Tetrahedron. Vol. 25, pp. 4853 to 4871. Pergamon Press 1969. Printed in Great Britain

THE STEREOCHEMISTRY OF DIHYDROJERVINE AND RELATED COMPOUNDS

THE ORD CURVES OF 11-OXOETIOJERVANES AND 11-OXOIMINOJERVANES*

T. MASAMUNE, A. MURAI, K. ORITO, H. ONO, S. NUMATA and H. SUGINOME
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

(*Received in Japan* 2 *June* 1969; *Received in the UK for publication* 27 *June* 1969)

Abstract—The configurations of C_{12}, C_{13} (and C_{17}) in an acetolysis product (IVa) of diacetyltetrahydrojervine (IIIa) and its derivatives (Va to VIIIa) have been established. It follows that dihydro- and tetrahydrojervine are correctly represented by formulas II and III, (C/D *trans*, 12βH) rather than XXXV and XXIX (C/D *cis*, 12αH), respectively. The stereochemistry of the hydrogenation results of jervine (I) and the related compounds is rationalized on the basis of these formulas and the spectral data. The ORD curves of 12-epimeric 11-oxoetiojervanes and 11-oxoiminojervanes with established configurations are also presented and the summarized result reveals that the amplitudes fall within the limits of −150 ~ −190° for the C/D *trans*-fused compounds and of −70 ~ −100° for the *cis*-fused.

THE catalytic hydrogenation of the two double bonds present in jervine[1] (I) proceeds most effectively by a two-step procedure: the reduction in the presence of platinum in ethanol[2] or more efficiently in *alkaline ethanol*[3] first leads to a good yield of the formation of 12,13-dihydrojervine (II), which in turn on the same treatment in *acetic acid* is converted smoothly into 5α,6,12,13-tetrahydrojervine (III).[2,4] The simultaneous hydrogenation of both the double bonds of I in *acetic acid* was studied by several groups,[5–7] but produced a complex mixture, from which compound III was isolated only in low yield and in impure state. The same treatment of diacetyljervine (Ia) took an entirely different course, involving the hydrogenolysis of the 17,23-oxido linkage.[7] Wintersteiner and Moore proposed a rationalization for these anomalous results on hydrogenation of I, Ia and other jervine derivatives on the basis of the stereostructures for the compounds,[7] when they assigned the α-hydrogen configurations to C_{12} and C_{13} of II and III.[8] Recently we have presented evidence in a preliminary communication[9] that the β-configurational assignment to the hydrogen at C_{12} is preferable for these compounds (Chart 1). The present paper describes the details on establishment of the configurations of II, III and related compounds as well as our attempts to rationalize the hydrogenation results in question. In connection with this we also discuss the ORD curves of C/D *trans*- and *cis*-fused 11-oxoetiojervanes and 11-oxo-22,27-iminojervanes.†

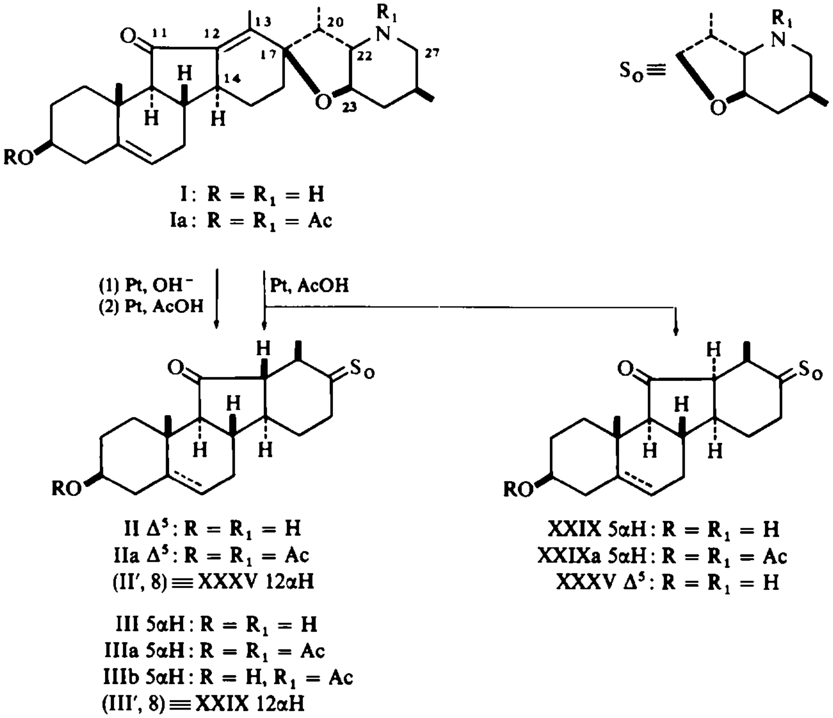
The previous α-assignment[8] (II′ and III′) to the hydrogens at C_{12} and C_{13} of both II and III was based on the following reasons (Chart 2): acetolysis of 3-O,N-diacetyltetrahydrojervine (IIIa) resulted in cleavage of the 17,23-oxido linkage to give Δ^{16}-olefin (IVa), which by treatment with alkali followed by acetylation was

