(ratio 1.87 at 250°) were obtained on chromatography, and a comparison of the ultraviolet and infrared spectra of the starting material and collected material indicated that a cyclization corresponding to the D_2 transformation had occurred. The observed retention times may be regarded as arising from pyrovitamin D_3 and isopyrovitamin D_3.

Although the chromatography of vitamins D_2 and D_3 is accompanied by a thermal change, it may be possible to use the resulting separation patterns for identification or estimation purposes. The "pyro" and "isopyro" compounds do not occur naturally, and the relative retention times are quite distinct from those of the provitamins. These methods might also be useful in studying irradiation mixtures.

The techniques used here were those described in previous work in steroid separations.[1]

(1) W. J. A. VandenHeuvel, C. C. Sweeley and E. C. Horning, THIS JOURNAL, **82**, 3481 (1960) (steroids); W. J. A. VandenHeuvel, C. C. Sweeley and E. C. Horning, *Biochem. Biophys. Res. Comm.*, **3**, 33 (1960) (sex hormones and bile acids); W. J. A. VandenHeuvel and E. C. Horning, *ibid.*, **3**, 356 (1960) (adrenal cortical steroid hormones); W. J. A. VandenHeuvel, C. C. Sweeley and E. C. Horning, "Separation of Steroids by Gas Chromatography," Symposium on Drugs Affecting Lipid Metabolism, Milan, Italy, June 2–4, 1960 (sterols and sterol esters); C. C. Sweeley and E. C. Horning, *Nature*, **187**, 144 (1960) (steroids); W. J. A. VandenHeuvel, E. C. Horning, Y. Sato and N. Ikekawa, *J. Org. Chem.*, in press (steroidal amines); R. K. Beerthuis and J. H. Recourt, *Nature*, **186**, 372 (1960) (sterols).

LABORATORY OF PHYSICAL BIOLOGY HERMAN ZIFFER
NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS W. J. A. VANDENHEUVEL
NATIONAL HEART INSTITUTE E. O. A. HAAHTI
BETHESDA 14, MARYLAND E. C. HORNING

RECEIVED NOVEMBER 18, 1960

EFFECT OF SOLVENT ON RATE OF BASE-CATALYZED PROTON ABSTRACTION FROM CARBON

Sir:

In connection with our study of electrophilic substitution at saturated carbon,[1] we observed that with potassium *tert*-butoxide as a basic catalyst, optically active 2-phenylbutane could be racemized at a much lower temperature in dimethyl sulfoxide than in *tert*-butyl alcohol as solvent. Kinetic studies have now revealed that the rates of proton abstraction from carbon by alkoxide anions can be made to vary by as much as an estimated nine powers of ten by simply a change in solvent.

Racemization of 2-methyl-3-phenylpropionitrile (I) was found to proceed at a convenient rate in mixtures of methanol and dimethyl sulfoxide with metal methoxides as bases. In other studies[2] hydrogen-deuterium exchange and racemization rates were found to be equal with this substrate in ethylene glycol and in *tert*-butyl alcohol, and these two rates for this nitrile are presumed to be equal in any solvent–base system. At concentrations of base up to 0.01 molar, the rates were found to be cleanly first order in base and in substrate, and independent of the nature of the cation of the base (lithium, sodium or potassium) over a solvent composition that ranged from pure methanol to 3% methanol–97% dimethyl sulfoxide (by weight). A single rate determination was made at 1.5% methanol–97% dimethyl sulfoxide (by weight) with potassium methoxide as base. Rates at 76.5% and higher dimethyl sulfoxide concentration were obtained at 25° by direct polarimetric measurement, whereas at lower concentrations, rates were determined at two higher temperatures with the ampoule technique, and rate constants were extrapolated to 25°. For purposes of comparison, a rate run was also conducted at 25° in *tert*-butyl alcohol with 0.0016 *M* potassium *tert*-butoxide as base. Table I records the relative rate factors.

TABLE I

RELATIVE RATES OF RACEMIZATION OF NITRILE (I)

Solvent (% by weight)	Base *M* is Li, Na, K	Rel. rates (25°)
100 CH_3OH–0(CH_3)$_2SO$	CH_3OM	1
75 CH_3OH–25 (CH_3)$_2SO$	CH_3ONa	3.2×10^1
49.6 CH_3OH–50.4 (CH_3)$_2SO$	CH_3ONa	1.6×10^2
23.5 CH_3OH–76.5 (CH_3)$_2SO$	CH_3OLi	4.9×10^3
10 CH_3OH–90 (CH_3)$_2SO$	CH_3OM	1.3×10^5
3 CH_3OH–97 (CH_3)$_2SO$	CH_3OM	1.4×10^6
1.5 CH_3OH–98.5 (CH_3)$_2SO$	CH_3OK	$\sim 1.05 \times 10^7$
0 CH_3OH–100 (CH_3)$_2SO$	CH_3OK	$\approx 10^9$ (estd.)
100 (CH_3)$_3COH$	(CH_3)$_3COK$	4.1×10^6

