oxa-5α-androstane (1.25 g.)[9] to hemiacetal III (0.32 g.) was also easily accomplished. A pure specimen melted at 226–228°. *Anal.* Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46; O, 15.56. Found: C, 74.14; H, 10.27; O, 15.73.

We also wish to report that diborane reduction of certain lactones in the presence of boron trifluoride etherate yields the corresponding ether derivative.[10] For example, when reduction of 3-oxo-4-oxa-5α-cholestane (0.39 g.) was repeated employing diborane–boron trifluoride etherate the product was 4-oxa-5α-cholestane[11] (Ic, 0.07 g.).

The stereochemistry assigned hemiacetals Ia, IId, and III received substantial support when each was recovered following equilibration in acidified (hydrochloric acid) tetrahydrofuran or methanol solution.

Several other facets of this unusually mild route to hemiacetals are now under investigation.

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Received August 9, 1961

(9) M. F. Murray, B. A. Johnson, R. L. Pederson, and A. C. Ott, *J. Am. Chem. Soc.*, **78**, 981 (1956).

(10) *Cf.*, G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

(11) The 4-oxasteroid (Ic) was identical with an authentic specimen kindly supplied by Dr. J. T. Edward. See, J. T. Edward and P. F. Morand, *Can. J. Chem.*, **38**, 1325 (1960).

17α-Acetoxy-6,16α-dimethylprogesterones

Sir:

In a recent communication[1] we reported the synthesis of a series of 6,16α-dimethylprogesterones.[2] We have now prepared the 17α-acetoxy derivatives of these compounds and find them to be one of the most potent series of orally active progestogens known to date.

A toluene solution of 5,6α-epoxy-16-pregnene-3β-ol-20-one acetate (I) was added to an excess of ethereal methyl magnesium bromide containing powdered cuprous chloride. The magnesium enolate so formed was treated *in situ* with acetic anhydride[3] for periods of up to 3 days to form 6β,16α-dimethyl-17(20)-pregnene-3β,5α,20-triol triacetate (II). The crude compound II on treatment with peracetic acid gave the 17(20)-epoxide which without purification was saponified with methanolic potassium carbonate. The crude 6β,16α-dimethylpregnane-3β,5α,17α-triol-20-one 5-acetate (IIIa) was purified as the 3,5-diacetate (IIIb), m.p. 206.5–208.5°, $[\alpha]_D^{26}$ −27.5°.[4] Saponification of IIIb with potassium bicarbonate in aqueous methanol gave IIIa as a hydrate, m.p. 186–190°, $[\alpha]_D^{26}$ −27.3°, which on oxidation with 8*N* chromic acid–sulfuric acid reagent in acetone gave 6β,16α-dimethylpregnane-5α,17α-diol-3,20-dione 5-acetate (IIIc), m.p. 161–163° (hydrated form), $[\alpha]_D^{26}$ −26.9°. Refluxing a solution of IIIc in ethanol containing hydrochloric acid effected β-elimination together with isomerization at C-6 producing 17α-hydroxy-6α,16α-dimethylprogesterone (IVa).[5] The 17α-acetate (IVb)[6] was prepared in the usual manner.[7] Dehydrogenation of IVa with chloranil in *t*-butanol[8] gave 17α-hydroxy-Δ^6-dehydro-6,16α-dimethylprogesterone (Va) which was also converted to its 17α-acetate (Vb). The Δ^1-dehydro com-

(1) R. P. Graber and M. B. Meyers, *Chem. & Ind.*, 1478, (1960).

(2) 6α,16α-Dimethylprogesterone has been reported recently by (a) S. Bernstein, E. W. Cantrall, and J. P. Dusza, *J. Org. Chem.*, **26**, 269 (1961) and (b) J. Iriarte and M. L. Franco, *J. Org. Chem.*, **26**, 2047, (1961).

(3) K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).

(4) All melting points determined on a micro hot stage; all rotations in chloroform. Satsifactory elemental analyses obtained for all new compounds described herein.