---

* Part XVI of *C-Nor-D-homosteroids and Related Alkaloids*; Part XV, ref. 13b.

† In this context all the compounds are represented by the revised formulas: the previous assignments and references concerned are denoted by "parenthesized formula numbers with dashes" such as (VI′, 8).

CHART 1



I: $R = R_1 = H$
Ia: $R = R_1 = Ac$

II Δ^5: $R = R_1 = H$
IIa Δ^5: $R = R_1 = Ac$
(II′, 8) ≡ XXXV 12αH

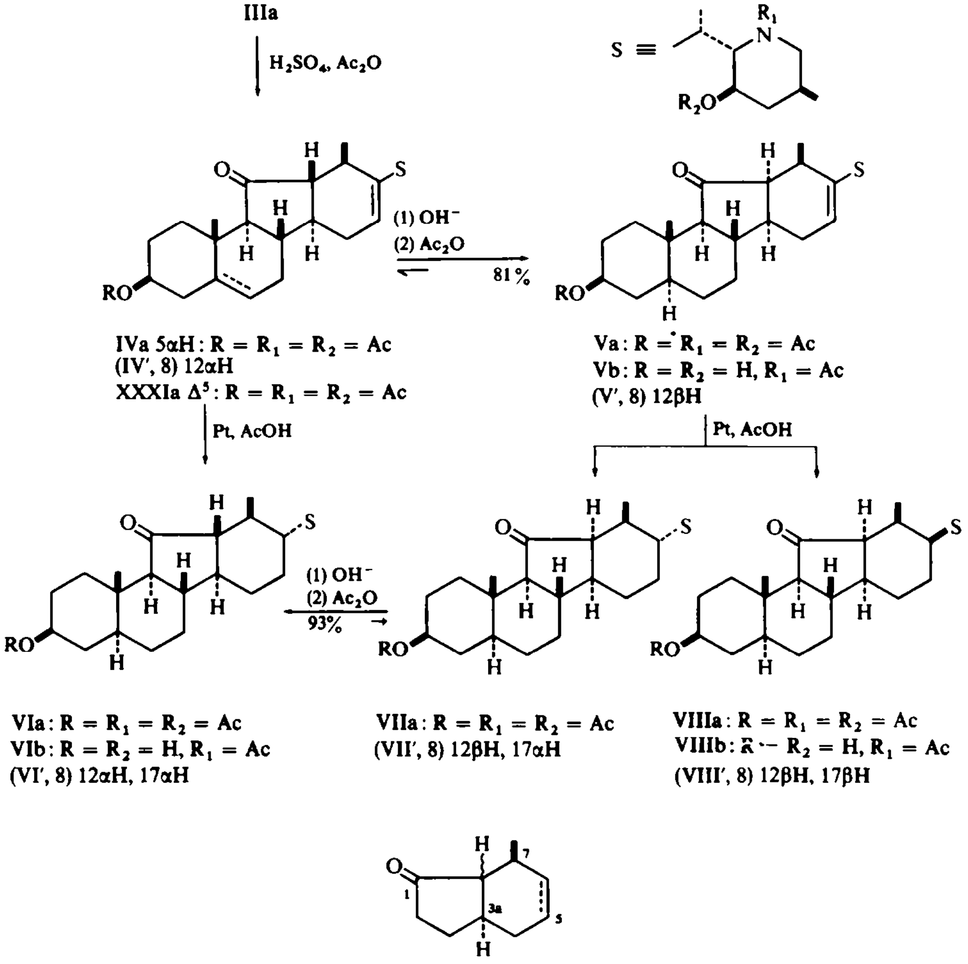
III 5αH: $R = R_1 = H$
IIIa 5αH: $R = R_1 = Ac$
IIIb 5αH: $R = H, R_1 = Ac$
(III′, 8) ≡ XXIX 12αH

