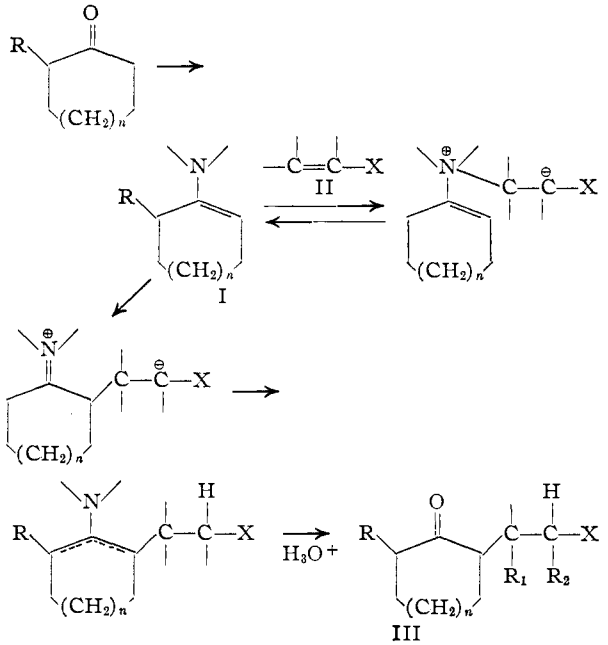
via their pyrrolidine enamines (I) to further scrutiny.

With respect to the introduction of *alkyl* groups α to a carbonyl two reactions may be distinguished: The first utilizes alkyl halides, and the second employs reactive α,β-unsaturated nitriles, esters, ketones, etc. (II, X = CN, CO_2R, O=C—R . . .). The important practical difference between these two reactions is that the undesirable N-alkylation of the enamine is *reversible* in the case of the latter which is therefore the more general reaction.



We have in fact found it of wide applicability to cyclic and acyclic ketones, as well as aldehydes, provided the carbonyl compound has at least one α-methylene group. The following examples will illustrate the usefulness of the new method:[2]

From cyclopentanone[3] were obtained the following alkylated ketones: III (n = 0, R = H): R_1 = R_2 = H, X = CN; b.p. 144–147° (13 mm.), in 65% yield with *acrylonitrile*[4a]; R_1 = R_2 = H, X = CO_2CH_3; b.p. 127–130° (11 mm.), in 55% yield with *methyl acrylate*.[4a]

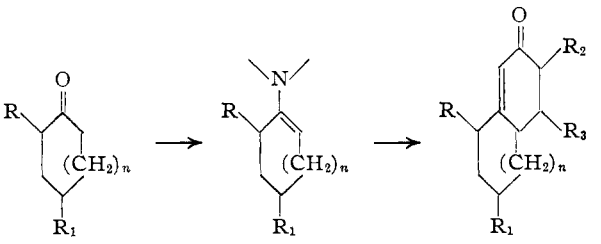
From cyclohexanone,[3] the following ketones III (n = 1, R = H) were formed: R_1 = R_2 = H, X = CN, in 85% yield with *acrylonitrile*[1,4b]; R_1 = R_2 = H, X = CO_2CH_3; b.p. 134–137° (11 mm.), in 65% yield with *methyl acrylate*[4b]; R_1 = CH_3, R_2 = H, X = $CO_2C_2H_5$; b.p. 165–170° (18 mm.), in 56% yield with *ethyl crotonate*[5]; R_1 = H, R_2 = CH_3, X = CO_2CH_3; b.p. 148–150° (18 mm.), in 81% yield with *methyl methacrylate*.[5]

From 2-methylcyclohexanone 42% III (n = 1, R = CH_3, R_1 = R_2 = H, X = CN), b.p. 132–133° (2 mm.), was obtained with *acrylonitrile*.[5,6] Similarly, 2-β-cyanoethylcyclohexanone gave, in only fair yield, III (n = 1, R = CH_2CH_2CN, R_1 = R_2 = H, X = CN), b.p. 190–195° (1 mm.).[5,6]

From cycloheptanone could similarly be obtained III (n = 2, R = R_1 = R_2 = H, X = CN), b.p. 140–145° (10 mm.).

