An assumption of spherical shape is made in calculating a particle radius r from the Stokes–Einstein equation,[15] $D = RT/6\pi Nr\eta$ in which η is the viscosity of the solvent. Actually the particles, particularly the monomeric ones, must be quite elongated. Somewhat better particle volumes were calculated by multiplying the diffusion coefficient by a correction factor[16] to account for the higher frictional resistance. This correction is based on the assumption that the particles resemble ellipsoids of revolution of dimensions estimated from their known structure and the assumption that they polymerize side by side. Using for the partial specific volume the value 0.64 ml./g. as measured for compound XXX, in agreement with Robinson[4] for a different dye, values of the degree of association n were calculated, as reported in Table I. The corrected values of n are smaller than uncorrected values by factors varying from 1 to 0.4. The error in n is seen to be more than three times the error in D, which may be large in itself, so that tests of the validity of the results are desirable. Several are available.

TABLE II

THE DEGREE OF ASSOCIATION FROM OSMOTIC PRESSURE DATA

	Concn. $\times 10^5$	Temp., °C.	Capillary rise, cm.	n
XXX	7	37.5	1.0	2
	7	37.5	1.2	2
XII	9.5	37.5	0.55	4
	9.5	37.5	0.7	5
XI	16	25	Adsorbed by osmometer	

For H-acid-azobenzene the values $n = 1$ and 1.3 from free diffusion and $n = 2$ from 27 porous diaphragm measurements may be compared with the partition experiments which showed this substance probably monomeric. Diffusion gave $n = 1$ for phenolphthalein, which is presumably monomeric in the colorless form, in which it lacks the resonating electrons necessary for association. Similarly, compounds XXXV and R′X′ in ethanol solution are probably monomeric, in agreement with the diffusion results, $n = 0.8$.

The osmotic pressure data are in poor agreement with the diffusion data, but nevertheless indicate some degree of association. Attempts to gain useful information by studying the changes in absorption spectrum with concentration showed that for compounds VI, VII, XI, XXX and XXXV there is no change, as is in general true for azo dyes,[17] except that in the presence of borate ions the spectra of XXX and XXXV change somewhat, an observation which has not been explained.

The measurement of Boyd and Behnke[6] ($n = 11$ for compound XI) seems reasonable. This compound was adsorbed by both the porous disk and the osmosis membrane, so that we were unable to obtain data for it.

This investigation was carried out with the aid of a grant from the Rockefeller Foundation. We wish to thank Dr. David Pressman for furnishing the synthetic antigens.

Summary

We have carried out measurements on the association of a number of polyhaptenic simple substances. Some of these colored simple antigens are probably associated several-fold in saline solution. Diffusion measurements seem to give an approximate measure of the degree of association, at least for those compounds which are not too highly associated.

(15) W. Sutherland, *Phil. Mag.*, [6] **9**, 781 (1905).

(16) T. Svedberg and K. O. Pederson, "The Ultracentrifuge," Clarenden Press, Oxford, 1940, p. 41.

(17) S. E. Sheppard and A. L. Geddes, THIS JOURNAL, **66**, 1995 (1944).

RECEIVED JUNE 9, 1948

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Structure and Chemistry of Actidione, an Antibiotic from Streptomyces Griseus[1]

BY EDMUND C. KORNFELD, REUBEN G. JONES AND THOMAS V. PARKE

Recently Ford and Leach[2a,b] of the Upjohn Research Laboratories reported the isolation from *Streptomyces griseus* of a new antibiotic substance which they named "Actidione."[3] This interesting material is highly active against most yeasts but is relatively inactive against other microörganisms. Subsequently, Leighty and Fortune of these Laboratories also isolated Actidione from Streptomycin residues, and we undertook a study designed to elucidate the chemical structure of the new antibiotic. A preliminary communication[4] regarding this work has been published, in which structure I was proposed. It is the purpose of the present paper to give the evidence upon which this formulation is based.

The empirical formula of Actidione as originally determined in these laboratories and also ascertained by the Upjohn workers[2a] is $C_{15}H_{23}NO_4$. Nitrogen analyses by either the Dumas or Kjeldahl methods gave concordant results. It was

(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Washington, D. C., meeting, 1948.

(2) (a) Ford and Leach, THIS JOURNAL, **70**, 1223 (1948). (b) Leach, Ford and Whiffen, *ibid.*, **69**, 474 (1947).

(3) The compound was given this name because it was originally believed to be a *di*ketone. However, the present work has shown the compound to be a *mono*ketone.

(4) Kornfeld and Jones, *Science*, **108**, 437 (1948).

then found that all of the nitrogen in Actidione was liberated as ammonia by simply boiling the compound with sodium hydroxide solution. This fact suggested the presence of an amide or imide grouping in Actidione. A determination of terminal methyl groups indicated that the molecule contained *two* such linkages.

Evidence for functional groups in Actidione was next sought, and it was found that the compound was easily converted to a *p*-nitrobenzoate and an acetate ($C_{17}H_{25}NO_5$).[2] Actidione also gave a qualitative test for primary or secondary alcoholic hydroxyl by the method of Fearon and Mitchell.[5] This test gives negative results with *tertiary* alcohols. The compound formed a monoxime[2] and a semicarbazone.[2] When subjected to catalytic reduction only *one* mole of hydrogen was absorbed, to yield dihydroactidione (II). The latter product was shown to be a *diol* by conversion to a diacetate ($C_{19}H_{29}NO_6$). However, it was not attacked by periodic acid, and, therefore, dihydroactidione was considered not to be a 1,2-diol. Actidione acetate, mentioned above, also underwent catalytic reduction to yield a dihydro derivative ($C_{17}H_{27}NO_5$). The dihydro compounds showed only end absorption in the ultraviolet, thus indicating that during the hydrogenation a carbonyl was reduced to a hydroxyl group.

Confirmation of the functional groups was found in further physical studies. The ultraviolet spectrum of Actidione (Fig. 1) showed a single maximum at 287 mμ (ϵ = 36.7), which is characteristic of a simple ketone group. The infrared spectrum (Fig. 3) contained bands at wave lengths which may be assigned to carbonyl (5.90 μ) hydroxyl (2.80 μ), C-methyl (7.28 μ), >NH (3.00 μ), aliphatic C–H (3.42 μ) and others. A semiquantitative

(5) Fearon and Mitchell, *Analyst*, **57**, 372 (1932).

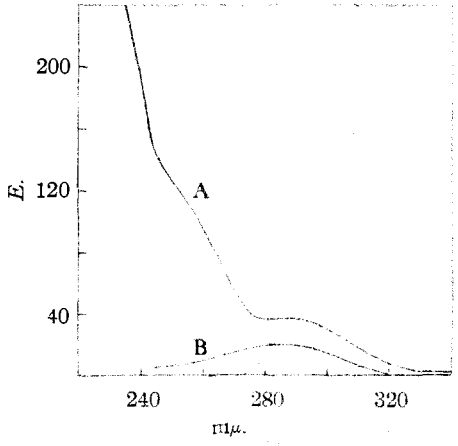


Fig. 1.—Ultraviolet absorption spectra of Actidione (A) and $C_8H_{14}O$ ketone (B) from Actidione.