XXIX 5αH: $R = R_1 = H$
XXIXa 5αH: $R = R_1 = Ac$
XXXV Δ^5: $R = R_1 = H$

epimerized to the 12-epimer (Va; 81%). Hydrogenation of IVa afforded the 16,17-dihydro derivative (VIa) as the sole product, indicative of the attack of hydrogens only from one side to the double bond. In contrast, the epimer Va on the same treatment produced a nearly 1:1 mixture of the dihydro derivatives (VIIa, crystalline, and VIIIa, amorphous). The latter (VIIIa) was completely stable to alkali at C_{12}, while the former VIIa was readily epimerized (93%) with alkali at the relevant carbon and on acetylation practically gave VIa. Since the behaviour on equilibration of IVa and Va paralleled that of *trans*- and *cis*-7-methyl-3a,4,7,7a-tetrahydroindanone-1 (IXa and IXb) with the 3a-H atom and 7-Me group *trans* (the ratio of IXa to IXb, over 50),[10] Wintersteiner and Moore assigned the β-hydrogen configuration to C_{12} (C/D ring juncture, *trans*) and the α-hydrogen to C_{13} (13-Me and 14-H, *trans*) to the predominant epimer Va in the equilibrium in question. This assignment, coupled with the behaviour on epimerization of the hydrogenation products VIa to VIIIa under alkaline conditions and also the hydrogenations, led to the conclusion that the H atoms at C_{12} and C_{13} were oriented (α and α, IV′) and (β and α, V′) in IVa and Va, and those at C_{12}, C_{13} and C_{17} (α, α and α, VI′), (β, α and α, VII′) and (β, α and β, VIII′) in VIa, VIIa and VIIIa, respectively. It followed that II and III possessed the α-H atoms at the relevant carbons (II′ and III′).

In our investigation on isojervine[11] it was observed that the Birch reduction of I effected the cleavage of the oxido linkage to give 8β,9α-dihydroisojervine (X). This β,γ-unsaturated ketone was transformed *via* N-acetyl-α,β-unsaturated ketone[11] (XIb) into N-acetyl-22,27-iminojerv-5-en-3β-ol[12] (XIIb), which on hydrogenation

