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Studies on Conformation and Reactivity. VIII.[1] Stereochemical Aspects of the Diels-Alder Reaction of Diethyl Azodicarboxylate with Steroid Homodienes. (1)

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The Diels–Alder reaction of diethyl azodicarboxylate (I) with steroid 2,4- and 5,7-dienes and its stereochemistry were reported. The azo–ester (I) reacted with cholesta-2,4-diene (II) to afford three one–to–one adducts, *i. e.* the 1,4-adduct (IV) at 2α and 5α positions and two addition–abstraction adducts (V and VI) isomeric at 3 position, and diethyl hydrazinedicarboxylate (VII) in 21.4%, 10.8%, 5.2%, and 12.2% yields respectively. The 1,4-adduct (IV) was chemically modified to its dihydro derivatives, VIII and IX. The reaction of the azo–ester (I) with 3β-benzoyloxycholesta-5,7-diene (III), on the other hand, led to the formation of two one–to–one adducts, *i. e.* the 1,4-adduct (XI) at 5α and 8α positions and an addition–abstraction adduct (XII) at 7α position in 4.2% and 36% yields respectively. The 1,4-adduct (XI) was converted to its dihydro derivative (XIII). The result showed that whereas with the 2,4-diene (II) as substrate, the 1,4-addition and addition–abstraction reactions take place to the almost same extent, with the 5,7-diene (III) as substrate the latter reaction is preferred. Stereochemical aspects of the different reactivity of the azo–ester (I) toward those dienes were discussed.

Introduction

The Diels–Alder reaction,[3] one of the most useful reactions in synthetic organic chemistry leading to the formation of valuable homo- and heterocycles, has been characterized by its striking stereospecificity.

Since the discovery of the reaction with dialkyl azodicarboxylates,[4,5] the important participation of these esters as reactive heterodienophile in Diels–Alder reactions has been recognized.[6,7] For some time we have been interested in the reactivity of azodicarboxylic esters as dienophile toward steroid homodienes. Our interest has been focused on the objective of evaluation of different stereochemical factors at various sites on the steroid nucleus which would direct the mode of the Diels–Alder reaction of azo–esters to dienes, and also of synthesis of modified steroids with a diaza function. Reactions have been performed with diethyl azodicarboxylate (I) as dienophile and 2,4-, 5,7-, or 16,20-dienes as substrate. Results have been presented in preliminary reports.[8,9] The present paper deals with the full data of reactions of the azo–ester (I) with cholesta-2,4-diene (II) and 3β-benzoyloxycholesta-5,7-diene (III). Reactions of the azo–ester (I) and its corresponding amide with 3β-benzoyloxypregna-5, 16,

1) Part VII: T. Koga and M. Tomoeda, *Tetrahedron*, in press.
2) Location: *Takara-machi, Kanazawa.*
3) O. Diels and K. Alder, *Ann.*, **460**, 98 (1928).
4) O. Diels and K. Alder, *Ann.*, **450**, 237 (1926).
5) O. Diels, J.H. Blom, and W. Koll, *Ann.*. **443**, 242 (1925).
6) H. Zollinger, "Azo and Diazo Chemistry. Aliphatic and Aromatic Compounds," International Science Publishers, Inc., New York, 1961, p. 286.
7) Jam Hamer (Ed.), "1,4-Cycloaddition Reactions. The Diels-Alder Reaction in Heterocyclic Syntheses," Academic Press, New York, 1967, p. 145.
8) M. Tomoeda, R. Kikuchi, and M. Urata, *Chem. Pharm. Bull.* (Tokyo), **13**, 517 (1965).
9) M. Tomoeda and J. Yoshizawa, *Tetrahedron Letters*, **1967**, 975.

20-triene will be dealt with in a subsequent paper. Reactions of azodicarboxylic esters with some 5,7-dienes have also been studied by other group[10,11] in recent years.

Reaction of Diethyl Azodicarboxylate (I) with Cholesta-2,4-diene (II)

The reaction of the azo-ester (I) and the slightly excess 2,4-diene (II) was carried out in refluxing benzene for 30 hr when it was almost complete, resulting in the formation of three main products as indicated by thin-layer chromatography (TLC). Removal of the solvent gave a pale yellow oily residue which was subjected to repeated chromatography over neutral alumina and silica gel, and three one-to-one adducts, IV, V, VI could be isolated in 21.4%, 10.8%, and 5.2% yields respectively. Diethyl hydrazinedicarboxylate (VII) was also obtained as the fourth and most polar product in 12.2% yield. The least polar product (IV), on treatment with aqueous methanol, gradually crystallized as colorless needles of mp 75.7—76.2° and $[\alpha]_D$ +36°. The microanalyses supported the molecular formula of the compound to be $C_{33}H_{54}O_2N_2$. The ultraviolet (UV) spectrum showed an absorption at 211 mμ due to a double bond but was transparent above 220 mμ proving the absence of absorptions whose presence in the starting material (267, 275 mμ) was associated with the conjugated dienes. The infrared (IR) spectrum showed characteristic absorptions due to N-$CO_2C_2H_5$ groups at 1727—1701 cm^{-1} and a double bond at 3077, 1635, and 1620 cm^{-1} but no NH absorption. The absence of NH group in the compound supported the structure to be the 1,4-adduct with the dicarbethoxyhydrazo function at 2α and 5α positions, 2α,5α-(N_1, N_2-dicarbethoxyhydrazo)- cholest-3-ene (IV). That the compound is α-oriented at 2 and 5 positions could be reasoned by a generally accepted knowledge that most reagents, including dienophiles,[12-15] attack the center of the steroid molecule from the less-hindered rear or α-side. Assignment of the structure was further supported by the nuclear magnetic resonance (NMR) spectrum. The 3- and 4-vinylic hydrogens gave rise to an asymmetrical multiplet at τ 3.26—3.71. The 6α-hydrogen under the deshielding effect of the N-$CO_2C_2H_5$ group[11] at 5α position gave a multiplet centered at τ 6.84. The fact that the signal of the 19-methyl group appeared at τ 9.12 which is 0.17 ppm