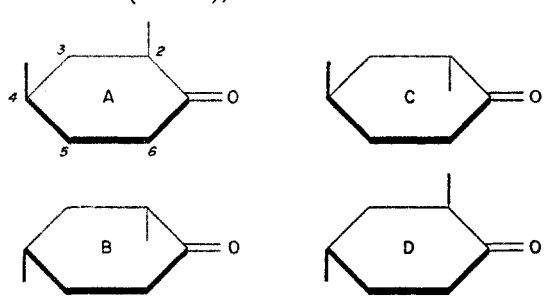
study of this spectrum in comparison with that of other compounds indicated that Actidione contained *three* carbonyl groups. Rapid electrometric titration in water showed no titratable group from *p*H 2 to *p*H 10. Beginning at about *p*H 10, however, a weakly acidic group was titrated with a mid-point or pK'_a of 11.2. Discussion of this titration data is presented later. Thus, in summary, it was indicated that Actidione had two terminal methyl groups, one hydroxyl group (primary or secondary), one ketone group and an amide or imide linkage.

Degradative studies were next undertaken to determine whether identifiable fragments of the molecule could be isolated. Ford, Leach and Whiffen[2] had already discovered that Actidione was extremely labile under basic conditions. We observed that exposure of the molecule to even one-hundredth normal alkali at room temperature resulted in rapid inactivation and cleavage to form, among other things, a fragrant, volatile liquid. This liquid was isolated with facility either by ether extraction of the alkaline degradation mixture or by steam distillation. It was found to be dextrorotatory and to have the empirical formula $C_8H_{14}O$ (III). The ultraviolet absorption spectrum (Fig. 1) had a single maximum at 284 mμ (ϵ = 20.2) characteristic of a carbonyl group. The presence of a carbonyl group was confirmed by the preparation of an oxime, semicarbazone, 2,4-dinitrophenylhydrazone, *p*-nitrophenylhydrazone and a bisulfite addition product. Upon catalytic reduction the compound absorbed *one* mole of hydrogen. Tests for an aldehyde group were negative, so the fragrant liquid was considered to be a *cyclic ketone*. A literature search revealed that there were at least three known cyclic ketones of the formula $C_8H_{14}O$ with physical properties hardly distinguishable from the natural degradation product (see Table I). Consequently, these three isomeric ketones were synthesized for comparison. The melting points of the semicarbazones were of little help in the identification because the natural product was optically active while the synthetic ketones were racemic. However, a comparison of the infrared spectra of the four compounds (Fig. 2) showed in a very convincing manner that the natural ketone was an optical isomer of 2,4-dimethylcyclohexanone (III). It may be noted that the spectra of the natural and synthetic 2,4-dimethylcyclohexanones are identical in every way, while marked differences are found in the spectra of the isomeric ketones. Additional confirmation of the identity of the natural degradation product was obtained by resolution of the synthetic *dl*-2,4-dimethylcyclohexanone. This was accomplished by fractional crystallization of the *l*-menthydrazones obtained from the *dl*-ketone. The least soluble *l*-menthydrazone was found to be identical with the *l*-menthydrazone of the natural dextrorotatory ketone. This identity was established by melting point, mixed melting point, optical rotation, and finally by comparison of the X-ray diffraction patterns[3] (see Experimental). Of the four possible optical isomers of 2,4-dimethylcyclohexanone (A to D), A and B would have identical infrared spectra as would also C and D.[6] The spectra of the *cis*- and *trans*-forms, however, would differ. Obviously, the natural and synthetic ketones must *both* be either all *cis* or all *trans* depending on which is the more stable, or each may consist of the same equilibrium proportion of *cis* and *trans* forms.

TABLE I[a]

Ketone	B. p., °C.	n_D	M. p., °C., of semicarbazone
$C_8H_{14}O$ from Actidione	175–176	1.4435	212–214
Isopropylcyclopentanone[15]	173–174	1.4395	201–202
2,4-Dimethylcyclohexanone[17]	175–176	1.4430	200–202
2,5-Dimethylcyclohexanone[19]	174–176	1.4406	155–157

[a] Experimental values as determined in this Laboratory.



With the identification of the C_8 ketone from Actidione there remained yet seven carbon atoms to be accounted for. At this point certain evidence on hand suggested that Actidione might be a glutarimide derivative. In the first place, the infrared spectrum of Actidione, mentioned above, indicated the presence of *three* carbonyl groups. One had been identified as a simple ketonic linkage, so there remained *two* carbonyl groups which *could*

(6) Thompson and Sutherland, *Trans. Faraday Soc.*, **41**, 197 (1945).

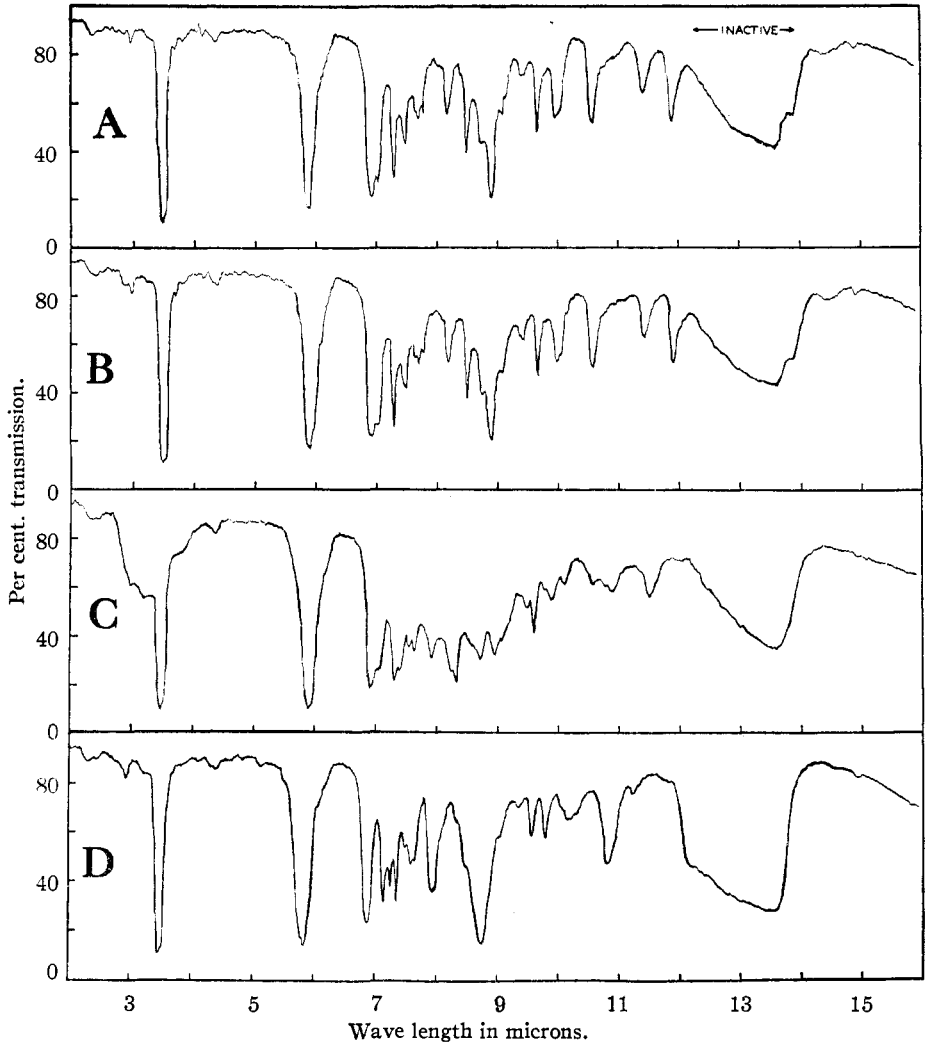


Fig. 2.—Infrared absorption spectra of $C_8H_{14}O$ from Actidione (A), 2,4-dimethylcyclohexanone (B), 2,5-dimethylcyclohexanone (C) and α-isopropylcyclopentanone (D). Concentration, 20% in carbon tetrachloride; cell length, 0.132 mm. Inactive region is due to solvent absorption.