CHART 2



IVa 5αH: $R = R_1 = R_2 = Ac$
(IV′, 8) 12αH
XXXIa Δ^5: $R = R_1 = R_2 = Ac$

Va: $R = R_1 = R_2 = Ac$
Vb: $R = R_2 = H, R_1 = Ac$
(V′, 8) 12βH

VIa: $R = R_1 = R_2 = Ac$
VIb: $R = R_2 = H, R_1 = Ac$
(VI′, 8) 12αH, 17αH

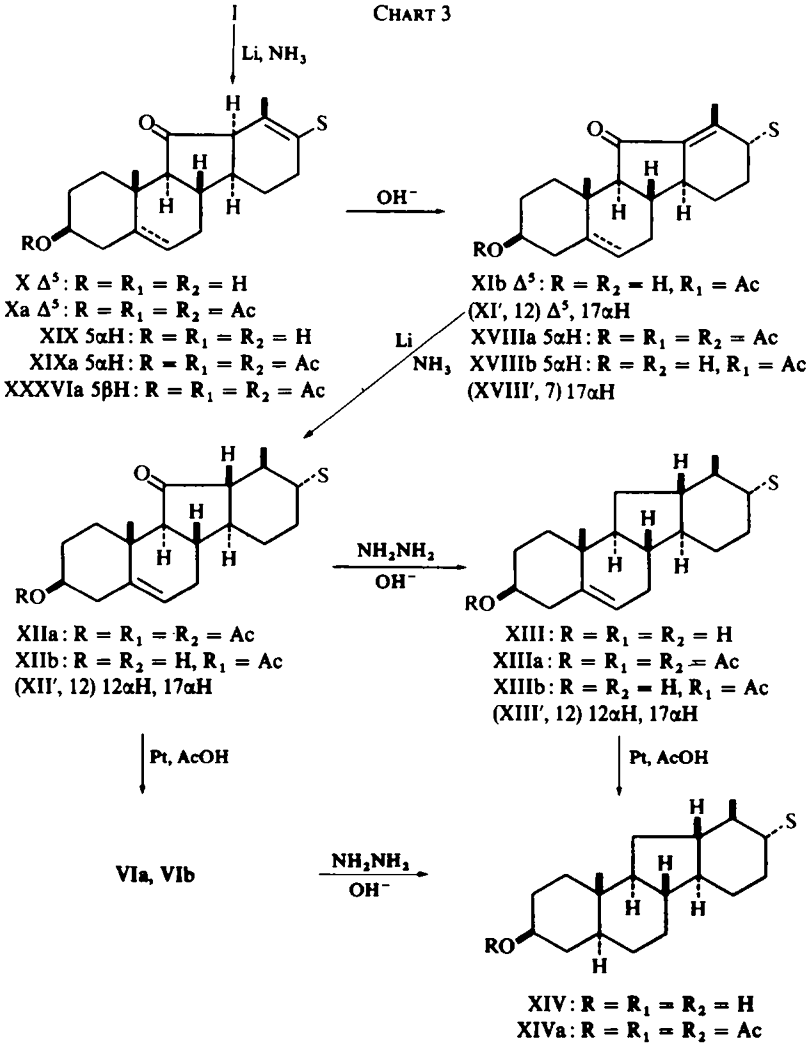
VIIa: $R = R_1 = R_2 = Ac$
(VII′, 8) 12βH, 17αH

VIIIa: $R = R_1 = R_2 = Ac$
VIIIb: $R = R_2 = H, R_1 = Ac$
(VIII′, 8) 12βH, 17βH

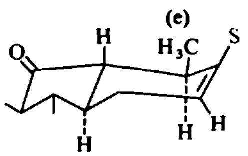
IXa: Δ^5, 7aβH
IXb: Δ^5, 7aαH
XVIa: 5H, 7aβH
XVIb: 5H, 7aαH

produced VIb, the 3-O,23-O-deacetyl derivative of VIa, in good yield.[12] This finding *then* led us to assign the α-hydrogen configurations (XII′) to C_{12}, C_{13} and C_{17} of XIIb.[12] In a continuing study this correlation between XIIb and VIb was supported by the following: hydrogenation of the 3-O,23-O-diacetyl derivative (XIIa) of XIIb over platinum in acetic acid naturally produced VIa in good yield. In addition, treatment of the N-deacetyl-11-deoxo derivative[12] (XIII) of XIIb under the same conditions led to a good yield of formation of the 5α,6-dihydro derivative (XIV), m.p. 207–208°. This was identical with a compound prepared from VIb by a modification of the Huang–Minlon procedure for Wolff–Kishner reduction (Chart 3). However, our recent investigation[13] has proved in an unambiguous manner that both the compounds XIIb, XIIa and XIII should possess the β-, α- and β-H atoms at the respective C atoms in question. This new assignment leads to revision of the configurations of all the compounds IVa to VIIIa as represented by the formulas.

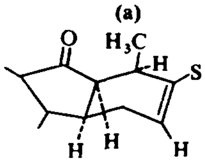
CHART 3



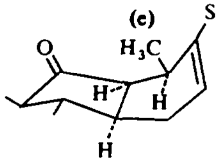
As described in the preceding paper,[13] the above configurational assignments have been deduced fundamentally on the premise that the interpretation is correct for the ORD curves of C/D *trans*- and *cis*-fused 17-oxoetiojervanes discussed by Kupchan,[14] Johns,[15] and collaborators as well as ourselves.[16,13] While this appears both reasonable and acceptable, the facts presented previously[8] must be rationalized in the light of the above revised formulas. *trans*-Tetrahydroindanone IXa is greatly favoured under equilibrating conditions over its *cis*-isomer IXb.[10] The situation becomes opposite in the case of the relevant epimers, IVa (C/D *trans*) and Va (C/D *cis*).[8] The plausible explanation for this dissimilarity is as follows: In compound IVa, the D-ring should adopt a somewhat distorted half-chair form as depicted in IV-A, in which the β-Me group at C_{13} is equatorial and an interaction between the group and 17-substituent is sterically hindered[17] as described later. In contrast, D-ring in Va should take a twist-boat form with the Me group pseudo-axial (V-A) as pointed out by Wintersteiner[8] and would, therefore, not be sterically hindered to the interaction.



