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.

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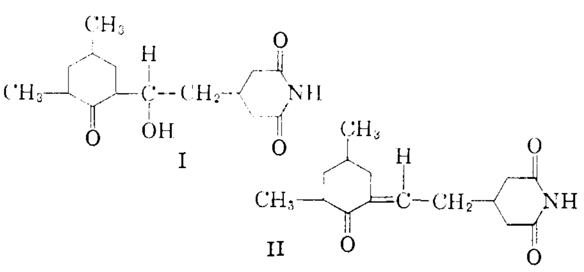
THE SYNTHESIS OF ANHYDROACTIDIONE

Sir:

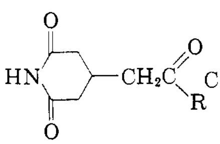
Actidione (cycloheximide), the well known antifungal antibiotic from streptomycin-producing strains of *Streptomyces griseus* was first reported[1] as a crystalline solid in 1947. Shortly thereafter the structure was shown to be *β*-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-glutarimide, I, as 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 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.



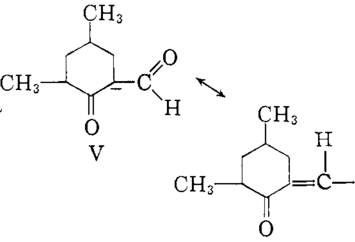
I

II

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-

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[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).

[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.

ture, crude, crystalline anhydroactidione. After one recrystallization from aqueous ethanol analytically pure material, m.p. 130–133°, $[\alpha]^{25}\text{D}$ −12.7 (c = 3.7, $CHCl_3$), was obtained in 46% yield. Exhaustive recrystallizations from aqueous acetonitrile afforded a single isomer of anhydroactidione, m.p. 139–141°, $[\alpha]^{25}\text{D}$ −33.2 (c = 1.7, $CHCl_3$), ultraviolet maximum at 240 mμ (log ϵ = 3.94) in ethanol,[10] (*Anal.* Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.55; H, 8.29; N, 5.25). This compound, by comparison of melting points and mixture melting points, infrared (potassium bromide disk) and ultraviolet spectra, and optical rotations, proved to be identical with authentic anhydroactidione, prepared by dehydration of Actidione with phosphorus pentoxide,[2] or with an aqueous solution of hydrochloric acid and acetic acid. In both cases repeated recrystallizations from aqueous ethanol were required to yield the pure isomer melting at 139–141°.

For comparison, racemic anhydroactidione was prepared. Hydrogenation of 2,4-dimethylphenol[11] followed by dichromate oxidation[2] yielded *dl*-2,4-dimethylcyclohexanone, b.p. 53–54° (8–9 mm.), $n^{25}\text{D}$ 1.4430, semicarbazone (96% yield) melting at 188–189°.[12] The relationship of this ketone with the alkaline degradation ketone already has been demonstrated.[2] Then essentially following the procedure outlined above, there was obtained racemic anhydroactidione, m.p. 118–120°, ultraviolet maximum at 240 mμ (log ϵ = 3.99), infrared spectrum (chloroform solution) identical with that of enantiomorphic anhydroactidione (Found: C, 68.33; H, 7.97; N, 5.33). The key step, namely, the condensation of an aldehyde (III) with the anion of an α-formyl ketone (V), exemplifies an interesting approach to the α,β-unsaturated ketonic moiety, and will be amplified in a full paper.

The author expresses his warm appreciation to Dr. Coy W. Waller and members of the Chemistry Staff at Mead Johnson, to Professor D. H. R. Barton, and to Professor John W. Huffman for helpful and stimulating discussions.

[10] Woodward's ultraviolet rule (R. B. Woodward, THIS JOURNAL, **64**, 76 (1942)) predicts this value for the α,β-unsaturated ketone embodied in anhydroactidione.

[11] H. E. Ungnade and A. D. McLaren, *ibid.*, **66**, 118 (1944).

[12] D. Capon and co-workers, *Bull. soc. chim.*, 837 (1958).