be accounted for by a cyclic imide structure. Furthermore, the weakly acidic character of Actidione (pK'_α 11.2) as revealed in the electrometric titration was consistent with a cyclic imide formulation. To confirm this point an electrometric titration of glutarimide was carried out, and it was found that the acidic >NH group had a pK'_α of 11.2, identical with that of Actidione. Succinimide, on the other hand, was found to have a pK'_α of 9.35. Having thus obtained evidence for the presence of a glutarimide ring system in Actidione it was of interest to determine the point of attachment of that ring to the other part of the Actidione molecule. Two model compounds, α-ethylglutarimide and β-ethylglutarimide, were synthesized, and their infrared spectra were compared with that of Actidione (Fig. 3). Both Actidione and β-ethylglutarimide had bands at 8.75 μ, while this band was completely missing in the spectrum of the α-ethyl isomer. This was tentatively accepted as evidence that Actidione was a β-substituted glutarimide.

Substantial *chemical* evidence for a β-substituted glutarimide structure was sought next. Proof of the presence of a cyclic imide grouping was furnished when dihydroactidione (II) was allowed to react with diazomethane to form an N-methyl derivative (IV). This is a characteristic reaction of glutarimide.[7] That the methyl group was attached to nitrogen was demonstrated by alkaline degradation of the N-methyldihydroactidione to yield methylamine. When Actidione was degraded in alkaline solution and the ammonia and 2,4-dimethylcyclohexanone so formed were removed, the residue yielded a seven-carbon acidic fragment, presumably propionaldehyde-2,2-diacetic acid. This product was not obtained in pure condition but on oxidation it afforded

(7) Irrera, *Gass. chim. ital.*, **65**, 464 (1935). Compare also Labruto, *ibid.*, **63**, 266 (1933).

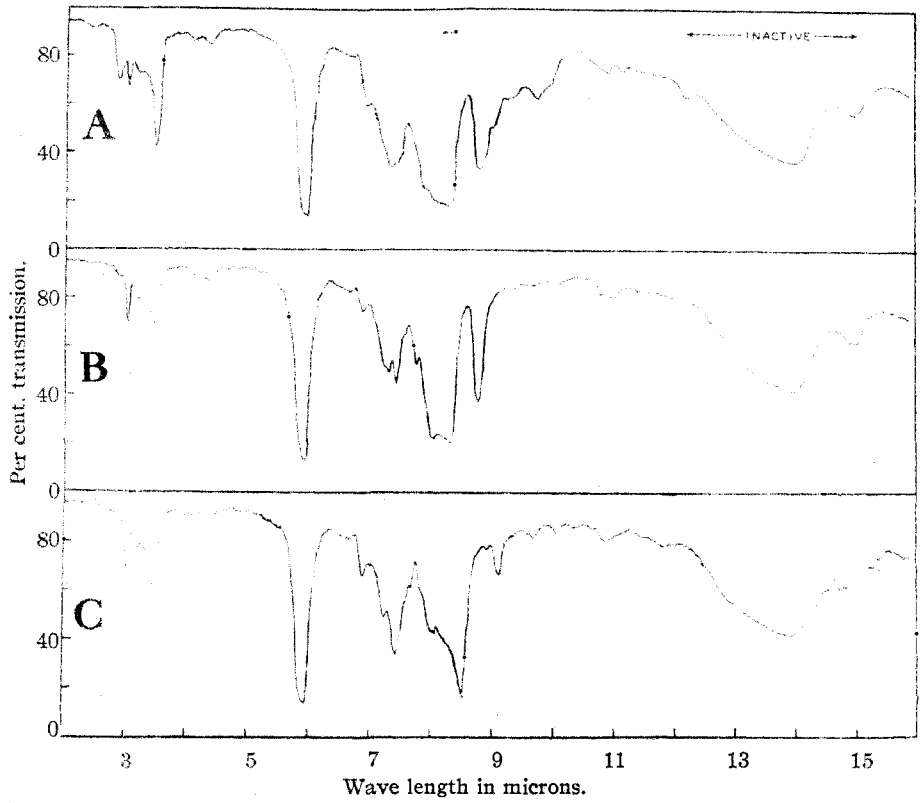


Fig. 3.—Infrared absorption spectra of Actidione (A), β-ethylglutarimide (B) and α-ethylglutarimide (C). Concentrations, 6.3%, 2.8% and 3.3%, respectively, in chloroform; cell length 0.132 mm. Inactive regions are due to solvent absorption.

methanetriacetic acid (V), which was identified by a mixed melting point determination with an authentic sample, and by conversion to the tri-*p*-bromophenacyl ester. In another experiment Actidione was first oxidized by means of chromic acid to the diketone, dehydroactidione (VI), which was characterized as a *1,3* diketone by its ultraviolet absorption spectrum ($\lambda_{max.}$ 292 mμ; ε, 9910)[8] and by conversion to a copper complex. Dehydroactidione was then degraded in alkaline solution to form 2,4-dimethylcyclohexanone, ammonia, and methanetriacetic acid (V). This hydrolysis of the 1,3-diketone took place almost exclusively by fission of the carbon–carbon bond *exo*cyclic to the cyclohexanone ring.

On the basis of the evidence presented up to this point then, structure I may be proposed for Actidione. The hydrolytic cleavage of the antibiotic may be looked upon as a reverse aldol reaction accompanied by opening of the glutarimide ring. Additional confirmation in support of structure I was obtained by a number of further transformations and reactions.

As was mentioned above the propionaldehyde-2,2-diacetic acid formed on alkaline degradation of Actidione was not obtained analytically pure. A derivative of this aldehyde–diacid was obtained, however, when Actidione was allowed to react with benzylamine. Benzylamine caused an opening of the glutarimide ring accompanied by a reverse aldol fission of the molecule. This was followed by condensation of the resulting aldehyde with benzylamine. The end-product of this series of reactions was the derivative VII.

Thus far it had not been established whether the point of attachment of the seven-carbon section of the Actidione molecule was at the 2 or 6 position on the 2,4-dimethylcyclohexanone ring (III). Evidence proving linkage through the 6 position was obtained by dehydration of Actidione in the presence of phosphorus pentoxide to form anhydroactidione (VIII). This product, which had a typical α,β unsaturated ketone absorption spectra in the ultraviolet ($\lambda_{max.}$, 241 mμ; ε, 8250)[9] could not result if attachment had been at position 2. Catalytic reduction of anhydroactidione gave tetrahydroanhydroactidione (IX).