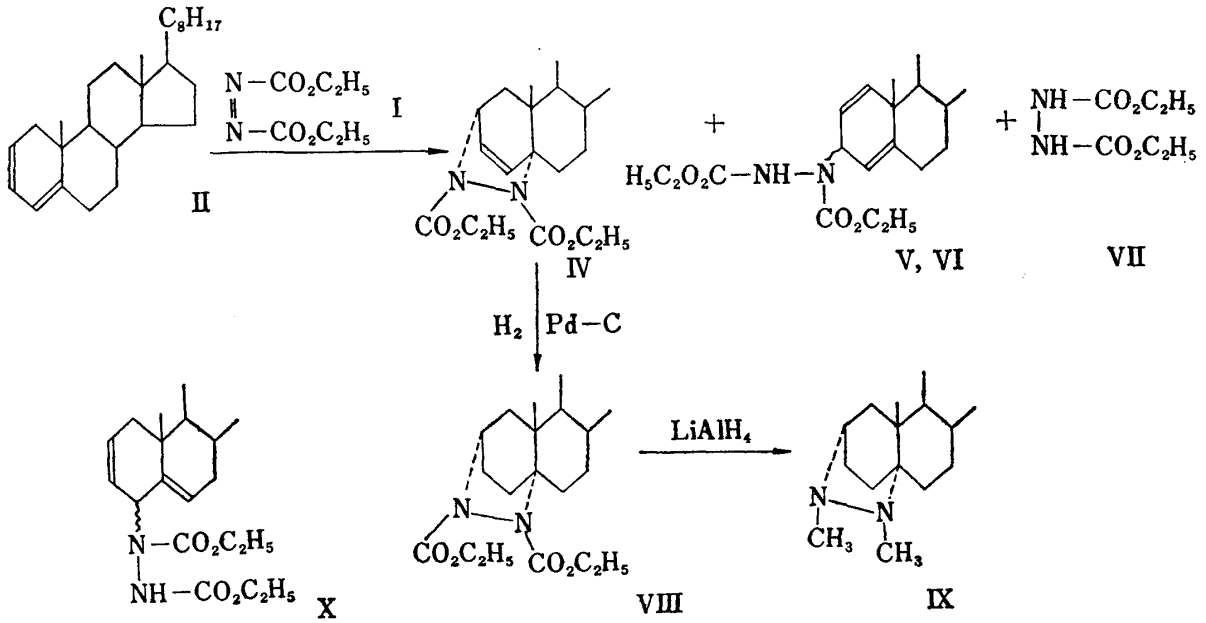

Chart 1

10) A. van der Gen, J. Lakeman, M.A.M.P. Gras, and H.O. Huisman, *Tetrahedron*, **20**, 2521 (1964).
11) A. van der Gen, W.A. Zunnebeld, U.K. Pandit, and H.O. Huisman, *Tetrahedron*, **21**, 3651 (1965).
12) R. Antonucci and K.J. Sax, *J. Org. Chem.* (Tokyo), **16**, 1351 (1951).
13) S. Akagi and Y. Okada, *Chem. Pharm. Bull.*, **9**, 476 (1961).
14) R. Antonucci and K.J. Sax, *J. Org. Chem.*, **16**, 1357 (1951).
15) K. Tsuda and N. Nozoe, *Chem. Pharm. Bull.* (Tokyo), **8**, 1128 (1960).

higher than that of the corresponding dihydro derivative (VIII) which will be referred to later, was a support for the presence of a double bond at 3 position in the compound with 5α configuration affording a shielding effect[16] toward the 19-methyl group. Other NMR informations were in agreement with the structure.

The structure of the 1,4-adduct (IV) was further supported by the fact that the adduct (IV) was hydrogenated with 20% Pd–charcoal as catalyst. Absorption of one equivalent of hydrogen was observed. The hydrogenated oily product was chromatographed over neutral alumina affording the non-crystalline but thin-layer chromatographically homogeneous dihydro compound, 2α,5α-(N_1, N_2-dicarbethoxyhydrazo)cholestane (VIII), in 72% yield. The IR and NMR spectra did not show absorptions from 3- and 4-vinylic hydrogens and 3(4)-double bond. The NMR spectrum exhibited the peak due to the 19-methyl group at τ 8.95, 0.17 ppm lower than that of IV. The spectrum further exhibited the peak due to the 6α-hydrogen as a multiplet at τ 7.24 under the deshielding effect of the N–$CO_2C_2H_5$ group at 5α position. Other IR and NMR informations were in agreement with the structure.

