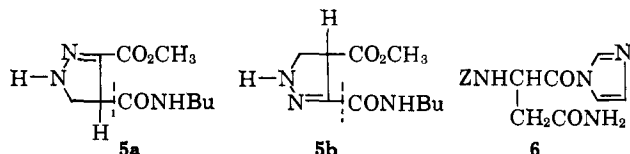


used isotopic oxygen to explore the dehydrations of *N*-butylmaleamic acid and carbobenzoxyasparagine by the action of *N,N'*-dicyclohexylcarbodiimide. A sample of *N*-butylmaleamic acid-1,1- O^{18} was prepared by reaction of the isoimide (**2**) with 1 equiv. of potassium hydroxide- O^{18} in water containing 11% O^{18} . The position of the isotope was confirmed by reaction of the labeled acid (**1**) with excess diazomethane to give crystalline methyl 4- (or 3) *N*-butylcarbamoyl-2-pyrazoline-3- (or 4) carboxylate (**5a** or **5b**).⁷ Mass spectrometry of **5** produced a major fragment at 127, assigned to the cleavage product shown by the dotted line. Comparison with the corresponding labeled fragment at mass 129 showed 10.7% of **5** contained one excess O^{18} per molecule in the carbomethoxy group.



Carbobenzoxyasparagine was labeled by treating it with *N,N'*-carbonyldiimidazole, to produce the acylimidazole^{8,9} (**6**) followed by hydrolysis with O^{18} -water at 0° . Since direct mass spectrometric analysis was not satisfactory in the asparagine series, the extent and position of the label were established by reaction of the tagged acid with *N,N'*-carbonyldiimidazole at -15° and mass spectrometric assay of the carbon dioxide liberated in acylimidazole formation.¹⁰ Since the carbon dioxide produced in this condensation derives one of its two oxygen atoms from the amino acid,¹¹ the assay value of 4.4 atom % COO^{18} indicated that the tagged asparagine (**3**) contained 8.8% molecules with one O^{18} in the carboxyl group.

The labeled acids (**1** and **3**) were separately subjected to the action of *N,N'*-dicyclohexylcarbodiimide, and the purified reaction products (**2** and **4**), as well as the corresponding *N,N'*-dicyclohexylurea by-products, were analyzed for O^{18} content; the results are given in Table I.

TABLE I

Compound	Per cent of the molecules containing one excess O^{18} predicted by			Found
	Path A	Path B		
<i>N</i> -Butylmaleamic acid-1,1- O^{18} ^a			± 0.3	10.7
<i>N</i> -Butylmaleisoimide- O^{18}	10.7	5.4		5.7
<i>N,N'</i> -Dicyclohexylurea from above	0	5.4		6.0
CO_2 from <i>Z</i> -asparagine-1,1- O^{18}				4.4
CO_2 from <i>Z</i> - β -cyanoalanine ^b	4.4	2.2		2.7
<i>N,N'</i> -Dicyclohexylurea from above	0	4.4		3.6

^a Determined as **5**. ^b Obtained from *Z*- β -cyanoalanine plus *N,N'*-carbonyldiimidazole.

It is concluded from the data in Table I that the principal if not exclusive pathway for the dehydration of **1** and **3** by dicyclohexylcarbodiimide involves an *internal acylation of an amide oxygen by an "activated" carboxyl group*.¹² Appropriate caution must be taken in extending this interpretation to formally similar

(7) M.p. 164.5–166°. *Anal.* Calcd. for $C_{10}H_{17}O_2N_2$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.45; H, 7.40; N, 18.45.

(8) R. Paul and G. W. Anderson, *J. Org. Chem.*, **27**, 2094 (1962).

(9) H. A. Staab, *Ann.*, **609**, 75 (1957); G. W. Anderson and R. Paul, *J. Am. Chem. Soc.*, **80**, 4423 (1958).

(10) Thin layer chromatography indicated no more than 5% of carbobenzoxy- β -cyanoalanine was formed during the reaction at -15° .

(11) R. Paul and G. W. Anderson, *J. Am. Chem. Soc.*, **80**, 4423 (1958).

(12) The possibility of **1b** forming a symmetrical anhydride and then going to **2** by an intramolecular reaction has not been eliminated by our study.

reactions utilizing other dehydrating agents or other bifunctional amide systems.¹³

Acknowledgment.—We wish to thank Dr. G. W. Anderson for his interest in this problem and Mr. A. H. Struck for carrying out the mass spectrometric analyses and interpretation.

(13) NOTE ADDED IN PROOF.—Dr. C. Ressler has informed the authors that an unpublished mass spectrometric study of the dicyclohexylcarbodiimide dehydration of *Z*-asparagine-1,1- O^{18} in her laboratories (with D. V. Kashelkar) is consistent with the predominance of path B in this reaction.