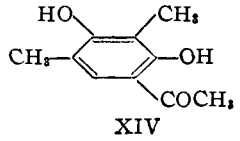
Several interesting transformations in the dihydroactidione (II) series were also carried out. Dihydroactidione was found to be stable to hydrolytic carbon–carbon cleavage because of the absence of the aldol configuration. Alkaline hydrolysis of this compound merely opened the glutarimide ring with elimination of ammonia.

(8) 2-Acetylcyclohexanone has $\lambda_{max.}$ = 290 mμ (ε = 8750).

(9) Woodward's rule (THIS JOURNAL, 64, 76 (1942)) predicts $\lambda_{max.}$ = 240 mμ.

On acidification of the hydrolysis mixture an acidic product, dihydroactidione acid, was isolated, which on the basis of its properties and reactions was formulated as the lactone acid (X). This acid formed a monomethyl ester (XI) on treatment with diazomethane, and the ester was converted by means of alcoholic ammonia to the diamide (XII). This diamide was also produced directly by the reaction of dihydroactidione (II) with ammonia, and it was reconverted by alkaline hydrolysis to dihydroactidione acid (X). When dihydroactidione acid (X) was treated with ammonia, the lactone ring was again opened to give the ammonium salt of a monoamide-acid which was isolated as the silver salt (XIII). Reaction of the lactone-acid (X) with two equivalents of alkali and two moles of *p*-bromophenacyl bromide gave a *di-p*-bromophenacyl ester. All of these transformations are adequately interpreted on the basis of the formulations presented.

Finally, it was of interest to discover if natural products similar to Actidione had been previously isolated. The literature reveals a mould metabolic product which has a skeletal arrangement resembling that of a portion of Actidione. Clavatol, a product isolated from *Aspergillus clavatus* by Hassall and Todd,[10] has the structure XIV. The glutarimide ring in Actidione, however, seems to be unique.



XIV

Acknowledgments.—The authors express their appreciation to Drs. W. W. Davis and R. B. Woodward for helpful discussions. Dr. Woodward was the first to suggest the possibility of a cyclic imide formula. We also thank Mr. R. A. Kern for some of the ultraviolet work, Mr. G. Vaughan for the X-ray diffraction data and Mr. W. L. Brown and Mr. H. L. Hunter for the microanalyses. We are especially indebted to Drs. J. H. Ford and B. E. Leach of the Upjohn Laboratories for their continued interest and for generously supplying part of the Actidione used in this work.

Experimental[11]

Purification of Actidione (I).—Actidione was purified for analysis by repeated recrystallization from water containing a little methanol, from which it separated slowly, m. p. 119.5–121°, $[\alpha]^{29}D$ −3.38° (*c* = 9.47 in ethanol).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.37; H, 8.55; N, 5.08. Nitrogen by Kjeldahl method, found: 5.11. Nitrogen by Kjeldahl method omitting acid digestion, found: 4.84. C-methyl determination,[12] found: 1.32. (Synthetic 2,4-dimethylcyclohexanone gave a value of 1.28).

Isolation of Ammonia from Alkaline Degradation of Actidione.—Actidione (5 g.) was dissolved in 100 ml. by 12 *N* sodium hydroxide solution. The solution was refluxed for one-half hour, and the evolved gas was absorbed in 25 ml. of ice-water. To this aqueous solution was added 1 g. of phenyl isothiocyanate, and the mixture was shaken well. Long prismatic crystals of phenylthiourea had separated from the solution after standing overnight, m. p. 157–158°. A mixed melting point with an authentic sample of phenylthiourea was also 157–158°.

Actidione-*p*-nitrobenzoate.—Actidione (1 g.) was dissolved in 3 ml. of dry pyridine, and 0.66 g. of *p*-nitrobenzoyl chloride was added. The mixture became warm and partly solidified. It was heated on a steam-bath until all solids were dissolved and was then cooled. Ice-water was added, and the aqueous phase was decanted. The residue was rubbed with a little ethanol, and the product was filtered, washed with ethanol, and dried; yield, 0.75 g. A sample was purified for analysis by recrystallization from aqueous dioxane, m. p. 215–220° (dec.).

Anal. Calcd. for $C_{22}H_{26}N_2O_7$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.13; H, 6.24; N, 6.53.

Actidione Acetate.—This was prepared by a method similar to that of Ford and Leach[2a]; m. p. after recrystallization from dilute ethanol, 150–152°.

Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.56; H, 7.67; N, 4.50; C-methyl, 2.17.

Reduction of Actidione Acetate.—A small sample of the acetate was reduced catalytically in glacial acetic acid using platinum oxide as catalyst. Absorption of hydrogen ceased after 1.03 moles had been taken up. The catalyst was filtered, and the solvent was distilled *in vacuo*. The residue was recrystallized several times from dilute ethanol. Dihydroactidionemonoacetate was obtained as shiny needles, m. p. 169–171°.

Anal. Calcd. for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.37; N, 4.31. Found: C, 63.10; H, 8.32; N, 4.26.

Actidione Semicarbazone.—This derivative was prepared by essentially the same method used by Ford and Leach.[2a] It was obtained as a hydrate, m. p. 187–188°.

Anal. Calcd. for $C_{16}H_{26}N_4O_4.H_2O$: C, 53.92; H, 7.92; N, 15.72. Found: C, 54.01; H, 7.89; N, 15.65, 15.75.

Dihydroactidione (II).—Actidione (3 g.) was reduced at atmospheric pressure in 40 ml. of glacial acetic acid using 1 g. of platinum oxide catalyst. Reduction was complete after 1.05 moles of hydrogen had been absorbed (two to three hours). The solution was filtered, and the acetic acid was removed *in vacuo*. The residue was recrystallized from water containing a little acetone; m. p. 137–139° after thorough drying *in vacuo*.

Anal. Calcd. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.50; H, 8.88; N, 5.29.

Dihydroactidione was recovered unchanged after being exposed at room temperature to aqueous periodic acid for twenty-four hours.

Dihydroactidione Diacetate.—Dihydroactidione (II) (1.1 g.) was dissolved in a mixture of 20 ml. of acetic anhydride and 10 ml. of dry pyridine, and the solution was allowed to stand overnight. The solvents were then evaporated *in vacuo*, and the residue was stirred with dilute ethanol. The product which soon crystallized was purified by recrystallization from dilute methanol, m. p. 72–75°.

Anal. Calcd. for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.01; H, 7.90; N, 3.78; C-methyl, 3.44.

***d*-2,4-Dimethylcyclohexanone (III) by Alkaline Degradation of Actidione.**—Actidione (10 g.) was dissolved in 200 ml. of 20% sodium hydroxide solution, and about one-half of the solution was distilled. The distillate was saturated with sodium chloride and extracted with ether. The extracts were dried over sodium sulfate, and the ether

(10) Hassall and Todd, *J. Chem. Soc.*, 611 (1947).

(11) All melting points were taken on a Fisher-Johns melting point block and are corrected.

(12) Ginger, *J. Biol. Chem.*, **156**, 453 (1944).

was removed. The residue was distilled, b. p. 175–176°, yield, 3.0–3.5 g., $[\alpha]^{29}D$ +11.52° (c = 5.417 in ethanol), $n^{25}D$ 1.4435.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.45; H, 11.08.