With optically active 1-phenylmethoxyethane as substrate, a similar but less extensive comparison was made between the rates of racemization with potassium *tert*-butoxide as base in dimethyl sulfoxide on the one hand, and *tert*-butyl alcohol on the other. In the latter solvent, the rate was measured at 173°, and in the former, at 49° and 75°. Extrapolation of the rate constant in dimethyl sulfoxide to 173° gave a value $>10^6$ greater than the value of the rate constant in *tert*-butyl alcohol. The rate of hydrogen–deuterium exchange is at least a factor of ten higher than the rate of racemization for this system in *tert*-butyl alcohol, but the two rates are equal in dimethyl sulfoxide.[3] Thus the rate of proton removal from 1-phenylmethoxyethane by potassium *tert*-butoxide is $\sim 10^7$ greater in dimethyl sulfoxide than in *tert*-butyl alcohol. The combined data represent a spread of eleven powers of ten between the rates of proton removal from carbon by methoxide ion in methanol and by potassium *tert*-butoxide in dimethyl sulfoxide. The vastly enhanced activity of alkoxide ions in dimethyl sulfoxide over their activity in alcohols is attributed to the absence of alkoxide-solvent hydrogen bonds in dimethyl sulfoxide which are present in the hydroxylic solvents. Preliminary experiments indicate that tetramethylene sulfone as solvent[4] also enhances the catalytic activity of alkoxide ions, but less than dimethyl sulfoxide.

These observations suggest that the rates of many base-catalyzed reactions can be enhanced greatly by substitution of dimethyl sulfoxide for the usual hydroxylic solvents. A dramatic ex-

(1) D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen and J. Allinger, THIS JOURNAL, **81**, 5774 (1959).

(2) D. J. Cram, W. D. Nielsen and B. Rickborn, *ibid.*, **82**, 6415 (1960).

(3) D. J. Cram, C. A. Kingsbury and B. Rickborn, *ibid.*, **81**, 5835 (1959).

(4) See C. H. Langford and R. L. Burwell, Jr., *ibid.*, **82**, 1503 (1960).

ample is found in the conversion of bromobenzene to *tert*-butyl phenyl ether in 86% yield by reaction at 25° in a solution of dimethyl sulfoxide saturated with sublimed potassium *tert*-butoxide (15 hr.). The same reaction was found to proceed 35% of the way in 9 hr. in *tert*-butyl alcohol at 175°. Through use of competition experiments, fluorobenzene was found to react with sublimed potassium *tert*-butoxide in dimethyl sulfoxide to give the same product, but at a rate approximately 1/25 as fast as bromobenzene. In similar experiments at 100° in dimethyl sulfoxide, sublimed potassium *tert*-butoxide was found to convert *o*-fluorotoluene to *o*-cresol which contained less than 3% *m*-cresol, and *o*-bromotoluene to a mixture of 4 parts of *m*-cresol to 1 part of *o*-cresol. These reactions probably produced *tert*-butyl aryl ethers as the initial products, which were converted to their respective phenols during vapor phase analysis of the products The results strongly support the hypothesis that the aryl bromides mainly underwent elimination reactions to give aryne intermediates, which added *tert*-butyl alcohol to give the aryl ethers. In contrast, the aryl fluorides appeared to undergo direct substitution reactions to give the aryl ethers. Thus substitution of dimethyl sulfoxide for the more ordinary hydroxylic solvents in both acid-base and substitution reactions gives a marked reaction rate enhancement.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
LOS ANGELES 24, CALIFORNIA

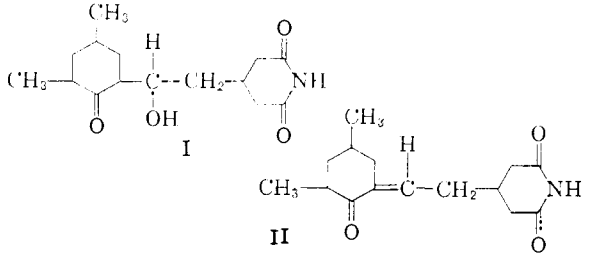
DONALD J. CRAM
BRUCE RICKBORN
GRAHAM R. KNOX

RECEIVED NOVEMBER 9, 1960

THE SYNTHESIS OF ANHYDROACTIDIONE

Sir:

