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PHOSPHASTEROIDS - I. CYCLOADDITION REACTIONS OF PHOSPHOLENES WITH VARIOUS DIENES.*

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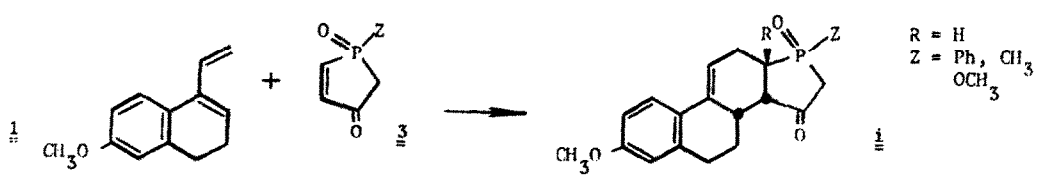
In connection with our interest in the synthesis of phosphorus heterocycles and phosphasteroids, we wish to report a facile total synthesis of the 17-phosphasteroidal skeleton, a synthesis which is based on the cycloaddition of a suitable phospholenic moiety to 1-vinyl-6-methoxy-3,4-dihydronaphthalene (1). This synthetic approach can be considerably generalized, and should be useful in the preparation of a whole variety of polycyclic systems containing the phospholanic moiety.

The attraction of the Diels-Alder reaction for steroid synthesis lies in the facile accessibility of the phospholenic ring, which in itself already contains the P-atom, as well as the accessibility of the diene system, which is well known as a precursor for such Diels-Alder reactions.[1] Even though we were aware of the C/D cis ring junction problem in such steroidal AB→CD type diene condensations[2], we thought it worthwhile to prepare and examine the stereochemistry of the 4,7,8,9-tetrahydrophosphinodoline system, as it is so far unknown.

Several 2- and 3-phospholenes were tested for their ability to undergo the Diels-Alder reaction. 2,3-Dimethyl-1,3-butadiene and 1-vinyl-6-methoxy-3,4-dihydronaphthalene (1) served as the diene substrates, but without success. The failure was not too surprising as the cycloaddition of 2-phospholene (the more reactive of the two above-mentioned phospholenes) and 1,4-diacetoxy-1,3-butadiene (a more reactive diene) yields only 50% after 10 days at 150°,[3] conditions which the above mentioned dienes did not overcome. It was clear that a more reactive dienophile had to be used, and this was achieved by having another attracting group on the double bond. 1-Aryl, alkyl or alkoxy-1-oxo-2-phospholen-4-one (3)[4], in which the double bond is activated by the phosphoryl as well as by the keto group, were checked and indeed gave adducts with all of the examined dienes, even at room temperature. The reaction of 3 with 1 thus yielded a series of compounds of type i:



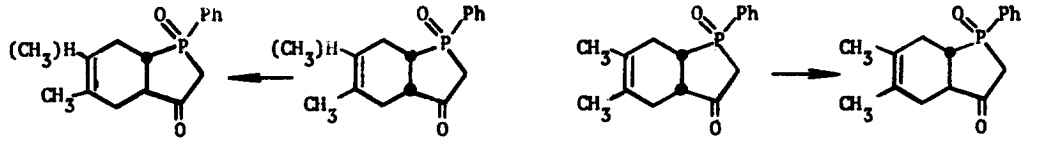
1 3 i

The addition of 1-phenyl-1-oxo-2-phospholen-4-one (3a) to 1 in benzene after 24 hrs. at room temperature gave a white precipitate (4) (1, Z=Ph), m.p. 162-164°.[5] IR (KBr): 2950, 1735, 1608, 1500, 1435, 1230, 1220, 1035, 760, 700 cm^{-1}. NMR ($CDCl_3$) : δ 1.2-2.2 m (2H), 2.2-3.2 m (9H), 3.7 s (3H, OCH_3), 6.38 m (1H, C-11-H), 6.50 d (J=2.5 Hz, C-4-H), 6.62 dd (J=2.5, 9 Hz, C-2-H), 7.48 d (J=9 Hz, C-1-H), 7.50 m (3H, Ph) and 7.70 m (2H, Ph). Mass spectrum: m/e 378 (15%, M^+), 211 (25%, M-PhP(O)CH_2CO), 140 (15%, PhP(OH)CH_3), 125 (7%, PhPOH) and 78 (100%).

Actually, four isomeric compounds could have been obtained from the cycloaddition, assuming a cis 8H, 13H and 14H relationship, according to the nature of the Diels-Alder reaction[2]: two P-epimeric 15-keto-17-phospha and two P-epimeric 17-keto-15-phospha estrane derivatives. Compound 4 turned out to be quite unstable and could be converted by a trace amount of base, or during chromatography on an alumina column, to compound 5, m.p. 232-234°. IR (KBr): 2900, 1735, 1610, 1500, 1235, 1187, 1040, 745, 690 cm^{-1}. NMR ($CDCl_3$): δ 2.1-2.5 m (11H), 3.78 s (3H, OCH_3), 6.15 m (C-11-H), 6.60 d (J=2 Hz, C-4-H), 6.68 dd (J=2, 9 Hz, C-2-H), 7.60 m (4H, C-1-H & Ph) and 7.90 m (2H, Ph).