The 2,4-dinitrophenylhydrazone of *d*-2,4-dimethylcyclohexanone was obtained in the usual manner and was recrystallized from dilute dioxane, m. p. 169–172°.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.64; H, 5.75; N, 18.76.

The *p*-nitrophenylhydrazone was prepared in ethanol using acetic acid as catalyst. The derivative separated as golden, matty needles from dilute ethanol, m. p. 152–153°.

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.33; H, 7.10; N, 15.82.

The oxime, prepared as usual, was sublimed for analysis, m. p. 48–51°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.71; H, 10.94; N, 10.32.

The semicarbazone was prepared and purified by recrystallization from dilute ethanol, m. p. 212–214°.

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.99; H, 9.35; N, 22.93. Found: C, 59.37; H, 9.47; N, 23.07.

The *l*-menthydrazone of *d*-2,4-dimethylcyclohexanone was prepared by the method of Woodward, Kohman and Harris[13] and was recrystallized from ethanol, m. p. 164–165°, $[\alpha]^{29}D$ −58.7° (c = 1.524 in ethanol).

Anal. Calcd. for $C_{19}H_{34}N_2O_2$: N, 8.69. Found: N, 8.91.

Resolution of Synthetic *dl*-2,4-Dimethylcyclohexanone.—A solution of 10 g. of the pure ketone (see below), 17 g. of *l*-menthydrazide, 4 g. of sodium acetate, and 2 ml. of glacial acetic acid in 200 ml. of ethanol was refluxed for forty minutes. The solution was seeded with *d*-2,4-dimethylcyclohexanone-*l*-menthydrazone and was cooled overnight. The first crop of crystals weighed 5.2 g., m. p. 135–143°. After four recrystallizations from ethanol the melting point was 164–165° and showed no depression when mixed with the *d*-2,4-dimethylcyclohexanone-*l*-menthydrazone obtained above from the natural 2,4-dimethylcyclohexanone; $[\alpha]^{29}D$ −56.8° (c = 1.54 in ethanol).

Anal. Calcd. for $C_{19}H_{34}N_2O_2$: N, 8.69. Found: N, 8.69.

X-Ray Diffraction Identification of the Natural and Synthetic *d*-2,4-Dimethylcyclohexanone-l-menthydrazones.—X-Ray powder patterns of the natural and synthetic *d*-2,4-dimethylcyclohexanone-*l*-menthydrazones were taken on a North American Philips Unit with a circular camera. The patterns obtained were identical. Calculated D values of identical lines on the two patterns were duplicated to an average error of ±0.01 Å. unit with a maximum deviation of 0.05 Å. unit. Relative intensities of the corresponding lines on the two patterns were identical.

N-Methyldihydroactidione (IV).—An ether solution of diazomethane was prepared from 5 g. of nitrosomethylurea, dried over potassium hydroxide, and filtered into a solution of 2.8 g. of dihydroactidione (II) in 40 ml. of methanol. The mixture was allowed to stand overnight and was then evaporated *in vacuo* to yield a colorless oil. Acetone and water were added, and after scratching the oil crystallized. The product was purified for analysis by recrystallization from aqueous acetone, m. p. 129–132°.

Anal. Calcd. for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.09; H, 8.91; N, 4.68.

Alkaline Degradation of N-Methyldihydroactidione (IV).—The N-methyl derivative (0.35 g.) was boiled in 2 ml. of water containing 0.5 g. of potassium hydroxide, and 1 ml. of distillate was collected under 1 ml. of ice-water. The aqueous solution containing the distillate was mixed with 0.1 g. of phenyl isothiocyanate, warmed to 40°, and shaken until the product crystallized. The N-methyl-N′-phenylthiourea was filtered, washed and dried, m. p. 119–121°. A mixed melting point with an authentic sample was also 119–121°.

The residue from the distillation was acidified with hydrochloric acid, and the product which separated was recrystallized from dilute ethanol. It was shown to be dihydroactidione acid (X) (see below) by melting point and mixed melting point determinations.

Degradation of Actidione to Methanetriacetic Acid (V).—Actidione (10 g.) was dissolved in a solution of 20 g. of sodium hydroxide in 100 ml. of water. The mixture was distilled until 150 ml. of distillate was collected, the original volume being kept constant by periodic addition of water. The residue was cooled and neutralized with 13.5 ml. of concentrated sulfuric acid. The solution was then cooled in an ice-bath while 3.74 g. of powdered potassium permanganate was added. The mixture was shaken until the permanganate color was discharged, after which it was warmed for a few minutes on a steam-bath, made just alkaline with sodium hydroxide and filtered to remove manganese dioxide. The filtrate was saturated with sodium sulfate, acidified with sulfuric acid and exhaustively extracted with ether. Evaporation of the ether left 4.8 g. of crude, sirupy methanetriacetic acid (V). The acid was dissolved in water and was added to an aqueous solution of excess lead acetate. The insoluble lead salt was filtered and washed with water. It was resuspended in water, and the mixture was saturated with hydrogen sulfide. Lead sulfide was removed by filtration, and the filtrate was concentrated *in vacuo* to a crude sirupy residue. Neutral equivalent, calcd. for methanetriacetic acid 63.4; found, 74.9. Part of the sirupy acid on long standing in ether solution crystallized to give methanetriacetic acid, m. p. 112–116°; a mixed m. p. with a sample of the synthetic acid was 114–117°. Another part of the crude acid (0.57 g.) was dissolved in 10 ml. of water and was neutralized with 0.636 g. of sodium bicarbonate. Ethanol (65 ml.) containing 2.12 g. of *p*-bromophenacyl bromide was added, and the mixture was refluxed for three and one-half hours. Most of the ethanol was removed by distillation *in vacuo*, and water was added. The gummy derivative which separated was taken up in dilute acetone. The product crystallized and was recrystallized twice from aqueous acetone, m. p. 110–112°. A mixed melting point with an authentic sample of methanetriacetic acid-tri-*p*-bromophenacyl-ester (m. p. 115–116°) was 112–115°.

Benzylamine Reaction Product (VII) from Actidione.—Three grams of actidione was warmed on a steam-bath for two hours with 7.5 ml. of benzylamine. The odor of 2,4-dimethylcyclohexanone was evident. The mixture was cooled, and the product was filtered and washed with chloroform; yield, 0.7 g. The derivative was recrystallized several times from methanol for analysis, m. p. 180–182°.

Anal. Calcd. for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.35; H, 6.75; N, 12.09.

Oxidation of Actidione; Dehydroactidione (VI).—Pure actidione (3 g.) was dissolved in 75 ml. of glacial acetic acid, and to this solution was added dropwise, during a period of ten minutes, a solution of 0.80 g. of 98% chromium trioxide in 10 ml. of water. The reaction mixture was allowed to stand at room temperature for two hours after which it was warmed for a few minutes on a steam-bath. The solvents were then removed completely *in vacuo*. Water was added to the residue, and the product was extracted with chloroform. The chloroform solution was washed with water, dried over sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from dilute ethanol, m. p. 177–180°; yield, 0.8 g.

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02. Found: C, 64.20; H, 7.39; N, 4.87.

