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HETEROCYCLIC STEROIDS XVI

A new synthesis of 13-aza-estrone

by

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Imines, in general unreactive in cycloaddition reactions[3], can be condensed with dienes either via a pseudo Diels-Alder type of reaction or via a suitable activation of the C=N bond[4]. The application of this type of cycloaddition, which potentially allows the construction of a heterocyclic ring system in one single step, would considerably expand the scope of a programme directed towards the total synthesis of heterocyclic steroids.

An example of the first reaction type is the condensation of a biscarbamate 1 with a diene 2 under influence of a Lewis acid[5] to yield the substituted tetrahydropyridines 3. When ethyl biscarbamate 1a (1, R_1= CH_2CH_2COOMe; R_2= Et) is condensed with diene 4a (4, R = H) (70°, benzene, 5 mol.% BF_3-etherate) the tricyclic system 5a (5, R_1= $CH_2CH_2COOCH_3$, R_2= Et) possessing the elements of ring D to be constructed, could be obtained in 30-40% yield after column chromatography.

The unique direction of the addition is in agreement with a polar intermediate in the transition state. The occurence of conformational effects[6], however, complicated an NMR-analysis, preventing thus the assignment of the correct stereochemistry. Furthermore, an unexpected problem was found in the extreme difficult hydrolysis of the carbamate group, which could not be completed in a satisfactory manner. In view of this negative result the corresponding benzyl-biscarbamate 1b (1, R_1= $CH_2CH_2COOCH_3$; R_2= CH_2Ph) was synthesized and condensed with diene 4a. After chromatography of the reaction product (Al_2O_3; C_6H_{12}-EtOAc) 47% of the adduct 5b (5, R_1= CH_2CH_2COOMe; R_2= CH_2Ph) was obtained *, m.p. 99-105°; IR (KBr): 1738, 1690 cm^{-1} (C=O); NMR ($CDCl_3$): δ 1.7-2.9

hump (10 protons); 3.54, 3.58, 3.6 three singlets[7] with total integrated intensity of 3 protons ($COOCH_3$); 3.75 s (OCH_3); 4.30-4.70 m 2 protons (N-CH)[8]; 5.13 s ($COOCH_2Ph$); 6.04 m (H=CH); 7.52 d (C_1-H) which could be isomerized to its 8,9-dehydro-isomer 6, m.p. 79-81°; IR (KBr) 1732, 1686 (C=O); NMR ($CDCl_3$). δ 6.90 d (C_1-H), upon treatment with HOAc. The diamagnetic shift of the C_1-H aromatic proton (0.62 ppm) and the disappearence of vinylic H are both in agreement with the 8,9-dehydro structure.

Decarbobenzoxylation of either 5b or 6 occurred readily upon treatment with HBr-Et_2O at r.t. and the resulting γ-amino ester could be cyclized by refluxing in ethanol. 8,9-Dehydro-13-aza-estrone 7 crystallized spontaneously from the solution; its spectra data were as reported before[9].

An advantage of the present procedure is the possibility of a combined hydrogenolysis of the benzylester 5b and catalytic hydrogenation of the 9,11 double bond. The resulting amino ester is directly cyclized to 13-aza-estrone 8, with unknown B/C stereochemistry[10], m.p. 169-172°; IR (KBr) 1670 cm^{-1} (C=O); NMR ($CDCl_3$): δ 1.5-3.0 m (13 protons), δ 3.74 s (OCH_3); 3.77 m (N-CH); 4.15 m (N-CH); 6.6-7.1 (aromatic H). The method was also applied to the synthesis of 11-oxygenated steroidal analogues. Upon addition of the diene 4b (4, R = OCH_3) to biscarbamate 1b a complex mixture of products was obtained from which the adduct 9 could not be isolated in pure form. The reversal of the addition mode, however, expected for mechanistic reasons, was evidenced from an inspection of the NMR-data of the steroid 10, m.p. 165-170°, which was obtained after HBr treatment of the oily reaction mixture and work-up in the usual manner. The spectral characteristics of 10 were as follows: IR (KBr) 1670 cm^{-1}, 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.5-3 m (10 protons), 3.76 (OCH_3); 3.80 d (C_9-H); 4.20-4.50 m (N-CH), 6.6-7.0 (aromatic H).

