Tetrahedron Letters No.1, pp. 81-86, 1966. Pergamon Press Ltd.
Printed in Great Britain.

POLYNUCLEAR HETEROCYCLIC SYSTEMS IV[1].

A total synthesis of 11,12-diazasteroid skeleton.

A.G.M. Willems[2], R. Ritsema v. Eck, U.K. Pandit and H.O. Huisman
Laboratory for Organic Chemistry,
University of Amsterdam, Nieuwe Achtergracht 129
Amsterdam, The Netherlands.

(Received 5 November 1965)

In continuation of our interest in the total synthesis of heterocyclic steroids we wish to report a convenient method for the preparation of 11,12-diazasteroid and 11,12-diaza-D-homosteroid skeletons (Ia - Id). This synthetic approach is based upon the addition of pseudo-dienes of type II to dimethyl azodicarboxylate, followed by hydrolytic decarboxylation and oxidation of the formed adducts (chart 1).

The intermediate olefins (IIa - IId) were readily obtained by condensing Grignard reagents of the appropriate aromatic halides with cycloalkanones[3a,b] and dehydrating the resulting alcohols[4]. Typical reaction conditions for adduct formation consisted in dissolving the pseudo-dienes in excess (four to tenfold) of the azoester and allowing the resulting homogeneous mixture to stand at room temperature for several days. The 1 : 2 (diene : azoester) adducts separated out from the solution as crystalline products in 70-80% yield (Table I). The composition of the adducts was revoaled from their analytical data.

Infrared spectra of these adducts exhibit a strong N-H absorption indicating that at least one of the azoester molecules had added according to the addition-abstraction scheme[5].

TABLE I

Diadduct of	Yield	M.p.
2-(1-cyclopentenyl)-naphthalene	80%	212-214°
6-methoxy-2-(1-cyclopentenyl)-naphthalene	71%	209-211°
2-(1-cyclohexenyl)-naphthalene	77%	197-200°
6-methoxy-2-(1-cyclohexenyl)-naphthalene	71%	206-208°

The NMR spectra of the products from IIa and IIb, however, show significant differences from those derived from IIc and IId. A particularly informative feature in the NMR spectra of IVa and IVb is the presence of two low field protons (between δ 3 and 4) attributable to H_{14} and H_{15} of the D-homosteroid systems. No corresponding hydrogen atoms were found in the spectra of IIIa and IIIb. Consideration of these facts prompts us to assign structures IIIa, IIIb and IVa, IVb to the adducts from IIa, IIb and IIc, IId respectively. While the difference between the structure of the two types of adducts is initially puzzling, it, however, becomes readily understandable when one examines the details of the mechanism of adduct formation (Chart I). IIIa and IIIb arise as a consequence of stepwise addition of two molecules of azoester to the dienes; the first step being a simple diene addition and the second one via an addition-abstraction mechanism. Since the last step results in the attainment of aromaticity of the naphthalene system it must be an energetically favoured process. That the second step is indeed a fast process is suggested by the fact

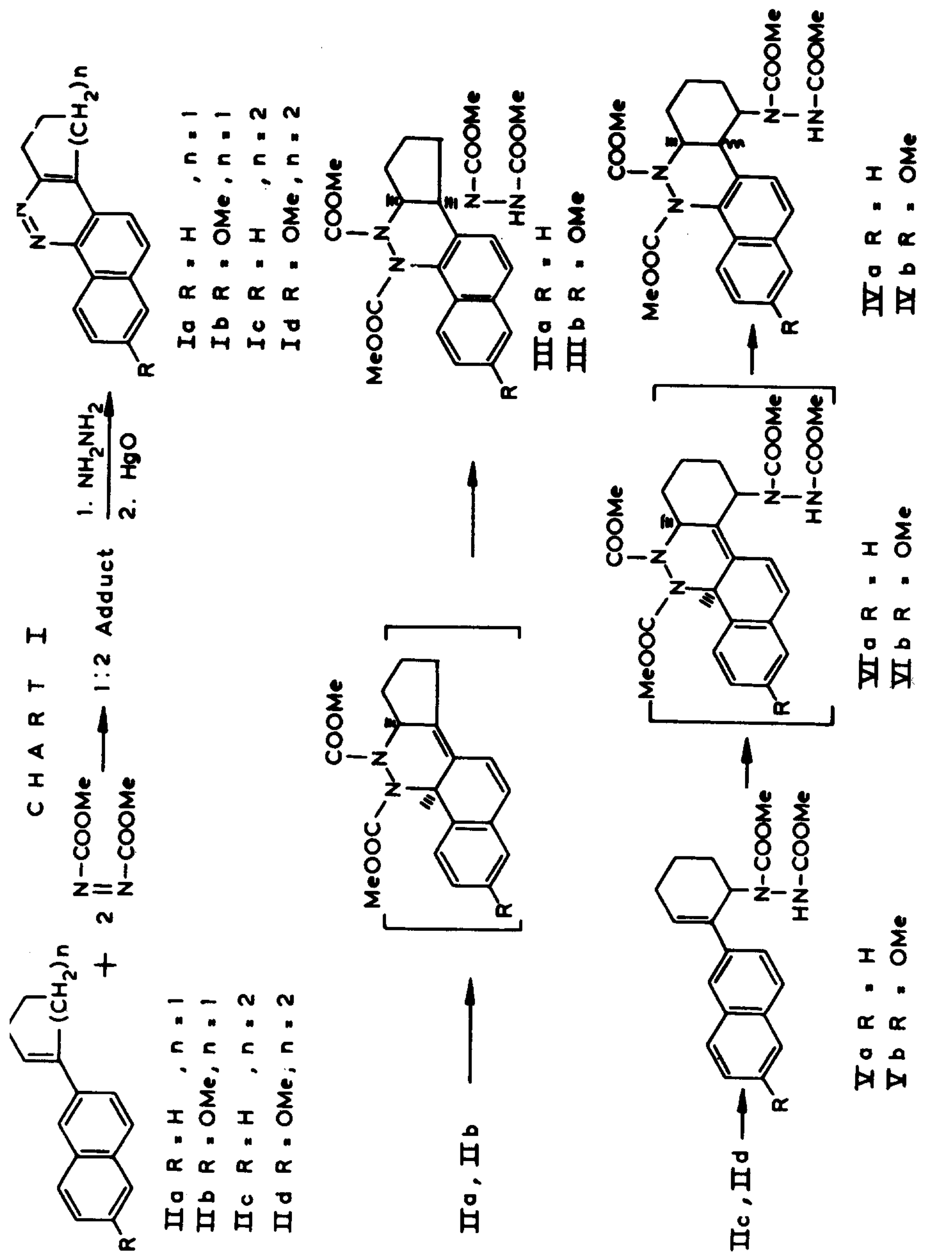
CHART I
2 N-COOMe ‖ N-COOMe
1:2 Adduct
1. NH2NH2
2. HgO
IIa R = H , n = 1
IIb R = OMe, n = 1
IIc R = H , n = 2
IId R = OMe, n = 2
Ia R = H , n = 1
Ib R = OMe, n = 1
Ic R = H , n = 2
Id R = OMe, n = 2
IIa, IIb
MeOOC
COOMe
N-COOMe
HN-COOMe
IIIa R = H
IIIb R = OMe
IIc, IId
Va R = H
Vb R = OMe
VIa R = H
VIb R = OMe
IVa R = H
IVb R = OMe
R
(CH2)n