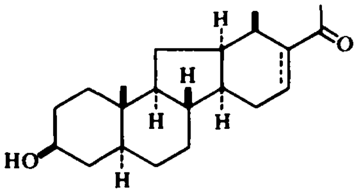
IV-A



V-A



V-B



XVa 17αH
(XV′, 15) 17βH
XVb Δ^{16}

The behaviour of IVa and Va on hydrogenation can be explained on the same grounds with the aid of Dreiding models. The three groups (H, Me and substituted piperidine) at C_{21} in IVa (C/D *trans*) must adopt a conformation in which the most bulky is remote from the D-ring and 13β-Me group and positioned at the lower side of the molecule. Accordingly, the Me group must be oriented in a nearly 1,3-diaxial relation to the 13β-Me as mentioned, since the absolute configuration of C_{21} has been established as shown by formula I.[1] This conformation would result in the approach of catalyst only from the upper side and hence only one dihydro product with β-hydrogen would be formed, as is actually the case. On the other hand, in compound Va (C/D *cis*) free rotation of the 17-substituent around the C_{17}—C_{20} bond appears possible to some extent. The steric hindrance against the catalyst approach caused by the pseudo-axial 13β-Me group would be comparable with that by the bulky piperidine. This would allow the absorption of catalyst to both the rear and front sides of the molecule, which leads to formation of two dihydro products, as is the case. It is to be noted that only 17β-acetyl-12α-etiojervan-3β-ol[15, 18] (XVa) is isolated in 60% yield* by hydrogenation of the corresponding 16,17-dehydro derivative (XVb), which differs from Vb, the 3-O,23-O-deacetyl derivative of Va, only by the 17-substituent and the absence of 11-oxo group.[15]

The equilibration result of the hydrogenation products VIa to VIIIa with alkali is interpretable well. Compounds VIa and VIIa are in the same situation regarding

---

* Comparison of the optical rotation of the whole product with those of XVa and its 17-epimer indicates that at least 80% of XVa is included in the product (refs. 15 and 18).

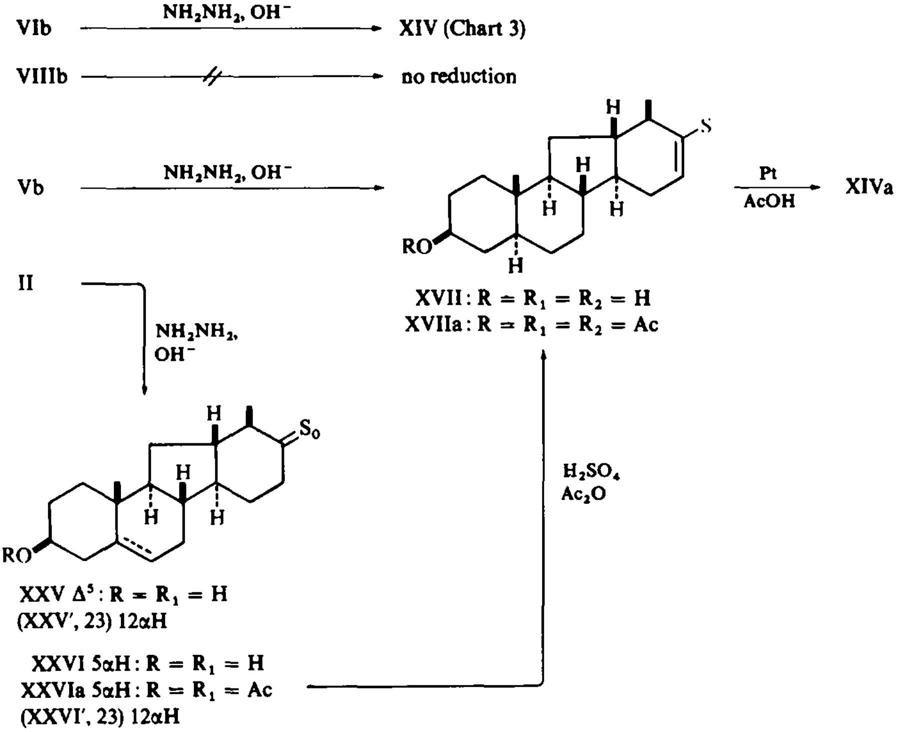
the two substituents at C_{13} and C_{17} of the D-ring: both groups are disposed *trans* and, accordingly, equatorial. Thus the stability relationship of simple *trans*- and *cis*-hexahydroindanones XVIa and XVIb[10] can be applicable approximately to the relevant compounds. In fact, in either case the *trans*-form (XVIa or VIa) predominates over the respective *cis*-form (XVIb or VIIa). It is also quite reasonable that compound VIIIa is stable to alkali at C_{12}. If the epimerization occurs, the bulky 17β-substituent of the resulting compound must become axial in a distorted chair-form or the D-ring must adopt an energetically unfavourable boat-form. These unquestionably render the compound unstable.

