhydrazones. Cholestanone (10). Cholestanone 2,4-DNP (0.34 g, 0.60 mmol) was dissolved in 30 ml of dry dimethoxyethane, and a 20% aqueous solution (1.6 *M*) of titanium trichloride (5.60 ml, 9.0 mmol) was added. The reaction mixture was refluxed for 30 min under a nitrogen atmosphere, then cooled, diluted with water, and extracted with ether. The combined ether extracts were washed with water and with saturated brine, then dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. The solid residue was recrystallized from 2-propanol to give 220 mg (95%) of pure cholestanone, mp 128–130°. The product was identified by melting point and by comparison of its infrared and NMR spectra with those of an authentic sample.

In a similar manner, the following compounds were prepared.

Testosterone (12) was prepared by reduction of its 2,4-DNP (0.26 g, 0.56 mmol) with a 20% aqueous $TiCl_3$ solution (5.3 ml, 8.4 mmol): yield 0.15 g (95%); mp 154–155; identified by melting point and by comparison of infrared and NMR spectra with those of an authentic sample.

α-Tetralone (8) was prepared by reduction of its 2,4-DNP (0.53 g, 1.62 mmol) with 20% aqueous $TiCl_3$ (15 ml, 24.2 mmol): yield 0.23 g (98%); purified by chromatography on silica gel; identified by comparison of infrared and NMR spectra with those of an authentic sample.

Cycloheptanone (2) was prepared by reduction of its 2,4-DNP (0.61 g, 2.1 mmol) with 20% aqueous $TiCl_3$ (19.6 ml, 31.3 mmol): yield 210 mg (90%); purified by chromatography on silica gel; identified by comparison of infrared and NMR spectra with those of an authentic sample.

3,4-Dimethylcyclohexenone (6) was prepared from its 2,4-DNP (0.50 g, 1.65 mmol) by reduction with 20% aqueous $TiCl_3$ (15.5 ml, 24.7 mmol): yield 164 mg (80%); purified by chromatography on silica gel and identified by comparison of infrared and NMR spectra with those of an authentic sample.

4-*tert*-Butylcyclohexanone (4) was prepared from its 2,4-DNP (0.40 g, 1.2 mmol) by reduction with 20% aqueous $TiCl_3$ (11.25 ml, 18 mmol): yield 175 mg (94%); purified by chromatography on silica gel and identified by comparison of infrared and NMR spectra with those of an authentic sample.

The above reactions could also be carried out at a buffered pH by adding ammonium acetate to the reaction until the desired pH was obtained.

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Concerning the Stereochemistry of Cyclohexenone Alkylations

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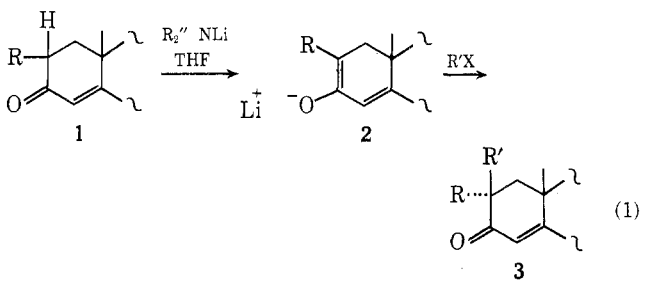
Recently we reported[1] that substituted cyclohexenone systems can be selectively alkylated at the α' position via the kinetically favored cross-conjugated dienolate base (eq 1). In the case of cholest-4-en-3-one (1, R = H) the product



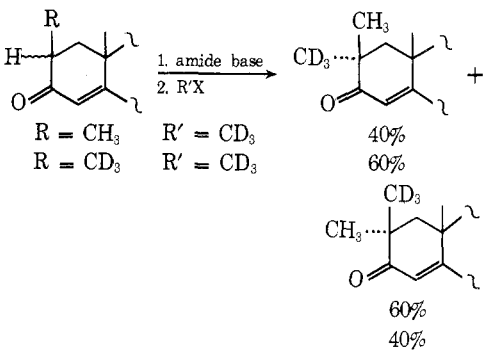
1 2 3 (1)

of methylation (R′X = CH_3I) was regarded as the previously unknown 2β-methyl epimer (3, R′ = CH_3, R = H) because it appeared to be homogeneous (TLC analysis on silical gel and alumina), melted sharply at 110–111°, and was different from the known α epimer[2] (mp 122–124°) into which it was transformed by the action of base.