In the same manner, the N-methyl-N-cyclohexyl enamine of 2-heptanone and *acrylonitrile*[4a] yielded 45% of 3-β-cyanoethyl-2-heptanone, b.p. 145–147° (11 mm.) while from the enamine of heptaldehyde, *acrylonitrile* produced 50% of 2-β-cyanoethylheptaldehyde, b.p. 145–148° (12 mm.).[4a]

The reactions of pyrrolidine enamines with α,β-unsaturated ketones such as methyl vinyl ketone and its homologs proved especially interesting: The product in this case is initially of type III (X = O=C—CH_3), but this intermediate undergoes cyclization and loss of pyrrolidine which then reacts with the resulting octalone (IV) to form *its* enamine. This relatively stable enamine can be decomposed to IV by *refluxing* with acetic acid–sodium acetate.[7] The following examples will give an idea of the scope of this new reaction (equimolar amount in dioxane at room temperature, unless otherwise noted)



From cyclohexanone[3] were obtained: With *methyl vinyl ketone* (4 hr.), 75% IV (n = 1, R = R_1 = R_2 = R_3 = H). With *methyl isopropenyl ketone* (14 hr. *at reflux*), 66% IV (n = 1, R = R_1 = R_3 = H, R_2 = CH_3). With *ethyl acetylacrylate* (14 hr.), 75% IV (n = 1, R = R_1 = R_2 = H, R_3 = $CO_2C_2H_5$), m.p. 50–52°.

From 4-hydroxycyclohexanone benzoate[3] and MVK (10 hr. in dimethylformamide) 51% IV (n = 1, R = R_2 = R_3 = H, R_1 = C_6H_5COO—), m.p. 110–112°.

From 2-methylcyclohexanone[3] and MVK (14 hr.) 56% IV (n = 1, R_1 = R_2 = R_3 = H, R = CH_3).[6]

From cyclopentanone[3] and MVK (14 hr.) 42% IV (n = 0, R = R_1 = R_2 = R_3 = H).[8]

(2) Boiling points or melting points are given for all new compounds. Analyses of these and/or their derivatives were satisfactory.

(3) *Via* the pyrrolidine enamine.

(4) Refluxing in dioxane-(a) 16 hours, (b) 3 hours.

(5) Refluxing for 36 hours in dimethylformamide.

(6) Note that alkylation of an α-substituted cyclohexanone gives *further alkylation on the α'-methylene* by this method.

(7) *Cf.*, F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(8) Compare the alternate method of synthesis, V. Prelog and M. Zimmermann, *Helv. Chim. Acta*, **32**, 2360 (1945).

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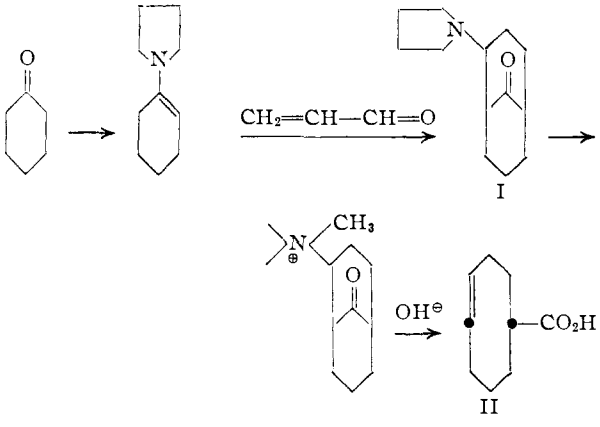
RECEIVED AUGUST 31, 1956

A NEW RING ENLARGEMENT SEQUENCE

Sir:

We have found a new method of ring enlargement which leads from a ketone to an unsaturated cyclic acid with two more carbon atoms. This is illustrated below with cyclohexanone.

Reaction of the pyrrolidine enamine of cyclohexanone with one equivalent of acrolein in dioxane, initially at 0°, gave 75% of I, b.p. 125–127° (0.5 mm.); picrate, m.p. 171–172° (found: C, 52.42; H, 5.51). I could be reduced in 72% yield by the Wolff–Kishner method to the corresponding desoxo compound, b.p. 145–147° (15 mm.); *picrate*, m.p. 147–148° (found: C, 54.33: H, 6.11).



The methiodide of I was transformed, on heating with aqueous base, to 4-cycloöctenecarboxylic acid (II), b.p. 118–120° (0.4 mm.); amide, m.p. 201–202° (found: C, 69.89; H, 9.63). Catalytic reduction of II gave the known cycloöctanecarboxylic acid.[1]

In a similar manner, the pyrrolidine enamine of cyclopentanone and acrolein led after one hour at room temperature to 55% of bicyclic aminoketone, b.p. 110–115° (0.5 mm.): *picrate*, m.p. 180–181° (found: C, 51.31; H, 5.39). This gave, *via* its methiodide, 4-cycloheptenecarboxylic acid, m.p. 65–67° (found: C, 68.38; H, 8.70). It is presumed that the new reaction will be applicable to substituted cyclic ketones and also to substituted acroleins. This point will have to be established.

(1) This was compared as its amide by mixed melting point with a sample kindly supplied by Prof. A. C. Cope: A. C. Cope and H. O. Van Orden, THIS JOURNAL, **74**, 175 (1952).