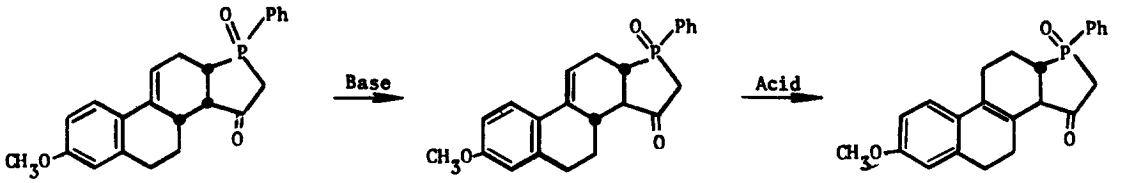
The fact that the C-11-proton could still be seen in the NMR spectrum excluded the double bond shift and indicated a C/D cis ⇌ trans isomerization which was made possible by the keto group α- to the ring junction. In order to examine this hypothesis, two other adducts of 3a were investigated: the reaction products of 2,3-dimethyl-1,3-butadiene and of isoprene, (6) and (7), respectively. Compound 6, m.p. 167-168°.[5] IR (KBr): 3080, 3050, 2915, 2500 (broad), 1590, 1440, 1320, 1230, 1120, 1085, 885, 750, 695 cm^{-1}. IR ($CHCl_3$): 2900, 1740, 1440, 1160 cm^{-1}.[6] NMR ($CDCl_3$) δ 1.66 s (6H, 2 CH_3), 2.00-2.60 m (4H, C_4, C_7), 2.74 m (C-8-H and C-9-H), 2.83 and 3.08 ABX system ($J_{H_AH_B}$=18 Hz, J_{PH_A}=10.5 Hz, J_{PH_B}=13.5 Hz, C_2), 7.52 m (3H, Ph) and 7.85 m (2H, Ph). Mass spectrum: m/e 274 (100%, M^+), 246 (19%, M-CO; M^* 221), 140 (62%, PhP(OH)CH_3), 125 (70%, PhPOH; M^* (140→125) 111.5). and Compound 7, m.p. 133-134°.[5] IR (KBr)[6]: 2900, 2500 (broad), 1590, 1440, 1320, 1230, 1190, 1120, 1085, 695 cm^{-1}. NMR ($CDCl_3$): δ 1.70 s (3H, CH_3), 1.90-2.60 (4H, C_4, C_7), 2.80 m (C-8-H and C-9-H), 2.92 and 3.10 ABX (J_{AB}=18.5 Hz, J_{PH_A}=10 Hz, J_{PH_B}=13 Hz), 5.40 m (C-6-H), 7.54 m (3H, Ph), and 7.85 m (2H, Ph). Mass spectrum: m/e 260 (60%, M^+), 232 (20%, M-CO; M^* 207.5), 140 (62%, PhP(OH)CH_3) and 125 (100%, PhP(OH); M^* (140→125) 111.5).

Both compounds turned out to be as susceptible to alumina or base as compound 4, yielding compounds (8), m.p. 210°, and (9), m.p. 182°, respectively.



9 7 6 8

As only cis-trans isomerization is possible in this case, it was obvious that the above trans tetrahydrophosphindoline systems are more stable than the cis isomers; this most probably is also the situation for compound 4. Compound 5 could be further isomerized under acidic conditions, in which case compound 10 was mainly obtained :



4 5 10

This double bond isomerization from the 9(11) to 8(9) position was important in deciding whether the 17-phospha-15-keto or 15-phospha-17-keto isomer was obtained. The 9(11) to 8(9) double bond shift was clear from the NMR spectrum (disappearance of the C-11-proton signal as well as shifting of the C-1-H from δ 7.40 to 7.20), and from the UV data (shift of the 262 band (ε -21000) for 4 and 264 (ε -22000) for 5 to 272 mμ (ε -17000)).[7] In addition to the 272 mμ band, further absorptions were observed in the acidified solution of 5: 295 (ε -9100), 360 (ε -2600) and 405 mμ (ε~1000) (intensities which were variable according to conditions) thus pointing to a Ph-C=C-C=C-C=O $\rightleftharpoons$ Ph-C=C-C=C-OH chromophore. This, together with the observation that in the IR of 10 in solution another weak CO stretching could be seen at 1700 cm^{-1}, suggested the 17-phospha-15-keto structure.

The 17P-methyl analog of 4, compound 11 (m.p. 168°, IR (KBr): 3035, 2830, 1730, 1605, 1500, 1290, 1235, 1220, 1100 cm^{-1}; NMR ($CDCl_3$) : δ 1.65 d (J_{PH}=11.5, P-CH_3) and 6.40 m (C-11-H); mass spectrum: m/e 316 (41%, M^+), 288 (4%, M-CO), 211 (100%, M-PhP(O)CH_2CO) and 63 (5%)), showed the same behaviour as 4 towards base and acid, yielding compound 12 (m.p. 224°, NMR ($CDCl_3$): δ 1.75 d (J_{PH}=11.5, P-CH_3) and 6.15 m (C-11-H)). Other derivatives of i are under preparation.

It is obvious that the principle embodied in this synthetic sequence leading to 4, 11 and other compounds of type i is capable of extension in the steroid as well as C-P heterocyclic fields. An assessment of the potentialities of this cycloaddition is under investigation.

References and Notes:

1. A.A. Akrem and Yu. A. Titov, "Total Synthesis of Steroids", p. 87, Israel Program for Scientific Translations, Ltd., 1969.

2. Ref. 1, p. 30.

3. T.H. Chan and L.T.L. Wong, Canad. J. Chem. 49, 530 (1971).

4. B.A. Arbuzov, A.P. Rakov and A.O. Vizel, Izv. Akad. Nauk. S.S.S.R. Ser. Khim., p. 85, 1970.

5. It was interesting to note that even during the determination of the m.p.'s of compounds 4, 6 and 7, isomerization already occurs.

6. The absence of the C=O stretching in the KBr spectrum and the appearance of C=C and OH absorptions is known in the literature for phospholan-3-ones; L.D. Quin and J.A. Caputo, Chem. Commun., 1463 (1968).

7. A.I. Scott, U.V Spectra of Natural Products, p. 97, Pergamon Press, 1964.

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