The dihydro compound (VIII) was then subjected to the reduction with lithium aluminum hydride in refluxing tetrahydrofuran to result in the formation of 2α,5α-(N_1, N_2-dimethylhydrazo)cholestane (IX) in 55% yield. The compound (IX) obtained as colorless prisms had mp 103—104.5° and $[\alpha]_D$ +102°, and its microanalysis supported the molecular formula of $C_{29}H_{52}N_2$. The IR spectrum showed a characteristic absorption due to the N-methyl group at 2800 cm^{-1}. Presence of the two N-methyl groups was supported by the NMR spectrum showing singlets at τ 7.58 and τ 7.73. The 6α hydrogen under the spatial interaction of the N–CH_3 group at 5α position showed a multiplet at τ 6.52 suggesting a larger deshielding effect of the N–CH_3 group than the N–$CO_2C_2H_5$ group to neighboring hydrogens. Other IR and NMR informations were in agreement with the structure. The structure of the dimethylhydrazo compound (IX) was further supported by the fact that the compound gave a picrate as yellow prisms of mp 229—230°. The microanalysis and physical properties proved the structure.

The remaining one-to-one adducts, V and VI, crystallized as colorless needles of mp 94—97°, $[\alpha]_D$ +31°, and colorless prisms of mp 149—151°, $[\alpha]_D$ +48°, in 10.2% and 5.2% yields respectively. The microanalysis supported the molecular formula of $C_{33}H_{54}O_4N_2$ for the adducts. The UV spectra of V and VI were transparent above 220 mμ, suggesting absence of conjugated double bonds in both compounds. The IR spectra showed similar patterns of absorptions for both compounds in which, added to the N–$CO_2C_2H_5$ peaks, those characteristic to the NH group (absorptions at 3401 and 1527 cm^{-1} for V and 3425 and 1547 cm^{-1} for VI) and also those attributable to vinylic hydrogens and double bonds (absorptions at 3086 and 1643 cm^{-1} for V and at 2980 and 1635 cm^{-1} for VI) were present.

Presence of the NH group in both V and VI suggested that these adducts should not be another 1,4-adduct with β configuration at 2 and 5 positions but addition–abstraction adducts[17–20] at 3 or 4 positions accompanied by migration of 2(3)- or 4(5)-double bonds. The NMR spectra of both adducts also showed similar patterns of peaks in which there appeared very broad multiplets at τ 3.85—4.74 for V and τ 3.85—4.76 for VI, corresponding to five protons and could be attributable to three vinylic hydrogens, an allylic hydrogen, and a NH group. The NMR spectra further exhibited the 19-methyl peak at τ 8.93 for both adducts suggesting the partial structure of both compounds around the 19-methyl group, particularly the location of double bonds which might affect the position of 19-methyl peaks to the largest extent, to be identical. Furthermore, the observed 19-proton resonance at τ 8.93 was found to be in

16) N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, 1964, p. 13.
17) B.T. Gillis and P.E. Beak, *J. Org. Chem.*, **27**, 1947 (1962).
18) B. Franzus and J.H. Surridge, *J. Org. Chem.*, **27**, 1951 (1962).
19) S.G. Cohen and R. Zand, *J. Am. Chem. Soc.*, **84**, 586 (1962).
20) G.O. Schenck, E.K. von Gustorf, B. Kim, G.V. Bünau, and G. Pfandt, *Angew. Chem.*, **74**, 510 (1962).

good agreement with the calculated value for the compound with double bonds at 1- and 4-positions but not at 2- and 5-positions.[16] It was concluded from these data and consideration of possible mechanisms involved in the reaction that these adducts should be 3-(N_1,N_2-dicarbethoxyhydrazino)cholesta-1,4-dienes. The alternative assignment of the structure of adduct(s) to be the 4-hydrazino-2,5-diene (X), isomeric to V and VI, was unlikely from the NMR evidence mentioned above. Furthermore, the approach of the reagent (I) to 6 position in ring B as the first step of the concerted addition–abstraction reaction toward the C_4=C_5–C_6–H system appeared to be sterically less favored to the approach of I to 1-H involved in the C_3=C_2–C_1–H system in ring A. The fact that the IR and NMR spectra of V and VI are in close similarity could be a support for the isomeric structure of V and VI which differ only stereochemically at 3 position in their molecules. However, no definitive physical and chemical evidence for the configurations at 3 position of V and VI has so far been obtained.

Indentification of the fourth and most polar product (VII) of colorless needles, mp 130—132°, as diethy hydrazinedicarboxylate was performed by comparison of its IR spectrum with that of an authentic specimen of the compound and by mixed mp determination.