(5) See ref. 2b. Reported m.p. 200–202°, $[\alpha]_D$ + 51.4°, $\lambda_{max}^{C_2H_5OH}$ 240–242 mμ, ϵ 16,600.

(6) See ref. 2b. Reported m.p. 170–172°, $[\alpha]_D$ + 71.1°, $\lambda_{max}^{C_2H_5OH}$ 240 mμ, ϵ 13,800.

(7) *Cf.* C. G. Bergstrom, P. B. Sollman, R. T. Nicholson, and R. M. Dodson, *J. Am. Chem. Soc.*, **82**, 2322 (1960).

(8) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

TABLE I

Compound	M.P.	$[\alpha]_D$[a]	$\lambda_{max}^{C_2H_5OH}$ mμ(ϵ)	Oral Activity[b]
17α-Hydroxy-6α,16α-dimethylprogesterone(IVa)	203–207°	+53.5°	242(15,400)	0.25
17α-Acetoxy-6α,16α-dimethylprogesterone (IVb)	169–171°	+69.0°	242(15,800)	55
17α-Hydroxy-Δ^6-dehydro-6,16α-dimethylprogesterone (Va)	220.5–229°	+27.9°	290(23,200)	—
17α-Acetoxy-Δ^6-dehydro-6,16α-dimethylprogesterone (Vb)	189.5–195°	+25.6°	288(24,900)	130
17α-Acetoxy-Δ^1-dehydro-6α,16α-dimethylprogesterone (VI)	168–173°	+21.7°	245(15,800)	40
17α-Acetoxy-$\Delta^{1,6}$-bisdehydro-6,16α-dimethylprogesterone (VII)	161.5–163°	−24.2°	228(12,000) 256(8470) 302(11,540)	120

[a] Temperature *ca.* 25°. [b] Clauberg assay; ethinyl testosterone = 1. Assays by Endocrine Laboratories, Madison, Wis.

pounds, VI and VII, derived from IVb and Vb were readily obtained by use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing benzene.[9]

Table I gives the physical constants of the series of 17-oxygenated-6,16α-dimethylprogesterones and their respective oral progestational activities.

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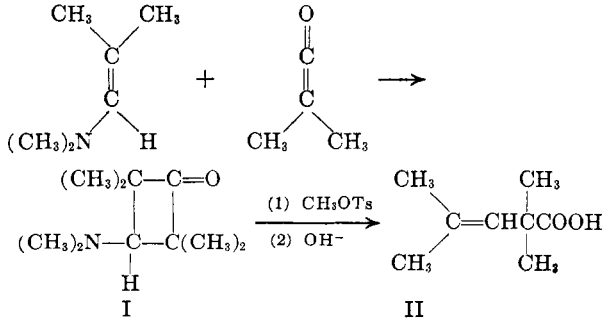
(9) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

Cycloaddition of Ketenes to Enamines

Sir:

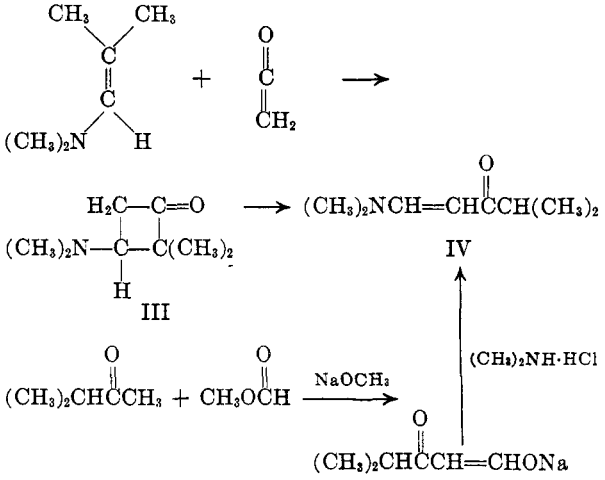
We wish to report some new reactions involving cycloaddition of ketenes to enamines derived from aldehydes. Ketene and dialkylketenes react with enamines having either one or no β-hydrogen to give 3-dialkylaminocyclobutanones. If the resulting cyclobutanones have one or more α-hydrogens (III, V, VII), they undergo an irreversible, ring-opening reaction; cyclobutanones that have no α-hydrogens (I) are quite stable.