A subsequent study of the 100-MHz ^1H NMR spectrum of this substance suggested that it might be a mixture of epimers, and this has now been confirmed by high-pressure liquid chromatography on a 15-cm column packed with Zorbex (a small diameter porous silica provided by Du Pont). The roughly 60:40 α:β composition of this epimeric mixture has been further indicated by careful europium shift measurements conducted by Dr. D. N. Kirk and R. D. Burnett of Westfield College, University of London. In the latter work the C-2 methyl doublets, which normally overlapped at ca. δ 1.05 ppm, were caused to shift to a lower field than the C-19 methyl signals for the α and β epimers. Although the methyl doublets still overlapped, they were easily discernible and well separated from the other methyl signals.

At this point, two possible explanations for the inhomogeneous nature of the methylation product were considered. (1) The alkylation reaction itself may have been essentially nonstereoselective. (2) A stereoselective alkylation step may have been followed by a partial epimerization of the kinetically favored β-methyl product. A combination of these factors may also be operating. Since the same mixture of product epimers was obtained from several experiments in which the time and temperature of the alkylation step varied, we were inclined to favor the first rationale. However, it seemed appropriate to settle the question by effecting the alkylation of a similar substrate, chosen so that product epimerization could not take place.

The possibility of effecting a second alkylation reaction at C-2 was demonstrated by methylation of 2α-methylcholest-4-en-3-one (1, R = CH_3) under the conditions noted in eq 1. Formation of 2,2-dimethylcholest-4-en-3-one (3, R = R′ = CH_3)[3] in 97% yield follows the previously stated general rule[1,4] that *α'-proton abstraction is kinetically favored in α,β-unsaturated ketones*. By effecting this sequential dimethylation with CH_3I followed by CD_3I, and in a second case with CD_3I followed by CH_3I, we have been able to ascertain the stereoselectivity of the second alkylation step (eq 2).



(2)

The very poor stereoselectivity observed for these alkylation reactions is similar to that reported for the methylation of 2-cyanocholest-4-en-3-one,[5] and is presumably due in part to a flattening of the six-membered ring caused by the double bond. Since other factors may influence the stereochemistry of β-keto nitrile alkylation reactions,[6] this similarity may not be very significant. While this manuscript was being prepared, Girard and Conia reported[7] that cyclopropanation of the trimethylsiloxy derivative of the 2-enolate base derived from testosterone proceeded with essentially no stereoselectivity.

Experimental Section

All reactions involving strong bases were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Melting points were obtained with a Hoover-Thomas apparatus or on a Reichert hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian A-60, T-60, and HA-100 spectrometers with deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

General Procedure for α'-Methylation. To a cold solution of 1.30 mmol of isopropylcyclohexylamine in 0.5 ml of dry tetrahydrofuran (THF) was added 1.25 mmol of *n*-butyllithium in hexane. After this mixture was stirred at 0° for 15 min, 1.0 mmol of the α,β-unsaturated ketone in 5 ml of THF was slowly added and the resulting solution was maintained at 0° for 90 min. Following rapid addition of 4.00 mmol of methyl iodide, the reaction mixture was allowed to warm to room temperature and held there for 3 hr before being mixed with water and extracted with ether. The combined ether extracts were washed (twice each) with water and brine, dried, and distilled under reduced pressure.

Results of Specific Methylations. A. Cholest-4-en-3-one. The yield of crude 2-methylcholest-4-en-3-one was 98%. Recrystal-