Reaction of the Azo-Ester (I) with 3β-Benzoyloxycholesta-5,7-diene (III)

The reaction of the azo–ester (I) with the 5,7-diene (III) in refluxing benzene was almost complete in 27 hr (TLC). Usual work up of the reaction mixture followed by chromatography over silica gel afforded two crystalline one–to–one adducts, XI and XII, in 4.2% and 36% yields respectively. The less polar and minor adduct (XI) crystallized as colorless needles of mp 110—112° and $[\alpha]_D$ +44°. The microanalysis supported the expected molecular formula of $C_{40}H_{58}O_6N_2$. The UV spectrum showed only an absorption at 230 mμ attributable to the benzoyloxy group, suggesting absence of extra conjugated double bonds in the compound. The IR spectrum did not display the presence of NH absorption suggesting the structure of the compound to be the 1,4-adduct possibly with α configuration at 5 and 8 positions, *i.e.*, 3β-benzoyloxy-5α,8α-(N_1,N_2-dicarbethoxyhydrazo)-cholest-6-ene (XI). The NMR spectrum showed an AB–type quartet at τ 3.63 with the J of 8 cps from the 6- and 7-vinylic hydrogens. The NMR spectrum further exhibited, added to the characteristic peak at τ 6.48 due to the 4α-hydrogen under the deshielding effect of the N–$CO_2C_2H_5$-group[11] at 5α-position, the 19-methyl peak at τ 8.99. The fact that the 19-methyl peak appears 0.19 ppm higher than that of the corresponding dihydro derivative (XIII) which will be referred to later, is in agreement

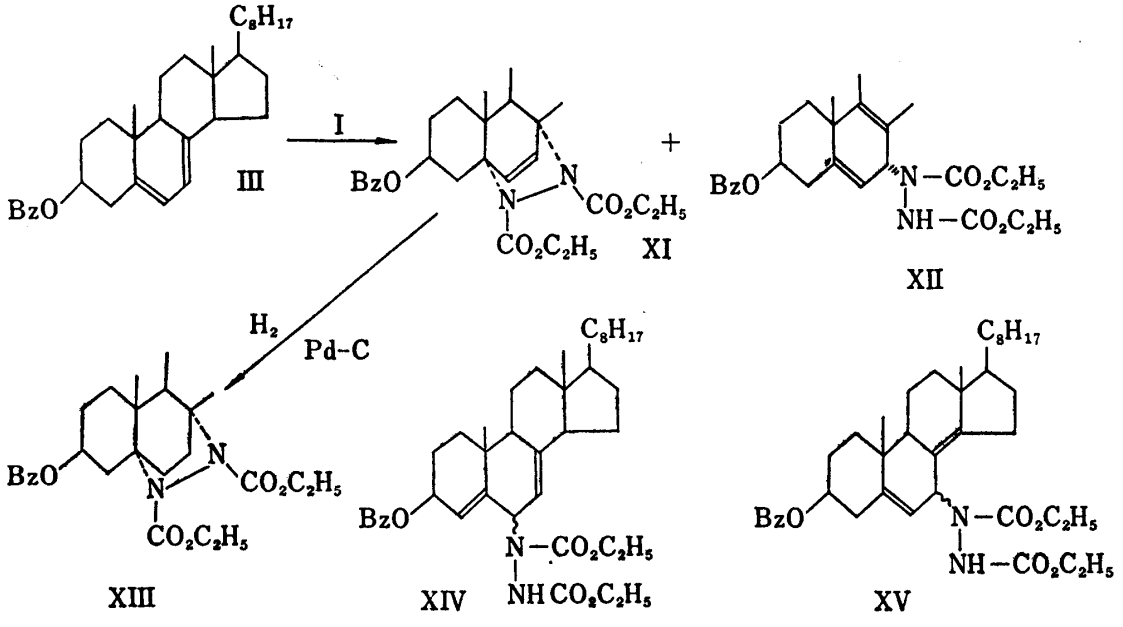

Chart 2

with the location of the double bond at 6 position[16] in the 1,4-adduct (XI) with 5α configuration. Other IR and NMR informations were in accord with the structure. The α configuration at 5 and 8 positions in the 1,4-adduct (XI) could be reasoned analogously as in the case of α configuration at 2 and 5 positions in IV.

The structure of the 1,4-adduct (XI) was supported by the fact that on catalytic hydrogenation with 20% Pd–charcoal as catalyst, the compound gave the corresponding dihydro derivative (XIII) as colorless needles of mp 133—134° and $[\alpha]_D$ +32°. The NMR spectrum did not display the presence of 6- and 7-vinylic hydrogens in the compound. The IR and other NMR informations supported the structure of the dihydro compound (XIII). Meanwhile, reduction of the 1,4-adduct (XI) with lithium aluminum hydride in refluxing tetrahydrofuran has failed to give crystalline products.

The more polar and major one-to-one adduct (XII) crystallized as colorless needles of mp 167—170° and $[\alpha]_D$ −38°. The microanalysis supported the molecular formula of $C_{40}H_{58}O_6N_2$. The UV spectrum showed only the benzoyloxy absorption at 230 mμ, suggesting absence of any other conjugated double bonds in the compound. The IR spectrum displayed the NH absorptions at 3298 and 1515 cm^{-1}, suggesting the structure of the compound not to be the another 1,4-adduct with β configuration at 5 and 8 positions but an addition-abstraction adduct[17-20] at 6 (XIV) or 7 (XII or XV) position accompanied by migration of 5(6)- or 7(8)-double bond. Assignment of the structure to be XII, *i.e.* 3β-benzoyloxy-7α-(N_1,N_2-dicarbethoxyhydrazino)cholesta-5,8-diene, and not XIV or XV, was carried out as follows. The negative sign of the optical rotation of the compound was a support for the location of a double bond in the compound at 5.[21] The NMR spectrum showed a very broad multiplet at τ 3.93—5.30 attributable to 3α-hydrogen, 6-vinylic and 7-allylic hydrogens and the NH group. The NMR spectrum further exhibited the 19-methyl peak at a relatively low field as τ 8.73 and the 18-methyl peak at a high field as τ 9.32. Those observed 19- and 18-proton resonances were found to be in reasonable agreement with the calculated values for the compound with double bonds at 5 and 8(9) positions but not at 4 and 7 or 5 and 8(14) positions.[16] The α orientation at 7 position could be reasoned that the first step of the reaction or the abstraction of the 9α-hydrogen by the azo-bridge of the reagent should take place from the α-side. The other IR and NMR informations were in agreement with the structure. The assignment of the structure of the major product to be XII thus made was further supported by the similar result obtained by other group.[10]