On catalytic reduction of a small sample of dehydroactidione in glacial acetic acid using platinum oxide as

(13) Woodward, Kohman and Harris, THIS JOURNAL, 63, 120 (1941).

catalyst 2.3 moles of hydrogen were absorbed. Separation of the resulting mixture of racemates of dihydroactidione in analytically pure condition has not been accomplished as yet.

Copper Complex from Dehydroactidione.—The diketone (VI) was dissolved in hot dilute ethanol, and the solution was filtered into an excess of aqueous copper acetate. The olive-green complex soon crystallized and was filtered and washed with water, ethanol and ether, m. p. 228–230° (dec.).

Anal. Calcd. for $C_{30}H_{40}N_2O_8Cu$: Cu, 10.25. Found: Cu, 10.20.

Under similar conditions no copper salts were formed with actidione, dihydroactidione or glutarimide.

Alkaline Degradation of Dehydroactidione (VI).—The diketone (VI) (2.3 g.) was dissolved in a solution of 4.6 g. of sodium hydroxide in 23 ml. of water. The solution was boiled, and 45 ml. of distillate was collected, while the volume of the hydrolysis mixture was kept constant by frequent addition of water. The distillate was mixed with 100 ml. of ethanol containing 1.6 g. of 2,4-dinitrophenylhydrazine. This solution was heated to boiling, and 2 ml. of concentrated hydrochloric acid was added. The mixture was boiled for a few minutes, cooled, and the derivative was filtered and washed with methanol. A 68% yield (1.7 g.) of 2,4-dimethylcyclohexanone-2,4-dinitrophenylhydrazone was thus obtained. The residue in the distillation flask was cooled and acidified with 5 ml. of concentrated sulfuric acid. The resulting solution was exaustively extracted with ether and the extract concentrated *in vacuo*. The crude sirup so obtained could not be induced to crystallize, so it was dissolved in 25 ml. of water containing 1 g. of Girard reagent P[14] and 1 ml. of acetic acid. The solution was refluxed for one-half hour, saturated with sodium sulfate, and again extracted continuously with ether overnight. Evaporation of the extract left 1.5 g. of sirup. On cooling an ether–nitromethane solution of the sirup overnight crystalline methanetriacetic acid (V) was obtained, m. p. 117–119°; mixed melting point with synthetic methanetriacetic acid, 119–121°.

Anal. Calcd. for $C_7H_{10}O_6$: C, 44.21; H, 5.30. Found: C, 44.50; H, 5.35.

Part of the crude acid above (0.8 g.) was neutralized with 11.15 ml. of 1 *N* sodium hydroxide solution and mixed with 100 ml. of ethanol and 3.1 g. of *p*-bromophenacyl bromide. The solution was refluxed for three hours, after which it was concentrated *in vacuo* to about half the original volume, and water was added. The gum which separated was washed with sodium bicarbonate solution, water and methanol. It was then taken up in acetone and methanol and cooled slowly. The crystalline product which separated was recrystallized from acetone–methanol, m. p. 115–116°. The mixed melting point with authentic methanetriacetic acid–tri-*p*-bromophenacyl ester was also 115–116°.

Anal. Calcd. for $C_{31}H_{25}Br_3O_9$: C, 47.65; H, 3.23; Br, 30.69. Found: C, 47.36; H, 3.09; Br, 30.32.

Dehydration of Actidione; Anhydroactidione (VIII).—Pure actidione (3 g.) dissolved in 100 ml. of dry benzene was mixed with 6 g. of phosphorus pentoxide. The mixture was heated slowly (15 min.) to boiling with frequent shaking and was then allowed to cool. The benzene solution was filtered, and the solvent was removed *in vacuo*. The residual colorless sirup was crystallized from benzene–petroleum ether; yield, 1.0 g. It was recrystallized for analysis from benzene–ether, m. p. 134–135°.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.53; H, 8.44; N, 5.48.

This product on warming in alkaline solution gave the volatile ketone, *d*-2,4-dimethylcyclohexanone (III).

Reduction of Anhydroactidione (VIII).—A small sample of anhydroactidione (VIII) on catalytic reduction in acetic acid using platinum oxide as catalyst absorbed 2.16 moles of hydrogen in one hour. The solvent was distilled *in vacuo*, and the crude tetrahydroanhydroactidione (IX) was purified by recrystallization from benzene–petroleum ether, m. p. 125–127°.

Anal. Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.57; H, 9.94.

Alkaline Degradation of Dihydroactidione; Dihydroactidione Acid (X).—Dihydroactidione (II) (1 g.) was dissolved in 10 ml. of 20% sodium hydroxide, and the solution was heated to boiling for five minutes. The reaction mixture was cooled, and 4.5 ml. of concentrated hydrochloric acid was added. The product which separated was filtered, washed with water and recrystallized from dilute ethanol; m. p. 180–183°, yield 85%.

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51; neut. equiv., 284.3. Found: C, 63.70; H, 8.71; neut. equiv., 284.0.

In an oxidation experiment using two-thirds mole (two equivalents) of potassium permanganate to one of dihydroactidione acid in dilute acetic acid, only unchanged starting material was isolated. This indicated the absence of a free secondary alcoholic group.

Di-*p*-bromophenacyl Ester of Dihydroactidione Acid.—One gram of the acid (X) was dissolved in 7.04 ml. of 1 *N* sodium hydroxide (two equivalents) and 60 ml. of ethanol, and 1.953 g. (two moles) of *p*-bromophenacyl bromide were added. The solution was refluxed for three hours and was then concentrated *in vacuo*. Water was added to the gelatinous product, and the solid was filtered, washed with water and methanol and dried; yield, 2.4 g. No suitable solvent for purification was found. The ester gelled out under all conditions tried, so the sample was dissolved in ethanol and precipitated with water, m. p. 130–135°.

Anal. Calcd. for $C_{31}H_{36}Br_2O_8$: C, 53.46; H, 5.21; Br, 22.95. Found: C, 53.39; H, 5.46; Br, 22.23.

Methyl Ester of Dihydroactidione Acid (XI).—Diazomethane was prepared in 20 ml. of ether from 2 g. of nitrosomethylurea. The solution was dried over potassium hydroxide and filtered onto 1.5 g. of dihydroactidione acid (X) in a few ml. of methanol. After standing for ten minutes the solution was filtered and concentrated *in vacuo*. The methyl ester which separated was crystallized from methanol–ether, m. p. 139–141°.

Anal. Calcd. for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.40; H, 8.46.

Diamide (XII) from the Methyl Ester of Dihydroactidione Acid.—The filtrate from the preparation of the crystalline methyl ester above was treated with 30 ml. of methanol saturated with ammonia and allowed to stand overnight. The solvents were then distilled *in vacuo*, and the crude diamide was recrystallized from dioxane–methanol. The product melted at about 100° with loss of solvent of crystallization, resolidified and remelted at 165–168°. Analysis showed that the compound contained one molecule of dioxane of crystallization.

Anal. Calcd. for $C_{15}H_{28}N_2O_4 \cdot C_4H_8O_2$: C, 58.75; H, 9.34; N, 7.21; loss at 120°, 22.68. Found: C, 57.57; H, 8.89; N, 7.08; loss at 120°, 22.36.

The sample was then dried at 120° *in vacuo* and reanalyzed, m. p. 167–171°.