Dimethylketene and *N*,*N*-dimethylisobutenylamine, when mixed in isopropyl acetate at room temperature, reacted to give a 64% yield of 3-dimethylamino-2,2,4,4-tetramethylcyclobutanone (I), b.p. 83–85° (24 mm.), n_D^{20} 1.4439, infrared maximum at 5.65 μ (cyclobutanone). The NMR spectrum of I was in complete agreement with the proposed structure. *Anal.* Calcd. for $C_{10}H_{19}NO$: C, 71.1; H, 11.2; N, 8.3. Found: C, 71.3; H, 11.2; N, 8.1. Quaternization of I with methyl tosylate followed by treatment with aqueous potassium hydroxide solution gave, after acidification, a 71% yield of 2,2,4-trimethyl-3-pentenoic acid (II), b.p. 86° (2 mm.), n_D^{20} 1.4472. *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.6; H, 9.9; neut. equiv., 142. Found: C, 67.6; H, 10.1; neut. equiv., 142.



I II

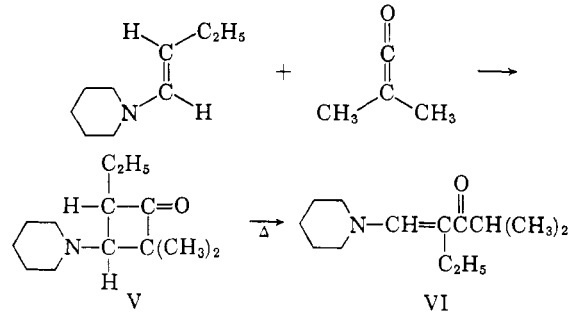
Ketene reacted with *N*,*N*-dimethylisobutenylamine in hexane at 0° to give the intermediate 3-dimethylamino-2,2-dimethylcyclobutanone (III), identified by the characteristic infrared absorption of cyclobutanones at 5.65 μ. When this reaction product was warmed, its infrared spectrum changed radically; the band at 5.65 μ disappeared and three new bands at 6.05, 6.25, and 6.38 μ appeared. Distillation gave a 93% yield of 1-dimethylamino-4-methyl-1-pentene-3-one (IV), b.p. 105–107° (2 mm.), n_D^{20} 1.5301. *Anal.* Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.6; N, 9.9. Found: C, 68.0; H, 10.9; N, 9.7. The structure of IV was confirmed by independent synthesis from 3-methyl-2-butanone, methyl formate, and dimethylamine.[1]



III IV

Berchtold, Harvey, and Wilson have isolated a cycloaddition product similar to III (*N*-morpholino in place of the dimethylamino group) and noted its thermal rearrangement to the acyclic aminovinyl ketone.[2] It has also been brought to our attention that a keto base is found in the acylation of an enamine with acetyl chloride, apparently by abstraction of hydrogen chloride to form ketene, and subsequent cycloaddition to the enamine.[3]

Dimethylketene and *N*-(1-butenyl)piperidine[4] in



V VI

hexane reacted at −20° to give 2-ethyl-4,4-dimethyl-3-piperidinocyclobutanone (V), which, on distillation, gave an 82% yield of 2-ethyl-4-methyl-1-piperidino-1-penten-3-one (VI), b.p. 119–121° (0.6 mm.), n_D^{20} 1.5424, infrared maxima at 6.05, 6.25, and 6.38 μ. *Anal.* Calcd. for $C_{13}H_{22}NO$: C, 74.6; H, 11.0; N, 6.7. Found: C, 74.6; H, 11.0; N, 6.8.

(1) E. Benary, *Ber.*, **63**, 1573 (1930).
(2) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, *J. Org. Chem.*, **26**, 4776 (1961).
(3) G. Opitz, private communication.
(4) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).