It has been reported[22] that while the thermal reaction of the azo-ester (I) with cyclohexa-1,3-diene favors the addition-abstraction reaction than the 1,4-addition reaction, the photochemical addition reaction of the dienophile and the diene favors formation of the Diels–Alder adduct. The reaction of I with III under illumination was therefore undertaken, which, however, resulted in the formation of the addition-abstraction adduct (XII) as the major product. It suggested that the mode of the reactions referred to in the present paper is not changed substancially by light.

Discussions

The Diels–Alder reaction of azodienophiles has been suggested[23] to proceed *via* a transition state similar to that proposed for carbodienophiles,[24] retaining the configuration of dienes to react. Meanwhile, we have speculated that so far as the first step of the reaction of the azo-ester (I) with homodienes is concerned, the 1,4-addition beginning with rupture of π bond may

21) L.F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, p. 178.
22) R. Askani, *Chem. Ber.*, **98**, 2551 (1965).
23) R. Daniels and K.A. Roseman, *Tetrahedron Letters*, **1966**, 1335.
24) J.A. Berson and A. Remanick, *J. Am. Chem. Soc.*, **83**, 4947 (1961).

be energetically more favored than the addition–abstraction reaction beginning with rupture of allylic C–H or σ bond.

It was now found that the 2,4- and 5,7-diene systems in the cholestane series show remarkably different reactivities toward the azodicarboxylic ester as heterodienophile. With the 2,4-diene (II) as substrate, the 1,4-addition at $2\alpha,5\alpha$ positions and the addition–abstraction reaction at 3 position accompanied by migration of the 2(3)-double bond appeared to take place almost to the same extent. With the 5,7-diene (III) as substrate, on the other hand, the 1,4-adduct at 5 and 8 positions could be isolated but was the minor product, and the addition–abstraction adduct at 7 position accompanied by migration of the 7(8)-double bond was the major product.

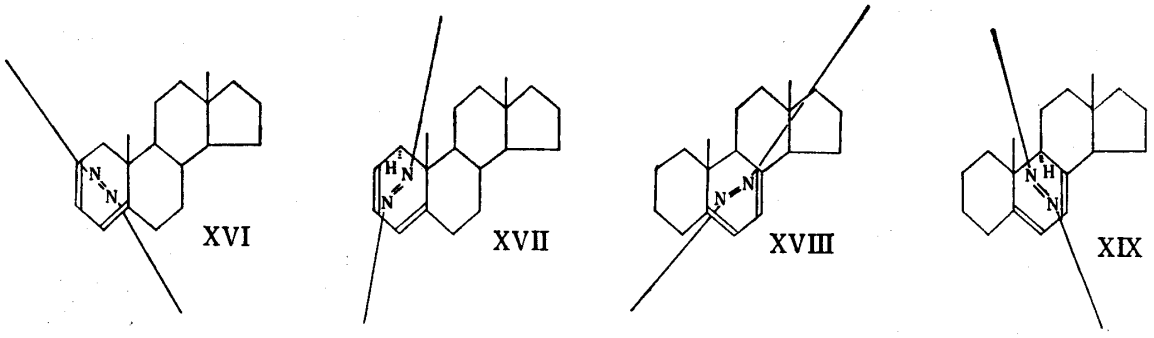

Chart 3

One would assume that the mode of reactions referred to in the present paper might mainly depend on steric factors governing the formation of transition states between the azo–ester (I) and dienes, II and III, leading either to the 1,4-adduct or the addition–abstraction adduct. Inspection of stereo models supports the idea as follows. With the 2,4-diene (II) as substrate the formation of transition states, XVI and XVII, leading to either type of products, appear to be sterically almost equally hindered. On the other hand, with the 5,7-diene (III) as substrate, the formation of the transition state (XVIII) leading to the 1,4-adduct seems to be more hindered than the formation of the transition state (XIX) leading to the addition–abstraction adduct. Preference of the addition–abstraction reaction to the 1,4-addition reaction in the reaction of the 5,7-diene system with esters of acetylenedicarboxylic acid as carbodienophile has been also reported in the literature.[25] The fact that two of three adducts derived from the 2,4-diene (II) and the azo–ester (I) are addition–abstraction adducts isomeric at 3 position, leads to a question of if the isomer with 3β configuration was formed as the result of abnormal β-approach of the reagent to the diene system in ring A of II or of epimerization at 3 position of the first and normal adduct with 3α configuration. The real reason for this anormaly is obscure. Meanwhile, the fact that diethyl hydrazinedicarboxylate (VII) was obtained as a by–product of the reaction of I with II, would not be an unexpected result, as the ready acceptance of hydrogen of the azo–ester from some suitable substrates including hydrocarbons is konwn.[26]

Experimental

mp were taken on a Kofler–type hot plate and are uncorrected. $[\alpha]_D$ refers to $CHCl_3$, UV absorption spectra to 95% EtOH, and IR spectra to nujol unless otherwise stated. NMR spectra were mainly run on a Varian Associates A-60 high resolution spectrometer, and the intensities or peak areas were measured by the integrator.

