(minimum inhibitory concentration) of 50 μg/ml against both *Staphylococcus aureus* SC 2399 and *Streptococcus pyogenes* SC 3862. The MIC of the parent cephalosporin against the same two organisms was 1 μg/ml. More extensive biological evaluation is in progress.

Further experiments are needed to determine to what extent the present results will require refinement or alteration of the proposed mechanism of inhibition[1,2] of bacterial enzymes by β-lactam antibiotics.[5]

Acknowledgment. We are indebted to Felix Pansy and Harold Basch for biological data and to Dr. Allen Cohen and Dr. M. Puar for spectroscopic data. We are especially thankful to Professor Strominger, who suggested the problem to us and has enthusiastically followed our work.

(5) NOTE ADDED IN PROOF. It is interesting to note that the 7-methoxycephalosporin C which has been isolated by R. Nagarajan, *et al.* (R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971)) is reported to be more active toward gram negative organisms than is cephalosporin C.

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A New Method for the 1,4 Addition of the Methylenecarbonyl Unit (-CH_2CO-) to Dienes

Sir:

Since the reaction of ketenes with 1,3-dienes leads to cyclobutanone formation rather than Diels–Alder addition,[1] other approaches are required for the synthesis of structures corresponding to the 1,4 addition of the -CH_2CO- unit to 1,3-dienes. The use of sequences involving the addition of 2-acetoxyacrylonitrile[2] and 2-chloroacrylonitrile[3,4] as dienophiles has been described for cyclopentadiene (and also cyclohexadiene in the case of the latter). However, these dienophiles are of only moderate reactivity and appear to be of limited utility with sensitive or less reactive dienes. Further, the requirement of strong base for the conversion of the initial adduct into the corresponding ketone precludes the use of this method for the synthesis of Δ^3-cyclohexenones from acyclic dienes.

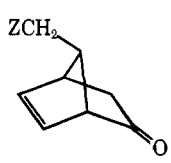
The discovery that the reaction of 2-chloroacrylonitrile with dienes is strongly catalyzed by dry cupric fluoroborate led to the successful synthesis of the 7-substituted bicyclo[2.2.1]heptenones Ia and Ib from the corresponding 5-monosubstituted cyclopentadienes.[5,6] This process represents the first example of the successful use of a 5-monosubstituted cyclopentadiene in this way and a key initial stage of the synthesis of the natural primary prostaglandins.[7-9] Although the cupric-catalyzed Diels–Alder addition extends the applicability of 2-chloroacrylonitrile to certain sensitive dienes, our interest in the general synthetic problem and the development of optimum synthetic routes to prostanoids[10] has prompted further studies in this area. These have led to the excellent general method which is described herein.

The readily accessible 2-chloroacrylyl chloride[11,12] exhibits high dienophilic reactivity (comparable to maleic anhydride) and further, because of its geminate substitution, reacts selectively with various 5-substituted cyclopentadienes (without prototropic isomerization) to form adducts in which the 7 substituent is *exclusively* anti to the bridge bearing the chloro and chloroformyl groups.[13] The effectiveness of 2-chloroacrylyl chloride as a dienophile and a process for the conversion of the resulting adducts to ketones by replacement of Cl and COCl by oxygen can be illustrated by the synthesis of the keto benzyl ether Ia *without isolation of intermediates.* An ethereal solution of 5-benzyloxymethylcyclopentadiene[6] (*ca.* 1 *M*) and 2-chloroacrylyl chloride at 0° for 18 hr furnished the adduct IIa (as a 2:1 mixture of exo and endo acid chlorides by nmr analysis) in *ca.* 99% yield. Treatment of IIa with sodium azide in dimethoxyethane gave the corresponding acyl azide which upon heating underwent Curtius rearrangement to the isocyanate, leading finally after hydrolysis with aqueous acetic acid to the bicyclic ketone Ia in *ca.* 90% yield (overall for the five reactions from cyclopentadiene and chloromethyl benzyl ether). The ease of operation and practicality of this synthesis can be seen from the following experimental procedure which is given as a model.

