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UNEXPECTED REACTION OF A DIENAMINE WITH METHYL ACRYLATE

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As part of another project, we wished to prepare the unsaturated keto ester 2. Although we eventually obtained the desired material in 58% yield by direct, base-catalyzed Michael reaction of enone 1[1,2] with methyl acrylate, this report is concerned with an unexpected reaction we encountered in our initial synthetic efforts.

Heating of enone 1 in excess pyrrolidine followed by dilution of the reaction mixture with methanol gave dienamine 3a [mp 135-137°; λ_{max} (C_2H_5OH) 278 nm (ϵ = 18,350); δ ($CDCl_3$) 4.96 (s, 1, $C_{10}\underline{H}$ and 5.08 ppm (m, 1, $C_{11}\underline{H}$)] in 97% yield as an analytically pure yellow-orange solid. Our reasons for feeling that the reaction of this material with methyl acrylate would give keto ester 2 were two-fold. Firstly, dienamine 3b is smoothly alkylated at C_{10} (steroid numbering) by 1,3-dichloro-2-butene[4]. Secondly, heating of dienamine 5 in dioxane with methyl acrylate[5,6] was reported to give, after hydrolysis with acetate buffer, a 50% yield of keto ester 6. When dienamine 3a was heated at

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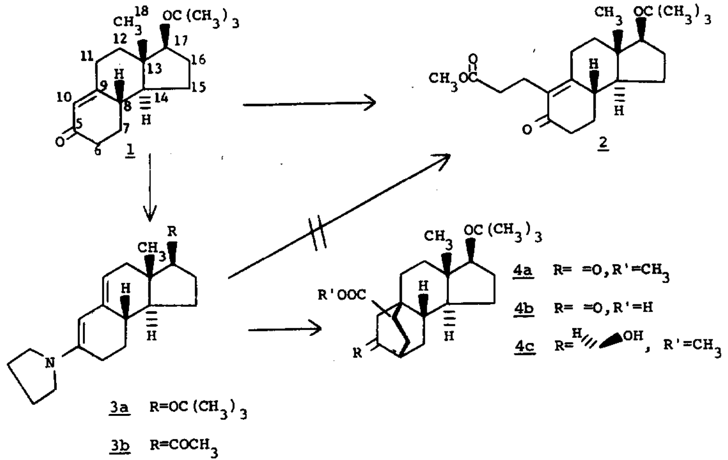
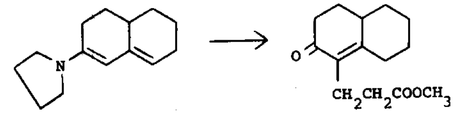

1
2
3a R=OC(CH3)3
3b R=COCH3
4a R= =O, R'=CH3
4b R= =O, R'=H
4c R= H, OH, R'=CH3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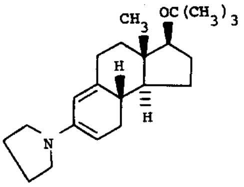
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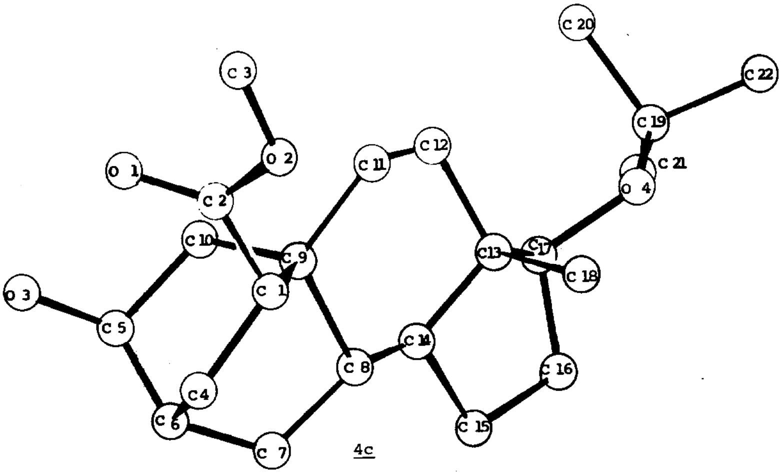
C 20
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C 1
O 3
C 5
C 14
C 8
C 16
C 4
C 6
C 15
C 7

4c

reflux in dioxane with 2 equivalents of methyl acrylate for 40 hours, followed by treatment with acetate buffer[7)], none of compound 2 was obtained. Chromatography of the reaction mixture gave, in addition to a small amount of 1, a 60% yield, after crystallization, of a new compound, mp 136-138°, $[\alpha]_D^{25}$ + 16.3° (c 1.73, $CHCl_3$).