Reaction of Diethyl Azodicarboxylate (I) with Cholesta-2,4-diene (II)- Formation of $2\alpha,5\alpha$-(N_1,N_2-Dicarbethoxyhydrazo)cholest-3-ene (IV) and 3ξ-(N_1,N_2-Dicarbethoxyhydrazino)cholesta-1,4-dienes (V and VI)——

25) A. van der Gen, J. Lakeman, U.K. Pandit, and H.O. Huisman, *Tetrahedron*, **21**, 3461 (1965).
26) Ref. 6, p. 289, 304.

An orange solution of the azo-ester (I)[27] (1.06 g, 6.1 mmole) and the 2,4-diene (II)[28] (mp 64—66°, $[\alpha]_D^{15}$ +145° (*c* 0.98), λ_{max} 267 (ε 5800) and 275 (ε 5400) mμ)) (2.684 g, 7.3 mmole) in benzene (20 ml) was refluxed for 30 hr; the color of the solution gradually faded to pale yellow and the reaction was almost complete in the period mentioned above (thin-layer chromatography). The solution was concentrated *in vacuo* to give a pale yellow oil, (wt. 3.30 g), which was chromatographed over neutral alumina (Woelm, grade III) (110 g). Elution with petr. ether (800 ml) gave colorless crystals, (wt. 91 mg). They had mp 55.5—58.0°, and were supposed to be the crude starting material, however, its further study was not carried out. Elution with 1:1 petr. ether–benzene (300 ml) afforded a colorless oil, (wt. 1.309 g). The half amount of the oil was rechromatographed over silica gel (Davison Co.) (66 g). Elution with benzene (1200 ml) gave non-crystalline but thin-layer chromatographically homogeneous 2α,5α-(N_1,N_2-dicarbethoxyhydrazo)chloest-3-ene (IV), (wt. 351 mg, 10.7% yield from the azo-ester (I)). The total yield was calculated to be 21.4%. The compound gradually crystallized from aqueous methanol as colorless needles. They were recrystallized from the same solvent to give sample of mp 75.7—76.2°. *Anal.* Calcd. for $C_{33}H_{54}O_2N_2$: C, 73.02; H, 10.03; N, 5.16. Found: C, 73.34; H, 10.02; N, 5.49. $[\alpha]_D^{19}$ +36.3° (*c* 1.0); λ_{max} mμ (ε): 211 (2420) ($\rangle C_3{=}C_4\langle$); ν_{max} cm^{-1}: 1727 (s) and 1701 (s) ($CO_2C_2H_5$), 3077 (w), 1635 (w) and 1620 (w) ($_H\rangle C_3{=}C_4\langle_H$); NMR τ: 3.62—3.71 (2 protons, multiplet) (3-H, 4-H), 5.69—6.02 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 6.84 (1 proton, multiplet)(6α-H), 8.69 (3 protons, triplet, J=7 cps), 8.82 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 9.12 (3 protons, singlet) (19-H), 9.32 (3 protons, singlet) (18-H).

Continuation of the rechromatography over silica gel with 9:1 benzene–ether (600 ml) as eluent afforded 3ξ-(N_1,N_2-dicarbethoxyhydrazino)cholesta-1,4-diene (V) as colorless needles of mp 83—92°, (wt. 121 mg, 3.7% yield from I). Recrystallization from aqueous ethanol gave sample of mp 94—97°. *Anal.* Calcd. for $C_{33}H_{54}O_4N_2$: C, 73.02; H, 10.03; N, 5.16. Found: C, 73.02; H, 9.83; N, 5.15. $[\alpha]_D^{15}$ +31° (*c* 0.96); λ_{max}: transparent above 220 mμ; ν_{max} cm^{-1}: 3401 (m) and 1527 (m) (NH), 3086 (w) and 1643 (m) ($_H\rangle C_1{=}C_2\langle_H$, $_H\rangle C_3{=}C_4\langle$), 1754 (s) and 1678 (s) ($CO_2C_2H_5$); NMR τ: 3.85—4.06 (2 protons, multiplet) ($_H\rangle C_1{=}C_2\langle_H$), 4.42 (1 proton, multiplet) (3-H), 4.74 (2 protons, multiplet) (4-H, NH), 5.62—6.03 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 8.71 (3 protons, triplet, J=7 cps), 8.73 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 8.93 (3 protons, singlet) (19-H), 9.30 (3 protons, singlet) (18-H).

Continuous elution of the original chromatogram of the reaction product over alumina with 1:1 petr. ether–benzene (1600 ml) gave another crops of V, mp 89—93°, (wt. 182 mg, 5.5% yield). Recrystallization from aqueous ethanol gave material of mp 94—97°. The total yield of V then reached 12.9%.