These revised formulas are furthermore consistent with the behaviour on Wolff–Kishner reduction of VIb, VIIIb (a 3-O,23-O-deacetyl derivative of VIIIa) and Vb (Chart 4). Compound VIb was converted into the 11-deoxo compound XIV in moderate yield (crude 80%, pure 25%), while VIIIb was unaffected by the same treatment. In VIb with C/D *trans*-fused linkage, the D-ring must take a slightly distorted chain form, in which the β-Me group at C_{13} is oriented equatorially. Then VIb is essentially flat regarding the B, C and D rings and only the 19-Me group would hinder the approach of hydrazine to C_{11}. The formation of the hydrazone must therefore proceed without much difficulty. With C/D *cis*-fused VIIIb, the D ring would assume a twist-boat or more probably a half-chair conformation, in each of which the bulky 17-substituent must become equatorial. Whatever the conformation is, the β-Me group at C_{13} would be disposed to the upper side of the molecule and exert the serious steric hindrance against the hydrazone formation.

Compound Vb, which possess the C/D *cis*-linkage as well as double bond at C_{16} and C_{17}, would probably adopt a boat-form with the 13- and 15-C atoms in a bowsprit-flagpole disposition. If the β-Me group at C_{13} is axial (V-A), the situation in the reduction of Vb is the same as that of VIIIb. Alternately, the D-ring might assume a boat form with the Me equatorial (V-B) during the reaction, when the bulky 17-substituent must crowd over the upper side of the molecule and, coupled with the 19-Me group, impede the hydrazone formation. In either case it was expected that the reduction of Vb under Wolff–Kishner conditions would be difficult. Contrary to the presumption, the reduction was achieved although in low yield (crude 60%, pure 8%) and, moreover, the resulting 11-deoxo compound (XVII), m.p. 193–196°, proved to have the C/D *trans*-juncture, because the triacetyl derivative (XVIIa), m.p. 200–202°, on hydrogenation over platinum in acetic acid, afforded the triacetyl derivative (XIVa), m.p. 214–215°, of XIV in good yield. The formation of XVII can be rationalized by assuming that Vb, with the C/D ring *cis*-fused, underwent the epimerization at C_{12} to some extent under the basic conditions and the resulting C_{12}-epimer was then submitted to the reduction to XVII.

Based on these revised configurations the following results are in good accord with the generally accepted view that the hydrogenation in neutral or acidic solvents, particularly in *acetic acid*, proceeds principally with the *cis*-addition of hydrogens.[20] (1) Wintersteiner and Moore hydrogenated Δ^{12}-11-ketone XVIIIb in the presence of platinum in acetic acid. Contrary to their expectation that VIa (then formulated by VI′) would be formed as a result of the *cis*-addition, they isolated VIIa in a yield of over 60% after acetylation together with the starting compound XVIIIb (10%).[7] The product VIIa was *then* assigned β- and α-hydrogens at C_{12} and C_{13}, respectively. Now it possesses the α-hydrogens at both the carbons, and the result implies that

Chart 4



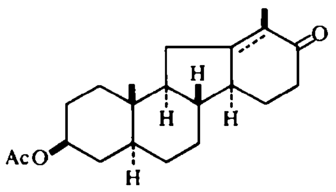
XVII : R = R$_1$ = R$_2$ = H
XVIIa : R = R$_1$ = R$_2$ = Ac