The coupling constant found for C_9-H (J=7.5 c/s) is indicative for a trans diaxial coupling[11], although the position of the C_1 aromatic hydrogen (δ 6.94 d; J=8 cps) is not compatible with an inplane structure of the 11-keto group and C_1 hydrogen[12]. From model studies, however, some distortion of the molecule is evident, which arises from the steric effects of the C_{13}-C_{14} amid-endo structure, a phenomenon most likely responsible for the apparently conflicting data.

The presently described method is by virtue of the potential variation of R_1 in biscarbamate 1 suitable for the construction of a variety of condensed heterocyclics. The only limitation so far observed is the necessity for the attainment of a planar transition state in the second

step of the cycloaddition[13]. In this connection the relatively lower yield of adduct 9 is best explained in terms of an unfavourable interaction of C_1-H and C_{11}-OCH_3 in the cyclization of the addition complex 11. Further work on the synthetic usefulness of this method is in progress.

References and Footnotes

* Satisfactory analytical data have been obtained for all crystalline compounds described in this communication.

1. To whom all correspondence should be addressed.
2. Part of the forthcoming thesis of R.J.P.Barends, University of Amsterdam.
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4. G.Kresze and R.Albrecht, Ber. 97, 490 (1964).
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7. High temperature (100°, PhOPh) recording effected the collapse of the three singlets, while one singlet for the ester OCH_3 emerged.
8. In systems similar to the present one the signal for two of the N-CH_2 protons is found at low field, see e.g. W.A.Zunnebeld, Thesis, University of Amsterdam, 1969.
9. J.C.Hubert, W.N.Speckamp and H.O.Huisman, Tetrahedron Letters 1551 (1969).
10. Upon lithium-ammonia reduction of ketone 7 a second stereoisomer of 13-aza-estrone methylether-3 was obtained. X-Ray analysis will be carried out to elucidate the B/C stereochemistry. J.C.Hubert, forthcoming thesis, University of Amsterdam.
11. U.K.Pandit and H.O.Huisman, Tetrahedron Letters 3901 (1969).
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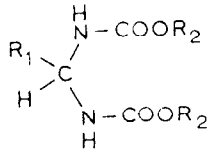
13. W.N.Speckamp, R.J.P.Barends and H.O.Huisman, to be published.



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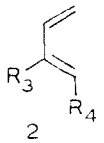

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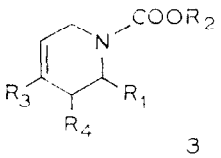

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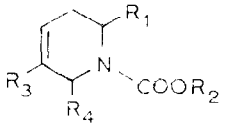

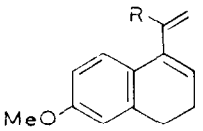

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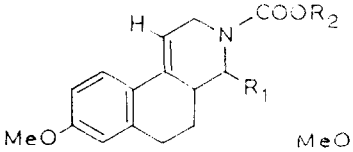

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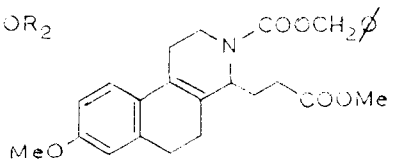

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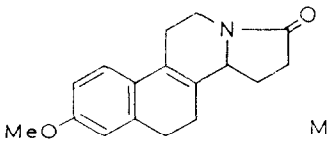

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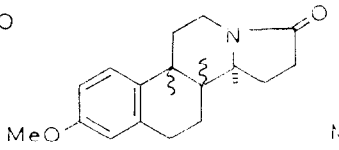

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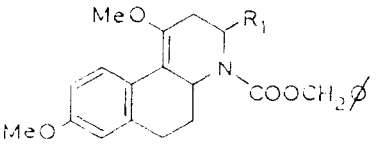

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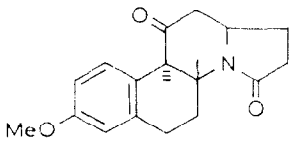

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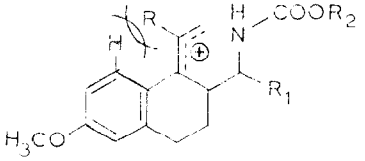

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