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RECEIVED OCTOBER 25, 1963

The Reductive Aromatization of Steroidal Dienones. A New Method for the Preparation of Estrone

Sir:

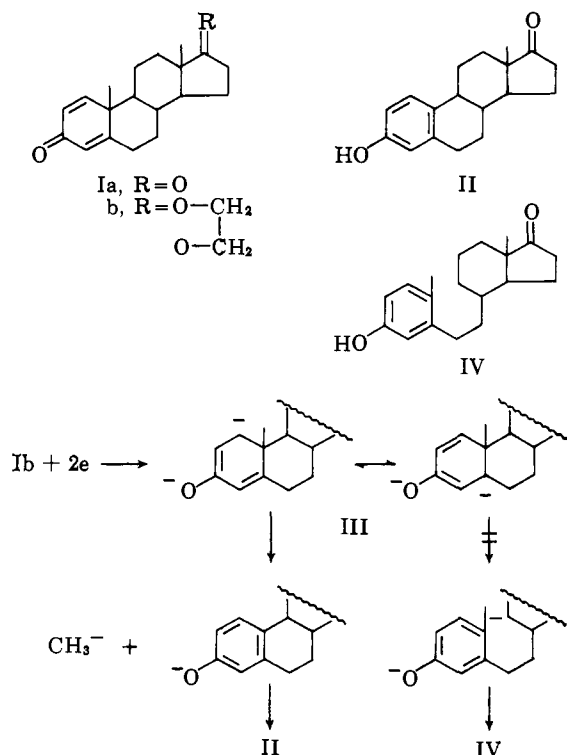
Estrone (II), a key intermediate in the preparation of medicinally useful 19-norsteroids,^{1a} hitherto has been prepared by the pyrolysis of androsta-1,4-diene-3,17-dione (Ia) in mineral oil-tetralin solution.^{1b} We wish to report a new reaction of steroidal A-ring dienones which constitutes the basis of a superior process for the conversion of androsta-1,4-diene-3,17-dione to estrone. Treatment of the 17-ethylene ketal (Ib)² of androstadienedione (obtainable from the dienedione in nearly quantitative yield) with an excess of the radical anion derived from lithium metal and biphenyl in boiling tetrahydrofuran solution effects aromatization of the A-ring with expulsion of the angular methyl group as methylolithium. Acidification of the reaction mixture hydrolyzes the ketal function and affords estrone in 55–58% yield. The addition of a suitably acidic hydrocarbon such as diphenylmethane or methylanthralene to the reaction mixture, in order to intercept the by-product methylolithium and prevent its unwanted addition to the carbonyl group of Ib,³ increases the over-all yield of estrone from Ib to about 75%. We suggest that this new reaction be known as reductive aromatization. A variety of aromatic hydrocarbons and ethereal solvents may be substituted for the biphenyl and tetrahydrofuran, respectively. Sodium and potassium metals may replace lithium but the yields of estrone are lower. The reaction has been applied successfully to a number of steroidal A-ring dienones and others are being studied. Although the reductive aromatization reaction involves the breaking of a C–C bond, it affords estrone from Ib in 70% yield at the remarkably low temperature of 35° .

We believe that the reductive aromatization reaction occurs by the addition of two electrons to the dienone ring to afford dianion III. In the absence of an effective proton donor, this dianion stabilizes itself by eliminating methyl carbanion with the concurrent formation of a phenoxide ion. The resonance energy thus gained must provide part of the driving force for rupture of the C–C bond; in addition, lithium ion probably coordinates with the departing methyl carbanion and assists the bond breaking process. The other possible product IV (from elimination of a C-9 carbanion)

(1) For key references see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959: (a) pp. 586–599; (b) p. 479.

(2) M. J. Gentles, J. B. Moss, M. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958); R. M. Dodson and R. C. Tweit, U. S. Patent 2,875,215 (1959).

(3) In the absence of the methylolithium interceptor, 1,4-dimethylestra-1,3,5(10)-trien-17-one, the product resulting from methylolithium addition to Ib, followed by dienol-benzene rearrangement during work-up, can be isolated from the reaction liquors. We are indebted to Dr. L. J. Chinn for an authentic sample of this material. The rate of addition of diphenylmethylolithium, formed from methylolithium and diphenylmethane, to the carbonyl group of Ib appears to be very slow compared to the rate of aromatization.



appears to be formed in only a minor amount, if at all.^{3a} This preferential elimination of methyl carbanion from III must be caused by the following factors: (a) elimination of the most stable carbanion would be expected, hence the I^o methyl carbanion in preference to the II^o C-9 carbanion; and (b) elimination of methyl carbanion involves a favored diaxial *trans* elimination with the electron pair at C-1 (or C-5) displacing the angular methyl group.⁴

(3a) NOTE ADDED IN PROOF.—Although to date we have neither isolated IV from our reaction nor been able to establish that it is formed in even a minor amount, we have just learned from Dr. R. M. Dodson that he has prepared IV by an unequivocal method. We are indebted to Dr. Dodson for informing us of his results prior to publication and for sending us a sample of IV.