XXV Δ^5 : R = R$_1$ = H
(XXV', 23) 12αH

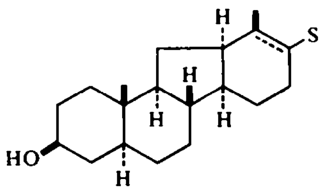
XXVI 5αH : R = R$_1$ = H
XXVIa 5αH : R = R$_1$ = Ac
(XXVI', 23) 12αH

both hydrogens have added mainly from the rear side. Compound XVIIIb[7] can be regarded as a 5α,6-dihydro derivative of XIb.[11] Both XVIIIb and XIb were obtained from the respective β,γ-unsaturated ketones XIXa[11, 19] and Xa[11] by alkali treatment, suggesting the 17-substituent to be equatorial and hence α-oriented. The above hydrogenation result confirms this assignment in XVIIIb and XIb, which means revision of the previous β-configuration[7, 12] (XVIII' and XI'). It is to be noted that the hydrogenation of etiojerv-12-en-3β-ol-17-one 3-acetate (XXa), another type of α,β(Δ^{12})-unsaturated ketone, has produced the corresponding 12α,13α-dihydro derivative (XXb) in good yield under comparable conditions (Pd, EtOH).[21]

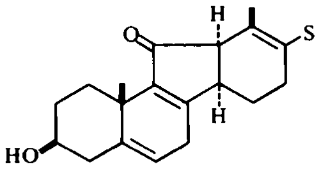
(2) The above *cis*-addition of hydrogens to the 12,13-double bond promoted us to investigate the hydrogenation of an isolated double bond at C_{13}–C_{17}. Compound XIX or XIXa,[12, 22] prepared by hydrogenation of X or Xa, resisted the hydrogenation over platinim in acetic acid.[12] Reduction of the relevant bond was accomplished by using rhodium–platinum catalyst: when treated in the presence of the catalyst in acetic acid, Xa afforded a mixture showing only two spots on TLC, from which VIIIa was isolated in 38% yield in pure state together with 25% of XIXa. The same type of hydrogenation was previously carried out with XXI, regarded formerly as an 11-deoxo derivative of XIX.[18] The major product proved to be XXII and hence possesses the configuration of VIIIa at each of the asymmetric centres.[18] These results not only indicate the *cis*-addition of hydrogens to the 13,17-double bond but also confirm the α-hydrogen configuration at C_{12} of XXI, XIX and X as well as isojervine[11, 19] (XXIII), which has been deduced from the spectral (NMR and UV) data.



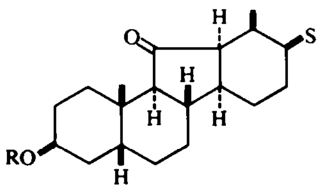
XXa Δ^{12}
XXb 12αH, 13αH



XXI $\Delta^{13(17)}$: $R_1 = R_2 = H$
XXII 13αH, 17αH: $R_1 = R_2 = H$



XXIII: $R_1 = R_2 = H$



XXIVb: $R = R_2 = H, R_1 = Ac$
XXIVc: $R = R_1 = Ac, R_2 = H$

(3) As already described, the hydrogenation of diacetyljervine Ia over platinum in acetic acid produced a complex mixture, from which Wintersteiner and Moore isolated three compounds,[7] 3-O,N-diacetyl-22,27-iminojervane-3β,23β-diol-11-one (XXIVc, compound XIIc in their paper) in about 15% yield, and XIXa and VIIIa after acetylation in about 20 and 10% yields (in crude state), respectively.[7] While the configurations at C_{12}, C_{13} and C_{17} of XXIVc were left undefined,[7] the present spectral study reveals that the compound should be represented by the formula, which possesses the same configuration at the three C atoms in question as VIIIa but differs from VIIIa only by the 5β-hydrogen (A/B *cis*-fused). Compounds XXIVc and its 3-O-deacetyl derivative XXIVb exhibit in the NMR spectra the proton at C_3 at τ 4·98 and 5·95 with half-widths of 7 and 10 c/s and the 19-Me protons at 8·98 and 8·975, respectively. These values, compared with those of the corresponding of A/B *trans*-fused iminojervanes (3-H, near τ 5·4 and 6·4, W_H about 20 c/s, and 19-Me, at higher field than τ 9·11), prove the β-hydrogen configuration at C_5 in XXIVc. The ORD curve of XXIVb displays a negative Cotton effect with amplitude of −82°, which indicates that the C/D ring is *cis*-fused, as discussed later. Furthermore, in view of the stability to alkali at C_{12}, it is improbable that the bulky 17-substituent is α oriented. Thus only the configuration of the 12-C atom remains undefined. In the NMR spectrum the 18-, 21- and 26-Me protons appear at τ 9·26, 9·11 and 8·92 as doublets, although at this stage it is difficult to assign these signals appropriately to the respective protons. However, this spectral pattern due to the secondary Me protons is characteristic of a number of iminojervane derivatives* and, moreover, superimposable on compound VIIIb. Although no evidence excluding the 13β- and 17α-hydrogen configuration[8] is presented, the afore-mentioned close resemblance has led us to assign the α-hydrogen configuration to C_{12}. On this reasonable premise,