The new compound 4a was shown to be a 1:1 adduct of 1 and methyl acrylate by high resolution mass spectrometry [$M^+ - (CH_3)_2C{=}CH_2$ at m/e 306.1817; $C_{18}H_{26}O_4$ requires 306.1830]. The absence of vinyl proton signals in the NMR and of any UV absorption, as well as a negative tetranitromethane test[8)], indicated that the material contained a new ring. The compound exhibited only a single carbonyl absorption band at 1730 cm^{-1}. Saponification of 4a gave acid 4b, mp 226-229° with gas evolution. The IR spectrum of this material, taken in chloroform containing piperidine to shift the carboxylate carbonyl signal away from the region of interest, showed an additional carbonyl signal, thus confirming the presence of both keto and ester functionalities in 4a. Compound 4a, upon treatment with acid or base, cleanly exchanged two protons for deuterium. NMR at 220 MHz showed signals for a $CH_2C{=}O$ and two $CHC{=}O$ groupings. The sum of this information was sufficient to allow us to tentatively assign structure 4a (without stereochemistry) to the new compound.

Hydrogenation of compound 4a over platinum in acetic acid gave hydroxy ester 4c, mp 157.5-160°, from which it could be regenerated by Collins oxidation[9,10)]. Since 4a crystallized as fine needles which were unsatisfactory for X-ray crystallographic analysis, the crystal structure of 4c was determined. Crystals of 4c are monoclinic, space group $P2_1$, with a=13.24, b=10.97, c=7.50 Å and β=104.59°. The intensity data were collected on a four-circle diffractometer using Cu Kα radiation and pulse height discrimination. The structure was solved by direct methods using tangent formula phase refinement. Least squares refinement with isotropic temperature factors was stopped when the structure and stereochemistry of 4c were no longer in doubt (R=13.5%).

The obtention of product 4a from the reaction of 3a with methyl acrylate implies the intermediacy of the homoannular dienamine 7[11)]. The Diels-Alder reaction of such dienamines is precedented[12)]. The enamine of isophorone is a mixture of linear- and cross-conjugated forms which reacts with Michael acceptors to give 2-4 products, depending upon the case. The highest yield of product of type 4 was 29%[12)]. Reasons for the highly selective nature of the reaction we have observed are not obvious.

The CD curve of compound 4a ($\Delta\epsilon_{314}$ = -0.043, $\Delta\epsilon_{302}$ = -0.078, $\Delta\epsilon_{291}$ = -0.11,

$\Delta\epsilon_{282} = -0.114$ and $\Delta\epsilon_{214} = 1.63$ in dioxane) is of interest in that comparison with reported spectra[13,14] initially led us to the erroneous conclusion that methyl acrylate had added to the alpha face of 3a. Our results indicate, once again, that one must use discretion in employing the sign of the Cotton effect in non-chair cyclohexane systems for predictive purposes.

References

1) Prepared by treatment of the known[3] (-)-17β-hydroxy-deA-gon-9-en-5-one with isobutylene and catalytic amounts of acid: mp 125-128°; $[\alpha]_D^{25}$ -10.9° (c 1.0, $CHCl_3$).
2) All new compounds gave IR, UV, NMR and mass spectra in accord with their structures, as well as satisfactory combustion analyses.
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5) A.A. Brizzolara, Ph.D. Thesis, Columbia University, New York, 1960 as reported by G.H. Alt in A.G. Cook, Ed., "Enamines: Synthesis, Structure and Reactions", Marcel Dekker, New York, 1969, p. 129.
6) After completion of this work, we were informed by Prof. Stork (personal communication to J.W.S.) that this result is likely to be erroneous. The product is probably a mixture of compounds of, as yet, unknown structure.
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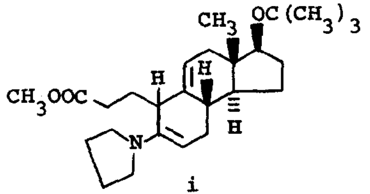
11) The simplest manner in which to envisage this isomerization would be by a deprotonation-protonation sequence. An alternate possibility for obtaining a homoannular dienamine would involve initial reaction at C_{10} to give alkylated product i. 1,3-Sigmatropic shift of the C_{10} proton to C_{11} followed by Diels-Alder addition of methyl acrylate and reverse Michael reaction during hydrolysis would also give 4a. We thank Dr. M. Uskoković for bringing this possibility to our attention.



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13) G.Hugel, L.Lods, J.M.Mellor and G. Ourisson, Bull.Soc.Chim.Fr., 2894 (1965).
14) P.Crabbé, L.H.Zalkow and N.N.Girotra, J.Org.Chem., 30, 1678 (1965).