that reaction of equimolar amounts of IIa and dimethyl azodicarboxylate also gives the 1 : 2 adduct as the sole product. The assigned stereochemistry of the adducts is based upon the known stereochemical patterns of the Diels Alder(6) and allylic addition reactions(5).

A reversal in the sequence of addition of the two ester molecules, to dienes IIc and IId, is responsible for the structure of final adducts IVa and IVb. The factors responsible for this alteration appear to be associated with the size of the cycloalkane rings. In principle both pairs of dienes are capable of undergoing a Diels Alder or an allylic addition. However, the accomplishment of a Diels Alder addition in the first step results in the migration of a double bond from an endocyclic to an exocyclic configuration with respect to the alicyclic ring. While such a transformation is prone to occur in the five-membered ring, it will be disfavoured in the case of the cyclohexene systems IIc and IId[7]. The allylic addition products Va and Vb can again react by a further addition of a second ester molecule according to one of the previously mentioned pathways. In this step, though, presumably owing to steric factors, the Diels Alder addition competes with the alternate favourable reaction course. It is interesting to note that the observed rate of formation of adducts IVa and IVb is considerably slower than that for IIIa and IIIb. This fact emphasizes the reluctance of Va and Vb to form intermediates (VIa and VIb) containing a double bond exocyclic to the six-membered ring(8).

Hydrolytic decarboxylation of the adducts was achieved by refluxing with hydrazine hydrate(9). Oxidation of the resulting products with mercuric oxide gave cinnolines Ia - Id. (Table II). The structure of the cinnolines was established by their analytical UV, IR, NMR and mass spectral data.

TABLE II

Structure	Name	Yield	M.p.
I a	8,9-dihydro-7H-benzo[h] cyclopenta[c]cinnoline	45%	180-183°
I b	2-methoxy-8,9-dihydro-7H-benzo[h]cyclopenta[c]cinnoline	47%	199-202°
I c	7,8,9,10-tetrahydro-naphtho[1,2-c]cinnoline	40%	160-163° (dec.)
I d	2-methoxy-7,8,9,10-tetrahydro-naphtho[1,2-c]cinnoline	68%	172-175°

Furthermore, one of the products, Ic, was found to be identical to a sample of 7,8,9,10-tetrahydronaphtho(1,2-c)cinnoline obtained by Braithwaite and Robinson[10)], via a completely different route.

The extension of the described synthetic approach to the synthesis of ring C aromatic 17-substituted 11,12-diazasteroids is in progress.

References.

1. Part III. U.K. Pandit and H.O. Huisman, Rec.Trav.Chim. In press.
2. Abstracted in part from the forthcoming Thesis of A.G.M. Willems, University of Amsterdam.
3. a. W.E. Backmann and M.C. Kloetzel, J.Am.Chem.Soc. 60, 2204 (1938); b. F. Bergmann and E. Bergmann, ibid. 62, 1699 (1940).
4. E.W. Gabisch, J.Org.Chem. 26, 4165, (1961).
5. B. Franzus, J.Org.Chem. 28, 2954 (1963).
6. J.G. Martin and R.K. Hill, Chem.Rev. 61, 537 (1961).

7. H.C. Brown, J.H. Brewster and H. Shechter, J.Am.Chem.Soc. 76, 467 (1954).

8. Attempts to isolate Va from a reaction of equimolar amounts of IIc and azoester are in progress.

9. K. Alder and H. Niklas, Ann. 585, 97 (1954).

10. R.S.W. Braithwaite and G.K. Robinson, J.Chem.Soc. 3671 (1962). We are grateful to Dr. R.S.W. Braithwaite for a sample of 7,8,9,10-tetrahydronaphtho(1,2-c)cinnoline.