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STUDIES OF HALOGEN ATOMS ABSTRACTION BY METHYL RADICALS[1]

Sir:

Although extensive studies were carried out on reactions involving abstraction of hydrogen by radicals and free atoms, very little is known about those processes in which these reagents abstract other atoms, *e.g.*, halogens. This note reports preliminary data pertinent to reactions of the type $RX + CH_3 \rightarrow R + CH_3X$, where X denotes I, Br or Cl. In determining the relative rate constants (k_2) of those reactions our usual technique[2,3] was applied. A radioactive labelling technique had to be used in studies of the exchange reactions $CH_3I + CH_3$ and $CH_3Br + CH_3$.

The results are summarized in Tables I and II. They show clearly the expected reactivity gradation in the series MeX, EtX, iso-PrX and *t*-BuX, as well as in the series CH_3X, CH_2ClX, $CHCl_2X$ and CCl_3X. They show also that the ratio $k_{2,I}/k_{2,Br}$ remains approximately constant ($\sim 9.10^3$ for Me, 1.2×10^3 for $PhCH_2$ and 4.6×10^3 for CH_2Cl). On assumption that the entropy of activation is approximately constant (this seems to be partially justified by the data quoted in Table II) the difference in $E_{2,Br} - E_{2,I}$ for any pair RBr and RI is calculated to be about 5–6 kcal./mole, corresponding approximately to $^1/_2\{D(R\text{–}Br) - D(R\text{-}I)\}$, *i.e.*, $^1/_2$ of 11–14 kcal./mole. A similar conclusion is arrived at from the data based on the only available example of CCl_3Br and CCl_3Cl.

TABLE I

RELATIVE RATE CONSTANTS FOR REACTIONS $RX + CH_3 \rightarrow R + CH_3X$ (k_2) EXPRESSED AS RATIO k_2/k_1, WHERE k_1 REFERS TO THE REACTION $CH_3 + PhCH_3 \rightarrow CH_4 + PhCH_2$ (k_1); ALL DATA AT 65°

R	1	Br	Cl	H[a]
CH_3	45	$\sim 5.10^{-3}$	.....	4×1.10^{-4}[b]
C_2H_5	180	......	.....	6×0.011
s-C_3H_7	870	......	.....	2×0.16
t-C_4H_9	1680	......	.....	1.85
$PhCH_2$	7560	6.5	.....	3×0.33
CH_2Cl	6400	1.4	.....	......
$CHCl_2$	....	131	.....	......
CCl_3	....	7400	4×1.1	......
CF_3	20,000		.....	......

[a] Extrapolated from results reported by Steacie (see Steacie's "Atomic and Free Radical Reactions"). [b] Using recent data by Dainton, Ivin and Wilkinson, *Trans. Faraday Soc.*, **55**, 929 (1959), a value of 4×5.10^{-5} is obtained.

TABLE II

$$RI + Me \rightarrow R + MeI \ \ldots.\ k_2$$
$$Ph{\cdot}CH_3 + Me \rightarrow Ph{\cdot}CH_2 + MeH \ \ldots\ k_1$$

R	$E_2 - E_1$, kcal./mole	A_2/A_1
CH_3	-1.8 ± 1.5	3
C_2H_5	-1.9 ± 1.0	10
s-C_3H_7	-2.9 ± 1.0	11

This "simple" relation does not hold when RX is compared with RH. As shown by the data in the last column of Table I, the H abstraction is relatively much faster than expected on the basis of the high values of $D(R\text{-}H)$'s. Whereas $D(R\text{-}H) - D(R\text{-}Br)$ is 30–35 kcal./mole, the calculated $E_{2,Br} - E_{2,H}$ are less than 2 or 3 kcal./mole if the assumption of a constant frequency factor is valid. It seems that A_{Br}/A_H or A_I/A_H are $\sim$10–30 (see Table II) which would make the $E_{2,Br} - E_{2,H}$ even smaller.

This striking observation may be accounted for in this way: The activation energy of the abstraction can be represented by a sum of two terms, the energy required to stretch the C–X bond to its length in the transition state and the repulsion energy required to bring the radical to the stretched

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[1] This investigation was supported by the National Science Foundation.

[2] M. Levy and M. Szwarc, THIS JOURNAL, **77**, 1949 (1955).

[3] R. P. Buckley and M. Szwarc, *Proc. Roy. Soc.* (*London*), **A240**, 396 (1957).