Actidione (cycloheximide), the well known antifungal antibiotic from streptomycin-producing strains of *Streptomyces griseus* was first reported[1] as a crystalline solid in 1947. Shortly thereafter the structure was shown to be β-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-glutarimide, I, as the result of an extensive degradation and transformation study.[2] One of the key transformations in that study was the treatment of Actidione with phosphorus pentoxide to yield the simple dehydration product anhydroactidione, II, and the purpose of this paper is to report the synthesis of anhydroactidione. This preparation represents



I

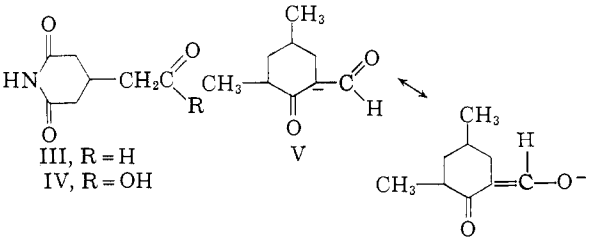
II

the first synthetic evidence for the over-all skeletal structure of Actidione, *i.e.*, the relationship of the moieties of glutarimide and 2,4-dimethylcyclohexyl.

(1) B. E. Leach, J. H. Ford and A. J. Whiffen, THIS JOURNAL, **69**, 474 (1947).

(2) E. C. Kornfeld, R. G. Jones and T. V. Parke, *ibid.*, **71**, 150 (1949).

Since Actidione is known[2] to undergo a reverse aldol reaction to yield *d*-2,4-dimethylcyclohexanone, the general approach to the synthesis of anhydroactidione was to selectively attach the proper glutarimide moiety to 2,4-dimethylcyclohexanone. Until now the intermediate glutarimide-β-acetaldehyde, III, represented the closest synthetic approach to the structure of Actidione,[3] and in the present study its preparation followed a somewhat different route. Diethyl glutaconate, prepared according to the method of Schaeffer and Baker,[4] underwent a Michael condensation[5] with ethyl cyanoacetate to yield diethyl-β-(α'-cyano-α'-carbethoxy)-methylglutarate, b.p. 132–134° (0.05 mm.),[6] $n^{25}D$ 1.4467 (*Anal.* Calcd. for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.29; H, 6.92; N, 4.81), and subsequent hydrolysis and decarboxylation in boiling concentrated hydrochloric acid afforded methanetriacetic acid, m.p. 126–127°.[5] Pyrolysis of the ammonium salt at about 250° afforded high yields of glutarimide-β-acetic acid, IV, m.p. 172.5–173°,[3] (*Anal.* Calcd. for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.26; H, 5.32; N, 8.21). Then essentially as reported,[3] IV was converted by reduction of the acid chloride to glutarimide-β-acetaldehyde (III), m.p. 121–123°.



III, R = H
IV, R = OH

V

The cyclohexyl portion, 2,4-dimethylcyclohexanone, was prepared both as a single isomer and as a racemate. Actidione underwent a reverse aldol reaction with 10% sodium hydroxide at 2–4° to afford *d*-2,4-dimethylcyclohexanone, b.p. 77–78° (27 mm.), $n^{25}D$ 1.4425, $[\alpha]^{25}D$ + 4.3 (*c* = 6, EtOH).[7] Formylation according to the procedure of Johnson and Posvic[8] yielded *l*-2-hydroxymethylene-4,6-dimethylcyclohexanone, b.p. 83.5–84.5° (9 mm.), $n^{25}D$ 1.4932, $[\alpha]^{25}D$ −27.4 (*c* = 9.6, EtOH)[9] (*Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.01; H, 9.23).

For the final step, it was found that the glutarimide portion, III, reacted with the anion, V, to afford anhydroactidione directly. Thus, an aqueous solution of equimolar quantities of *l*-2-hydroxymethylene-4,6-dimethylcyclohexanone, potassium carbonate, and glutarimide-β-acetaldehyde readily deposited, on standing at room tempera-

(3) D. D. Phillips, M. Acitelli and J. Meinwald, *ibid.*, **79**, 3517 (1957).

(4) H. J. Schaeffer and B. R. Baker, *J. Org. Chem.*, **23**, 625 (1958).

(5) E. P. Kohler and G. H. Reid, THIS JOURNAL, **47**, 2803 (1925).

(6) R. P. Evstigneeva and co-workers, *J. Gen. Chem.* (*U.S.S.R.*), **22**, 1467 (1952).

(7) When prepared by distilling the ketone from 20% sodium hydroxide, as reported,[2] an $[\alpha]^{25}D$ +10.58 was obtained (lit. +11.52), and the infrared spectrum was identical with that of ketone used in the synthesis.

(8) W. S. Johnson and H. Posvic, THIS JOURNAL, **69**, 1361 (1947).

(9) On standing for one day the observed rotation, α, had dropped from −4.5° to −2.64°, the final value corresponding to $[\alpha]^{25}D$ −27.4.