(4) Although our reaction bears an apparent resemblance to the zinc dust-pyridine aromatization of certain steroidal dienones and trienones reported recently by K. Tsuda, E. Ohki, and S. Nozoe [*J. Org. Chem.*, **28**, 783 (1963)], the two reactions must be very different mechanistically. The zinc dust-pyridine aromatization of Ia is reported to give only a 4% yield of estrone; the major product (80%) is 4-methylestra-1,3,5(10)-trien-1-ol-17-one resulting from dienone-phenol rearrangement.

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RECEIVED DECEMBER 28, 1963

Molybdate- and Tungstate-Catalyzed Fixation of Nitrogen

Sir:

The apparent correspondence between the catalysis by molybdates of the reduction of nitrate in acidic solution¹ and the molybdenum requirement of nitrate reductase² in biochemical systems led us to consider whether or not molybdate would catalyze the reduction of molecular nitrogen in aqueous acid. Molybdate is a requirement of nitrogen-fixing legumes which suggests that it might catalyze nitrogen fixation in inorganic systems.

We have attempted cathodic reduction using platinum electrodes and porous graphite electrodes through which nitrogen was bubbled and by bubbling nitrogen

TABLE I

Reducing agent	Catalyst ^a	Medium	NH ₄ ⁺ formed, moles/l.
Pt cathode	MoO ₄ ⁻²	3 M HCl	~10 ^{-4b}
Porous graphite cathode (PGC)	MoO ₄ ⁻²	3 M HCl	10 ⁻⁴ -10 ^{-3b}
PGC	MoO ₄ ⁻²	Phosphate buffer, pH 7	~10 ^{-4b}
PGC	MoO ₄ ⁻² + catechol	Phosphate buffer, pH 7	<10 ⁻⁶
Zn metal	MoO ₄ ^{-2c}	3 M HCl	~10 ⁻⁴
SnCl ₂	WO ₄ ^{-2c}	12 M HCl	~10 ^{-3d}

^a Less than 10⁻⁶ M NH₄⁺ was obtained during all electrolyses done in the absence of catalyst for periods of 1-7 days. ^b NH₄⁺ production ceased when all Mo(VI) was reduced to Mo(III), usually during first 24 hr. ^c No experiments without catalyst were performed. ^d NH₄⁺ still increasing after 2 weeks.

through aqueous acids containing molybdic acid under conditions previously found favorable to the reduction of nitrate¹ and in phosphate buffers at pH 7.0. We have also bubbled nitrogen through solutions of tungstic acid containing stannous chloride in which perchlorate has been found to be reduced.³ In all cases, small concentrations of ammonium ion were found (10⁻⁴ to 10⁻³ M, or 10 to 100 times the detection limit using our sampling procedure). A Kjeldahl separation followed by a spectrophotometric test using Nessler's reagent was employed for detecting ammonium ion. No ammonium ion was found after electrolysis was performed in the absence of molybdenum, nor when molybdate was bound in a chelate complex with catechol [Mo(VI)-(catechol)₂] during the electrolysis.

All reagents were determined to be free of nitrate and ammonium ions. Nitrogen gas was scrubbed with 3 M hydrochloric acid and found free of ammonia. Great care was taken to prevent introduction of ammonia from any source other than reduction of nitrogen gas.

Successful electrolyses ceased to produce further ammonium ion during the first 24 hr., at which time the molybdenum was quantitatively reduced to Mo(III).

One experiment employing a zinc reductor gave positive results, but no control on the catalyst has been tried.

One experiment involving bubbling nitrogen through a stannous chloride and tungstic acid solution in concentrated hydrochloric acid gave continuously increasing concentrations of ammonium ion (~10⁻³ M) over a 2-week period. The ammonium ion must come from nitrogen, but whether tungstic acid is necessary is not yet known.

Some similarities to patterns of catalytic behavior of Mo(VI) and W(VI) toward reduction of oxy-ions is noted.^{1,3,4} Catalysis ceases if Mo(VI) is reduced to Mo(III) in reductions of perchlorate,⁴ nitrate,¹ and nitrogen. Tungsten(VI) is not reduced by Sn(II), thus it remains in a catalytically active higher state.³

Mo(IV) has been postulated to be much more catalytically active than Mo(V) or Mo(VI) at room temperature^{1,4} in reference to oxy-ion reduction. Since Mo(IV) and Mo(V) form stable complexes with CN⁻, which is isoelectronic with N₂, interaction of N₂ with Mo(IV) or Mo(V) to form activated complexes in which the N-N bond is weakened is a fair possibility.

Although the production of ammonium ion is small, the failure to produce it in the absence of catalyst and our fortuitous finding of a catalyst poison (catechol) lend credence to the results. It is certain that 10⁻⁴ M ammonium ion would represent a large concentration

(1) G. P. Haight, Jr. and A. Katz, *Acta Chem. Scand.*, **16**, 659 (1962).

(2) D. J. Nicholas, A. Nason, and W. D. McElroy, *J. Biol. Chem.*, **207**, 341 (1954).

(3) G. P. Haight, Jr., *J. Am. Chem. Soc.*, **76**, 4718 (1954).

(4) G. P. Haight, Jr., and W. F. Sager, *ibid.*, **74**, 6056 (1952).