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RECEIVED AUGUST 31, 1956

LOCATION OF THE SIXTH HYDROXYL GROUP IN OUABAGENIN

Sir:

On the basis of evidence summarized recently[1] the positions (1, 3, 5, 14, and 19) of five of the six hydroxyl groups of ouabagenin may be regarded as firmly established. The location of the sixth (secondary) hydroxyl function has remained unsettled, although certain observations of Tschesche and Snatzke[2] suggest that this group is attached at C.11 (α) in agreement with a tentative proposal advanced some years ago by Fieser and Newman.[3]

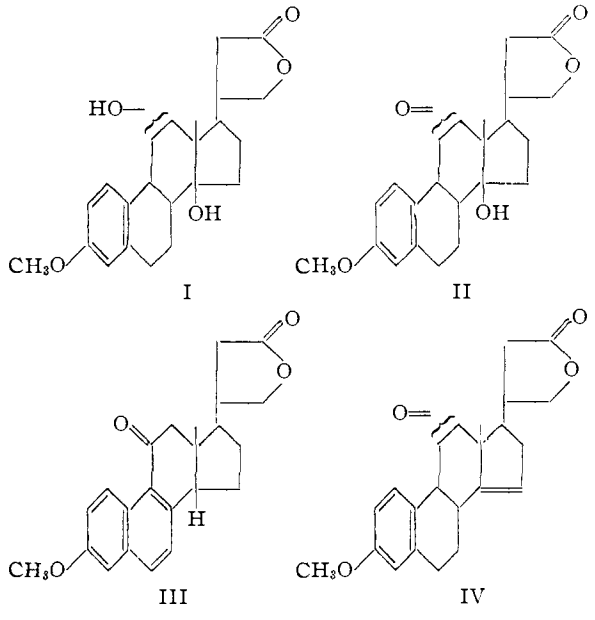
(1) K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1174 (1954); R. P. A. Sneeden and R. B. Turner, THIS JOURNAL, **77**, 130 (1955); Ch. Tamm, *Helv. Chim. Acta*, **38**, 147 (1955).

(2) R. Tschesche and G. Snatzke, *Ber.*, **88**, 1558 (1955).

(3) L. F. Fieser and M. S. Newman, *J. Biol. Chem.*, **114**, 705 (1936); see also C. Mannich and G. Siewert, *Ber.*, **75**, 737, 750 (1942).

We have now obtained definitive evidence in support of the C.11 assignment.

Oxidation of the diol I, obtained in the earlier investigation,[1] with the chromium trioxide–pyridine complex furnishes a ketol (II), m.p. 189–191°, $[\alpha]D$ +182° (*c* 1.34, acetone), $\lambda_{max.}$ 2.80, 5.62, 5.80 μ, (*Anal.* Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.60; H, 7.54). The ultraviolet spectrum of II ($\lambda_{max.}$ 276, 284 mμ, ϵ 1626, 1522) shows only anisole absorption, and the absence of a conjugated carbonyl system in this substance is



further established by the position (5.80 μ) of the ketonic absorption band in the infrared. The suggestion of Djerassi and Ehrlich[4] that the hydroxyl group in question may occupy the 6-position in ouabagenin is thereby excluded.

Palladium dehydrogenation of II at 260° proceeds with concomitant loss of the 14-hydroxyl group, and yields a product (III), m.p. 260.5–262.5°, $[\alpha]D$ +159° (*c* 0.97, chloroform), (*Anal.* Calcd. for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.91; H, 6.91), the ultraviolet absorption of which ($\lambda_{max.}$ 220, 246, 312, 348 mμ, log ϵ 4.75, 4.56, 3.94, 3.63) is virtually indistinguishable from that of *cis*-3-methoxy-11-ketoequilinane ($\lambda_{max.}$ 220, 246, 312, 348 mμ, log ϵ 4.79, 4.60, 3.93, 3.64), synthesized in an unambiguous manner by Eglinton, Nevenzel, Scott and Newman.[5] Compound III can also be obtained by dehydrogenation of IV, m.p. 236–242° (dec.), $[\alpha]D$ +270° (*c* 1.01, chloroform), $\lambda_{max.}$ 276, 284 mμ, ϵ 1559, 1471, (*Anal.* Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.15; H, 7.24), which was prepared from I by acetylation and dehydration,[1] hydrolysis and oxidation with the chromium trioxide–pyridine complex.

There can be no doubt that the chromophoric systems present in III and in *cis*-3-methoxy-11-ketoequilinane are the same. This evidence estab-

(4) C. Djerassi and R. Ehrlich, *J. Org. Chem.*, **19**, 1351 (1954).

(5) G. Eglinton, J. C. Nevenzel, A. I. Scott and M. S. Newman, *Chem. and Ind.*, 686 (1953); THIS JOURNAL, **78**, 2331 (1956). We are indebted to Professor Newman for samples of *cis*- and *trans*-3-methoxy-11-ketoequilinane for direct spectral comparison with III.