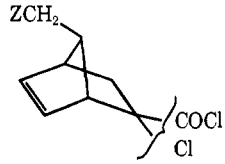
7-*syn*-Benzyloxymethyl-2-norbornen-5-one (Ia). Chloromethyl benzyl ether (15.65 g) was added over 20 min to a cooled (−22 to −20°), stirred slurry of thallous cyclopentadienide[6] in 40 ml of dry ether (under argon). After 7 hr the mixture was filtered (at below −20°), the solid (TlCl) was washed with dry ether (three 20-ml portions), and the combined chilled ethereal solution was treated with 2-chloroacrylyl chloride (16.25 g). After 18 hr at 0°, the solvent was removed under reduced pressure to afford the Diels–Alder adduct (30.82 g, 99%) as a colorless oil.[14a] A solution of the adduct in 306 ml of dry dimethoxyethane was stirred with 12.8 g of sodium azide at 25° for 1.5 hr, and the mixture was filtered. The filtrate was heated to reflux for 2 hr, cooled to 25°, and treated with 60 ml of acetic acid–water (2:1) at 55–60° until infrared analysis of an aliquot indicated the lack of isocyanate absorp-

(1) See, for example, J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962).
(2) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956).
(3) H. Krieger, *Suom. Kemstilehti B*, **36**, 68 (1963); J. Paasivirta and H. Krieger, *ibid.*, *B*, **38**, 182 (1965); J. Paasivirta, *ibid.*, *A*, **39**, 120 (1966).
(4) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, **33**, 2211 (1968).
(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).
(6) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971).
(7) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).
(8) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970).
(9) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971).
(10) We have found this to be a useful term which can be applied to designate the whole family (superset) of natural prostaglandins and prostaglandin-like compounds.
(11) C. S. Marvel, J. Dec, H. G. Cooke, Jr., and J. C. Cowan, *J. Amer. Chem. Soc.*, **62**, 3495 (1940).
(12) M. Seefelder, German Patent 1,167,819 (April 1964); *Chem. Abstr.*, **61**, 1761 (1964).
(13) Not surprisingly, maleic anhydride and dimethyl acetylenedicarboxylate add to 5-monosubstituted cyclopentadienes to afford mixtures of 7-syn and 7-anti isomers.
(14) (a) Infrared and nmr spectra were in agreement with the assigned structure. (b) Satisfactory analytical data were obtained for this intermediate.

tion at 2250 cm^{-1} (*ca.* 30 min). Evaporation of solvent under reduced pressure (25°), addition of water, extraction with pentane, and removal of pentane afforded the bicyclic ketone Ia, 20.53 g (90.6%) of 97–98% purity by gas chromatographic (gc) analysis. The identity of this product with Ia prepared by the previously described route was established by spectroscopic, chromatographic, and chemical comparison.[15]



Ia, Z = $C_6H_5CH_2O$
Ib, Z = CH_3O
Ic, Z = C_6H_5CONH

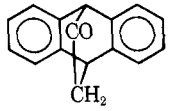


IIa, Z = $C_6H_5CH_2O$
IIb, Z = CH_3O
IIc, Z = C_6H_5CONH

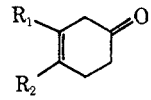
In a similar manner the Diels–Alder adduct IIb was prepared *via* 5-methoxymethylcyclopentadiene[6] and 2-chloroacrylyl chloride and transformed into the pure bicyclic ketone Ib[5-7] (yield 82%, based on chloromethyl methyl ether and thallous cyclopentadienide). The benzoylamino ketone Ic,[14] mp 125.5–126°, was also formed in good yield by the above described process from the adduct IIc, which in turn was obtained by alkylation of thallous cyclopentadienide by iodomethylbenzamide (in tetrahydrofuran) followed by addition to 2-chloroacrylyl chloride.

Cyclopentadiene and 2-chloroacrylyl chloride in ether (*ca.* 1.2 *M*) at 0° for 18 hr gave the expected mixture of exo and endo Diels–Alder adducts in 94% yield, and this mixture was converted *via* the Curtius route to 5-norbornen-2-one[14a] in 94% yield (gc analysis).

Anthracene and 2-chloroacrylyl chloride in dimethoxyethane solution (1 *M*) at reflux for 5 hr afforded the Diels–Alder adduct quantitatively, and this was transformed by the Curtius route to the ketone III, mp 146–147°,[14] in 87% overall yield from anthracene.