Anal. Calcd. for $C_{15}H_{28}N_2O_4$: C, 59.97; H, 9.39; N, 9.32. Found: C, 60.26; H, 8.99; N, 8.53.

Diamide (XII) from Dihydroactidione.—The dihydro compound (II) (2 g.) was dissolved in 30 ml. of methanol, and 30 ml. of liquid ammonia was added. The mixture was allowed to stand overnight after which the solvent was distilled *in vacuo*, and the residue was recrystallized twice from water. The colorless needles melted at about 100° with loss of water of hydration, resolidified and remelted at 174–177°.

Anal. (Dried at 25°.) Calcd. for $C_{15}H_{28}N_2O_4 \cdot 0.5H_2O$: C, 58.23; H, 9.45; N, 9.06. Found: C, 58.86; H, 10.18; N, 8.68.

(14) Girard, *Helv. Chim. Acta*, **19**, 1095 (1936).

A sample was then dried at 120° *in vacuo* and reanalyzed, m. p. 176–178°.

Anal. Calcd. for $C_{15}H_{28}N_2O_4$: C, 59.97; H, 9.39. Found: C, 59.64; H, 8.84.

A mixed melting point with the slightly less pure diamide (m. p. 167–171°) prepared from the methyl ester of dihydroactidione acid was 170–174°.

Dihydroactidione Acid (X) from the Diamide (XII).—The above diamide (0.15 g.) was boiled in a solution containing 0.25 g. of sodium hydroxide in 3 ml. of water until no more ammonia was evolved (five minutes). The mixture was cooled and acidified with hydrochloric acid. The product was filtered, washed and recrystallized from dilute ethanol, m. p. 179–183°. A mixed m. p. with dihydroactidione acid (X) was 180–183°.

Silver Salt of the Amide Acid (XIII) Obtained from Dihydroactidione Acid.—The dihydroacid (X) (1 g.) was mixed with 30 ml. of methanol and 50 ml. of liquid ammonia and allowed to stand for several days. The solvents were evaporated *in vacuo* leaving the amorphous ammonium salt of the amide acid, which was not obtained in crystalline condition. A portion was dissolved in water, filtered and the silver salt (XIII) precipitated with aqueous silver nitrate solution. The salt was collected on a filter and washed with water, m. p. 171–174°.

Anal. Calcd. for $C_{15}H_{26}AgNO_5$: N, 3.43; Ag, 26.43. Found: N, 3.17; Ag, 26.33.

2-Isopropylcyclopentanone.—This ketone was prepared by a modification of the method of Cornubert and Borrel.[15] Acetone was condensed with cyclopentanone to give isopropylidenecyclopentanone, b. p. 94–97° (32 mm.); yield, 20%. Catalytic hydrogenation of the unsaturated ketone to isopropylcyclopentanone was effected smoothly in the presence of 5% palladium–charcoal catalyst in glacial acetic acid. The product had a b. p. 172–174°; yield, 88%. It was purified by conversion in the usual fashion to the semicarbazone (m. p. 201–202°). Regeneration of the ketone was brought about by hydrolysis in 20% sulfuric acid. The pure ketone boiled at 173–173.5°, $n^{29}D$ 1.4395.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.82; H, 11.56.

***dl*-2,4-Dimethylcyclohexanone.**—1-Hydroxy-2,4-dimethylbenzene (145 g.) was hydrogenated in 100 ml. of glacial acetic acid in a 500-ml. steel bomb at 4000 pounds pressure at room temperature using 5 g. of platinum oxide catalyst.[16] The reduction was complete in one hour. The catalyst was filtered and the acetic acid was neutralized with aqueous sodium hydroxide solution. The 2,4-dimethylcyclohexanol was extracted with ether, and the extracts were dried over sodium sulfate. The ether was removed and the product distilled, b. p. 175–179°; yield, 60%.

The alcohol (183 g.) was then added to a solution of 135 ml. of concentrated sulfuric acid in 1500 ml. of water. The resulting mixture was warmed to 45°, and with vigorous stirring 291 g. of powdered potassium dichromate was added portionwise during a period of eleven to twelve minutes while the temperature was maintained at 42–48° by external cooling in ice water. The reaction mixture was stirred for one-half hour longer, after which the product was extracted with ether. The extracts were washed thoroughly with 5% sodium hydroxide and water and were dried over calcium chloride and distilled, b. p. 175–178°; yield, 79%. The ketone was purified in the usual manner by conversion to the semicarbazone, m. p. 198–200°. The pure 2,4-dimethylcyclohexanone had a b. p. 175–176°, $n^{25}D$ 1.4430. Sabatier[17] gives b. p. 176.5°.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.00; H, 11.37.

Determination of C-methyl gave a value of 1.28. A sample of the ketone was exposed to the known[18] racemizing action of 90% sulfuric acid, but it was recovered unchanged. The portion so treated gave a semicarbazone identical with the untreated material. Therefore, if any preferential *cis* hydrogenation occurred in the reduction step above, racemization must have taken place during the chromic acid oxidation to give an equilibrium mixture of racemates.

2,5-Dimethylcyclohexanone.—This isomeric ketone was prepared from 1-hydroxy-2,5-dimethylbenzene in a manner similar to that described above for 2,4-dimethylcyclohexanone except that the reduction was carried out in ethanol at 150–165° using Raney nickel catalyst. After purification through the semicarbazone (m. p. 155–157°) the 2,5-dimethylcyclohexanone was obtained as a colorless liquid, b. p. 175–176°, $n^{29}D$ 1.4406. Sabatier[19] gives b. p. 174–177°.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.07; H, 11.19.

Methanetriacetic Acid and Derivatives.—This acid (m. p. 119–121°) was prepared by the procedure of Kohler and Reid[20] using glutaconic ester prepared by the method of Lochte and Pickard.[21] The tri-*p*-bromophenacyl ester was made using the general directions of Shriner and Fuson.[22] It was recrystallized from dilute acetone, m. p. 115–116°.

Anal. Calcd. for $C_{31}H_{25}Br_3O_9$: C, 47.65; H, 3.23; Br, 30.69. Found: C, 47.36; H, 3.11; Br, 30.76.

The benzylisothiouronium salt was prepared by the method of Shriner and Fuson.[22] Dilute ethanol was the solvent used in the purification of this derivative, m. p. 139–140°.

Anal. Calcd. for $C_{31}H_{40}N_6O_6S_3$: N, 12.20; S, 13.96. Found: N, 11.38; S, 14.23.