Further elution with benzene (1800 ml) gave 3ξ-(N_1,N_2-dicarbethoxyhydrazino)cholesta-1,4-diene (VI) as colorless prisms, mp 147—150°, (wt. 205 mg, 6.2% yield from I). Recrystallization from petr. ether gave material of mp 149—151°. *Anal.* Calcd. for $C_{33}H_{54}O_4N_2$: C, 73.02; H, 10.03; N, 5.16. Found: C, 73.13; H, 10.01; N, 5.25. $[\alpha]_D^{15}$ +48° (*c* 1.02); λ_{max}: transparent above 220 mμ; ν_{max} cm^{-1}: 3245 (m) and 1547 (m) (NH), 2980 (w) and 1635 (m) ($_H\rangle C_1{=}C_2\langle_H$ and $_H\rangle C_4{=}C_5\langle$), 1742 (s) and 1664 (s) ($CO_2C_2H_5$); NMR τ: 3.85—4.05 (2 protons, multiplet) (1-H, 2-H), 4.38 (1 proton, multiplet) (3-H), 4.76 (2 protons, multiplet) (4-H, NH), 5.63—6.05 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 8.73 (3 protons, triplet, J=7 cps), 8.79 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 8.93 (3 protons, singlet) (19-H), 9.31 (3 protons, singlet) (18-H).

Further elution with methanol (200 ml) gave diethyl hydrazinedicarboxylate (VII) as colorless crystals, mp 126—129°, (wt. 129 mg, 12.2% yield). Recrystallization from methanol gave colorless needles of mp 130—132°, alone and on admixture with an authentic specimen of the compound.[27] Their IR spectra were superposable.

Catalytic Hydrogenation of the 1,4-Adduct (IV): Formation of 2α,5α-(N_1,N_2-Dicarbethoxyhydrazo)-cholestane (VIII)——The 1,4-adduct (IV) (630 mg) in ethyl acetate (35 ml) was hydrogenated with 20% Pd–charcoal (125 mg) as catalyst at 21°; the compound absorbed almost one equivalent (27.9 ml) of hydrogen in 4 hr. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give a colorless oil, (wt. 515 mg). The oil was chromatographed over neutral alumina (Woelm, grade III) (15.5 g). Elution with 1:1 petr. ether–benzene (150 ml) gave the non-crystalline but thin-layer chromatographically homogeneous dihydro derivative, 2α,5α-(N_1,N_2-dicarbethoxyhydrazo)cholestane (VIII), (wt. 452 mg, 72% yield). λ_{max}: transparent above 210 mμ; ν_{max} cm^{-1}: 1729—1695 (s) ($CO_2C_2H_5$); NMR τ: 5.62—5.97 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 7.24 (1 proton, multiplet) (6α-H), 8.70 (3 protons, triplet, J=7 cps), 8.76 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 8.95 (3 protons, singlet) (19-H), 9.33 (3 protons, singlet) (18-H). The compound was used for the reduction with lithium aluminum hydride without further purification.

Lithium Aluminum Hydride Reduction of VIII——Formation of 2α,5α-(N_1,N_2-dimethylhydrazo)cholestane (IX): A solution of VIII (300 mg) and lithium aluminum hydride (700 mg) in anhydrous tetrahydrofuran (25 ml) was refluxed with stirring for 10 hr. To the reaction mixture, after ice-cooling, were added successively 10% aqueous tetrahydrofuran (25 ml) and 4% NaOH (25 ml), and the mixture extracted into

27) S.G. Cohen, R. Zand, and C. Steel, *J. Am. Chem. Soc.*, **83**, 2895 (1961).
28) E.L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).

ether. The ethereal layer was washed with water and dried (anhyd. Na_2SO_4). Concentration of the filtrate followed by addition of methanol gave 2α,5α-(N_1,N_2-dimethylhydrazo)cholestane (IX) as crystals, mp 95—100°, (wt. 130 mg, 55% yield). Recrystallization from methanol gave colorless prisms, mp 103—104.5°. *Anal.* Calcd. for $C_{29}H_{52}N_2$: C, 81.54; H, 12.38; N, 6.14. Found: C, 81.24; H, 12.23; N, 6.53). $[\alpha]_D^{24}$ +102° (*c* 0.40); λ_{max} mμ (ε): 210 (200); ν_{max} cm^{-1}: 2800 (m) (N–CH_3); NMR τ: 6.52 (1 proton, multiplet) (6α-H), 7.58 (3 protons, singlet), 7.73 (3 protons, singlet) (N–CH_3), 8.99 (3 protons, singlet) (19-H), 9.32 (3 protons, singlet) (18-H). Picrate: yellow prisms, mp 229—230°. *Anal.* Calcd. for $C_{35}H_{55}O_3N_5$: C, 63.91; H, 8.40; N, 10.65. Found: C, 64.34; H, 8.42; N, 10.54.