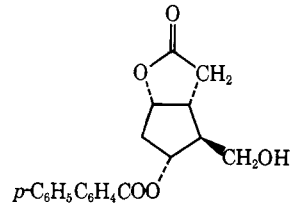
III



IV, $R_1 = H$; $R_2 = CH_3$
V, $R_1 = R_2 = CH_3$

The known ketone IV[14a] was obtained by the new method from isoprene in 83.5% overall yield, and the ketone V[14a] was prepared from 2,3-dimethylbutadiene (77%).[16]

(15) Using this procedure in the route previously described [E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971)], the key prostanoid intermediate i is obtained in a stereospecific process having an average yield per step of 95% and not involving chromatography.



i

(16) The Diels–Alder reactions with isoprene and 2,3-dimethylbutadiene were conducted at 0° for 16 hr. In the preparation of the ketones IV and V, the thermal rearrangement of the acyl azide was carried out in benzene at reflux for 1.5 hr. The hydrolysis of isocyanate was accomplished using a 1:1 mixture of tetrahydrofuran and 5% aqueous oxalic acid at 25° for 10 hr; under these conditions the β,γ-unsaturated ketones IV and V were obtained with little or no α,β isomer. The more stable conjugated isomers can be prepared by isomerization with 1 *N* hydrochloric acid at 25° for 15 hr.

The method described herein for the 1,4 addition of the $-CH_2CO-$ unit to 1,3-dienes is operationally simple, broadly applicable, and basically efficient. Many interesting uses can be foreseen for the synthesis of cyclic ketones.

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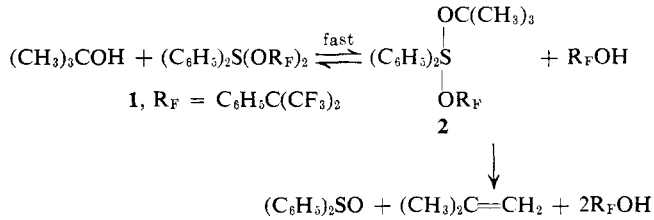
Sulfuranes. III. A Reagent for the Dehydration of Alcohols

Sir:

The use of stable, crystalline sulfurane **1** as a dehydrating agent for the conversion of alcohols to alkenes was suggested by our preliminary observation[1] that the alkoxy ligands of **1** rapidly exchange with added alcohols, and by the earlier observation[2] of isobutylene in the product mixture from a perester decomposition postulated to give a sulfurane as an intermediate. We here report results which suggest that **1** is indeed a dehydrating agent with unique properties, potentially of great synthetic utility.



1, $R_F = C_6H_5C(CF_3)_2$

2

$(C_6H_5)_2SO + (CH_3)_2C{=}CH_2 + 2R_FOH$

The dehydration of *tert*-butyl alcohol by sulfurane **1** in chloroform at −50° is complete within seconds to yield isobutylene. We suggest that the ionization of sulfurane **2** to give the *tert*-butoxysulfonium ion (perhaps catalyzed by a molecule of the acidic R_FOH) is followed by rapid abstraction of a β proton. Secondary alcohols, which dehydrate more slowly, give nmr evidence for the postulated rapidly equilibrating mixtures of sulfuranes at −50°.

Earlier attempts to dehydrate tricyclopropylcarbinol (**3**) using sulfuric acid or phosphorus pentoxide failed to yield any of olefin **4**.[3] Dehydration with sulfurane **1**, however, gives 32% (by nmr, 25% by isolation) of **4** in a striking demonstration of the synthetic utility of this new dehydrating agent. The method used for isolation of **4** is of rather general applicability. The acidic R_FOH is removed by washing with 10% aqueous sodium hy-

(1) For earlier papers in this series, see J. C. Martin and R. J. Arhart, *J. Amer. Chem. Soc.*, **93**, 2339, 2341 (1971).
(2) W. G. Bentrude and J. C. Martin, *ibid.*, **84**, 1561 (1962); D. L. Tuleen, W. G. Bentrude, and J. C. Martin, *ibid.*, **85**, 1938 (1963); see also C. Walling and M. J. Mintz, *J. Org. Chem.*, **32**, 1286 (1967).
(3) H. Hart and P. A. Law, *J. Amer. Chem. Soc.*, **84**, 2462 (1962).