Glutarimide.—Glutaric anhydride (20 g.) was heated to 130–140°, and ammonia gas was bubbled in rapidly for one-half hour. The mixture was then heated slowly to 250° (twenty-five minutes), and the imide was distilled at 275–280°. It was purified by recrystallization from acetone, m. p. 163–165°. Wolffenstein gives m. p. 154.5°.[23]

α-Ethylglutarimide.—α-Ethylglutaric acid was prepared by the following modification of the method of Auwers.[24] One mole of sodium was dissolved in 400 ml. of absolute ethanol, and one mole of ethyl diethylmalonate was added. To the hot solution was then added with stirring one mole of ethyl β-bromopropionate at such a rate as to maintain a gentle reflux (ten minutes). Stirring was continued twenty minutes longer, after which the sodium bromide was removed by filtration and the ethanol distilled *in vacuo*. Water and a little chloroform were added to the residue, and the organic layer was separated and fractionated *in vacuo*. A 61% yield of diethyl α-ethyl-α-carbethoxyglutarate was obtained, b. p. 177–182° at 13 mm. The ester was refluxed with a mixture of 600 ml. of concentrated hydrochloric acid and 500 ml. of water for seventeen hours. The solvents were removed completely *in vacuo*, and the residual α-ethylglutaric acid was refluxed with 450 g. of acetyl chloride for two hours. Excess reagent was distilled *in vacuo*, and the α-ethylglutaric anhydride was fractionated, b. p. 163–165° at 13 mm.; yield, 51% based on ethyl diethylmalonate.

The anhydride was converted to the cyclic imide by the procedure given above for glutarimide. It had a b. p. 265–280°; yield, 85%. Purification was effected by recrystallization from acetone–ether, m. p. 107–108°.

(15) Cornubert and Borrel, *Bull. soc. chim. France*, [4] **47**, 958 (1930).

(16) Baker and Schuetz, THIS JOURNAL, **69**, 1250 (1947), have developed this method of high pressure room temperature hydrogenation using platinum oxide.

(17) Sabatier, *Compt. rend.*, **142**, 553 (1901).

(18) Beckmann, *Ann.*, **250**, 334 (1889).

(19) Sabatier, *Compt. rend.*, **142**, 553 (1901).

(20) Kohler and Reid, THIS JOURNAL, **47**, 2808 (1925).

(21) Lochte and Pickard, *ibid.*, **68**, 721 (1946).

(22) "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y.

(23) Wolffenstein, *Ber.*, **25**, 2777 (1892).

(24) Auwers, *Ann.*, **292**, 144, 213 (1896).

Anal. Calcd. for $C_7H_{11}NO_2$: N, 9.92. Found: N, 10.02.

β-Ethylglutarimide.—This imide was prepared in a manner similar to that for the α-isomer starting with β-ethylglutaric acid, which was made by the procedure of Jeffery and Vogel.[25] It had a m. p. 88–89°. Sircar[26] gives m. p. 87°.

Absorption Spectra.—The ultraviolet spectra were determined in 95% ethanol solution using a Beckman Model DU spectrophotometer. The infrared spectra were obtained on a Baird recording infrared spectrophotometer. Pertinent data are included with the spectrograms.

(25) Jeffery and Vogel, *J. Chem. Soc.*, 446 (1939).

(26) Sircar, *ibid.*, 600 (1927).

Summary

1. Actidione, a new antibiotic isolated from *Streptomyces griseus*, has been shown to have the structure I.

2. A number of reactions and transformations of Actidione have been carried out.

INDIANAPOLIS, INDIANA RECEIVED JULY 10, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

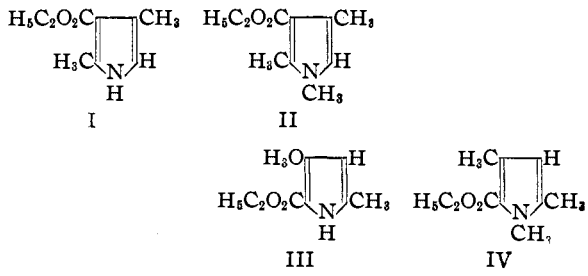
Kinetics of Pyrrole Substitutions. The Iodination Reaction[1]

BY KENNETH W. DOAK[2] AND ALSOPH H. CORWIN

Wibaut[3] first showed that the presence of a methyl group in the benzene ring greatly increases its reactivity toward nitration. Ingold and Shaw[4] conclude that the rate of nitration by nitric acid in acetic anhydride is increased about 40–55-fold in each ortho and para position, while the reactivity in a meta position is increased threefold. McDuffie and Dougherty[5] have observed that toluene is acetylated about thirteen times as rapidly as benzene. The explanation for this increased reactivity is given in the general electronic theory of organic reactions, developed to a large extent by Lapworth, Robinson and Ingold,[6] which assumes that the attacking reagent seeks a pair of electrons from the aromatic nucleus. The methyl group facilitates the donation of an electron pair, by favoring polarization of the type $CH_3-\overset{+}{\bigcirc}-$ and thus lowering the energy of the activated intermediate.[7]

Kinetic investigations of substitution reactions are entirely lacking in pyrrole chemistry. A fundamental difference between the benzene and pyrrole systems exists, since the major resonance in benzene is between two normal valence forms while the resonance in pyrrole[8] is mainly ionic, involving five principal structures.[6b] The ionic structures should have fairly low energy, since no octets are broken and no double bonds are lost. The large contribution of these structures to the normal state of the molecule makes the nitrogen positive, with the result that the N—H group is weakly acidic[9] instead of basic, as would be expected for a secondary amine. Activated structures involving them probably have much lower energy than the activated structures in benzene; this accounts for the well-known fact that pyrrole is more reactive than benzene to electron-seeking reagents. For example, when pyrrole is treated with bromine, chlorine or iodine, in dilute solution, the mono-alpha derivative is formed first. If excess halogen is used, the tetrahalogenated pyrrole is formed[10a] more readily than monohalogenated benzenes.

In order to obtain kinetic data upon the substitution of pyrroles, the velocity of iodination of four pyrrole derivatives has been measured.



I II III IV

In the presence of potassium iodide in a buffered solution, the iodinations proceed almost to completion with velocities which can be measured accurately. Pyrroles which have substituents in all α- and β-positions except one were chosen in order to eliminate competing reactions. The N-methylated compounds were studied in order to determine whether or not the N-methyl group has an effect similar to that of a methyl group in the benzene nucleus. A comparison of pyrroles II and IV, in which steric effects should be quite

(1) Studies in the Pyrrole Series. XXII. Paper XXI, Corwin and Straughn, THIS JOURNAL, **70**, 2968 (1948). This work represents a portion of a doctoral dissertation by Kenneth W. Doak, The Johns Hopkins University, Baltimore, Md.

(2) The William R. Warner and Co., Inc., Fellow, The Johns Hopkins University. Present address: United States Rubber Company, Passaic, New Jersey.

(3) Wibaut, *Rec. trav. chim.*, **34**, 241 (1915).

(4) Ingold and Shaw, *J. Chem. Soc.*, 2918 (1927); 1959 (1931); 905, 918 (1938).

(5) McDuffie and Dougherty, THIS JOURNAL, **64**, 297 (1942).

(6) Ingold, (a) *Rec. trav. chim.*, **48**, 797 (1929); (b) *J. Chem. Soc.*, 1120 (1933); (c) *Chem. Rev.*, **15**, 225 (1934); (d) Robinson, "Outline of Electronic Theory of Organic Reactions," Inst. of Chem. of Gr. Br. and Ireland, London (1932).

(7) Wheland, THIS JOURNAL, **64**, 900 (1942).

(8) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1940, p. 137.

(9) Bamberger, *Ber.*, **26**, 1946 (1893); McEwen, THIS JOURNAL, **58**, 1124 (1936); Ingold and Goss, *J. Chem. Soc.*, 1268 (1938).

(10) Fischer, "Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, (a) p. 75, 83, 101; (b) p. 102.