Reaction of the Azo-ester (I) with 3β-Benzoyloxycholesta-5,7-diene (III)——Formation of 3β-Benzoyloxy-5α,8α-(N_1,N_2-dicarbethoxyhydrazo)cholest-6-ene (XI) and 3β-Benzoyloxy-7α-(N_1,N_2-dicarbethoxyhydrazino)-cholesta-5,8-diene (XII): A solution of the azo-ester (I) (500 mg, 2.9 mmole) and the 5,7-diene (III)[29] (1.30 g, 2.7 mmole) in benzene (26 ml) was refluxed for 27 hr when the reaction was almost complete (thin-layer chromatography). The reaction mixture was concentrated *in vacuo* to give an yellow oil, (wt, 1.80 g). The oil was chromatographed over silica gel (Davison Co.) (54 g). Elution with 49:1 benzene–ether (750 ml) afforded a colorless oil, (wt. 486 mg). This was subjected to thin-layer chromatography over 1 mm silica gel layer (Kiesel Gel G nach Stahl, Merck) using benzene as eluent, affording 3β-benzoyloxy-5α,8α-(N_1,N_2-dicarbethoxyhydrazo)cholest-6-ene (XI) as colorless needles, mp 106—107.5°, (wt. 72 mg, 4.2% yield). Recrystallization from methanol gave material of mp 110—112.° *Anal.* Calcd. for $C_{40}H_{58}O_6N_2$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.50; H, 8.95; N, 4.37. $[\alpha]_D^{18}$ +44° (*c* 0.70); λ_{max} mμ (ε): 230 (15800); ν_{max} cm^{-1}: 1710 (s) and 1688 (s) ($CO_2C_2H_5$ and C_6H_5COO), 1599 (w), 1585 (s) and 1483 (m) (C_6H_5); NMR τ: 1.86 and 2.48 (5 protons, multiplet) (C_6H_5), 3.63 (2 protons, quartet, J=8 cps) (6-H and 7-H), 4.50 (1 proton, multiplet) (3α-H), 5.65—6.11 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 6.48(1 proton, multiplet) (4α-H), 8.72 (3 protons, triplet J=7 cps), 8.83 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 8.99 (3 protons, singlet) (19-H), 9.17 (3 protons, singlet) (18-H).

Further elution of the original chromatogram with 19:1 benzene–ether (790 ml) afforded 3β-benzoyloxy-7α-(N_1,N_2-dicarbethoxyhydrazino)cholesta-5,8-diene (XII) as colorless needles, mp 166—169°, (wt. 628 mg, 36% yield). Recrystallization from methanol gave material of mp 167—170°. *Anal.* Calcd. for $C_{40}H_{58}O_6N_2$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.45; H, 8.40; N, 4.25. $[\alpha]_D^{14}$ −38° (*c* 1.00); λ_{max} mμ (ε): 230 (13600) (C_6H_5COO); ν_{max} cm^{-1}: 3298 (m) and 1515 (m) (NH), 1748 (s) and 1680 (s) ($CO_2C_2H_5$), 1706 (s) (C_6H_5COO); NMR τ: 1.95 and 2.52 (5 protons, multiplet) (C_6H_5), 3.93—5.30 (4 protons, multiplet) (3α-H, 6-H, 7β-H, NH), 5.58—5.95 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 8.70 (3 protons, triplet, J=7 cps), 8.83 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 8.73 (3 protons, singlet) (19-H), 9.32 (3 protons, singlet) (18-H).

Catalytic Hydrogenation of XI——Formation of 3β-Benzoyloxy-7α-(N_1,N_2-dicarbethoxyhydrazino)cholestane (XIII): The 1,4-adduct (XI) (601 mg) in ethyl acetate (10 ml) was hydrogenated with 20% Pd–charcoal (170 mg) as catalyst at 18°; 520 mg of the catalyst was added to the hydrogenation mixture after 5 hr, and hydrogenation continued for 14 hr. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give a pale yellow oil, (wt. 574 mg). Repeated thin-layer chromatography of the oil over 1 mm neutral alumina (Woelm, grade III) layer with 19:1 benzene–ethyl acetate as eluent, afforded the dihydro compound, 3β-benzoyloxy-7α-(N_1,N_2-dicarbethoxyhydrazino)cholestane (XIII), as colorless needles, mp 130—131.5°. Recrystallization from methanol gave material of mp 133—134°. *Anal.* Calcd. for $C_{40}H_{60}O_6N_2$: C, 72.45; H, 9.10; N, 4.21. Found: C, 72.68; H, 9.30; N, 4.39. $[\alpha]_D^{18}$ +32° (*c* 0.93); λ_{max} cm^{-1}: 229 (13400) (C_6H_5COO); ν_{max}^{KBr} cm^{-1}: 1708 (s) and 1688 (s) ($CO_2C_2H_5$ and C_6H_5COO), 1598 (w), 1585 (w) and 1483 (m) (C_6H_5); NMR τ: 1.97 and 2.52 (5 protons, multiplet) (C_6H_5), 4.59 (1 proton, multiplet) (3α-H), 5.58—6.02 (4 protons, multiplet) ($CO_2\underline{CH_2}CH_3$), 6.67 (1 proton, multiplet) (4α-H), 8.69 (3 protons, triplet, J=7 cps), 8.77 (3 protons, triplet, J=7 cps) ($CO_2CH_2\underline{CH_3}$), 8.80 (3 protons, singlet) (19-H), 9.17 (3 protons, singlet) (18-H).

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29) A. Windaus, H. Lettré, and Fr. Schenck, *Ann.*, **520**, 98 (1935).