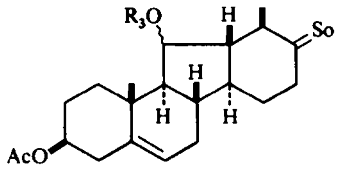
---

* Signals due to the 21- and 26-methyl protons largely depend not only on substituents on the N and C_{23} atoms but also the presence and position of a double bond in the D-ring. These will be summarized and published later. Cf. ref. 11, Table 1.

the isolated hydrogenation products, XXIVc, XIXa and VIIIa, all possess the α-oriented hydrogen at C_{12}, C_{13} and C_{17} (only C_{12} for XIXa), confirming the *cis*-addition of hydrogens from the rear side.

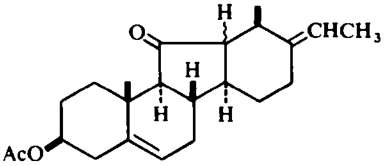
The C/D *trans*-configuration in dihydrojervine II and tetrahydrojervine III is based on the following facts: (1) compound IIIa is transformed to IVa by acetolysis[8] in which epimerization at C_{13} is improbable. The retention at C_9 has been pointed out.[8] The configurational change in question at C_{12}, located adjacent to the 11-ketonic group, is also unlikely, because the reactant IIIa is essentially stable to alkali at C_{12} and the product IVa is a less stable isomer as compared with the corresponding 12-epimer Va. (2) The Wolff–Kishner reduction of II proceeds smoothly to yield the 11-deoxo compound (XXV), which on hydrogenation forms the 5α,6-dihydro derivative (XXVI).[23] The C/D *trans*-configuration in these compounds was established by transformation of the 3-O,N-diacetyl derivative[23] (XXVIa) into XVIIa with C/D *trans*-linkage under the conditions of acetolysis of IIIa (Chart 4). If II is *cis*-fused at the C/D juncture like VIIIb, it would be unaffected by the Wolff–Kishner reduction. (3) The proton at C_{11} of 11-nitrite[24] (XXVIIa) of 11β-alcohol[23] (XXVII), one of the reduction products of IIa, at τ 3·95 is a clear triplet with coupling constants of 7·3 c/s in the NMR spectrum and that of the epimeric nitrite[24] (XXVIIIa) of 11α-alcohol[23] (XXVIII) at τ 4·08 is a poorly resolved quartet with coupling constants of ca. 4·0 and 5·6 c/s. Examination of the Dreiding model reveals that, if the C/D ring is *cis*-fused (12αH) and the flexible D-ring adopts a half-chair form with the β-Me at C_{13} equatorial, a conformation considered to be the most stable, dihedral angles between hydrogens at (C_{11} and C_{12}) become ca. 40° and 160° for XXVIIa and XXVIIIa, which, using Conroy's graph,[25] give the constants of 4·6 and 10·1 c/s, respectively. When both the compounds possess the assigned structures (12βH), coupling constants calculated from the angles between hydrogens at (C_{11} and C_{12}) and at (C_{11} and C_9) are 7·7 (ca. 140°) and 7·6 c/s (ca. 10°) for XXVIIa and 6·6 (ca. 25°) and 6·1 c/s (ca. 130°) for XXVIIIa. This finding supports the assigned structure, the C/D *trans*-fused linkage, in compound II. (4) A 12-epimer (XXIXa) of diacetyltetrahydrojervine IIIa obtained by hydrogenation of I described later displayed a negative Cotton effect with amplitude of −96° in the ORD curve and also a singlet peak due to the 19-Me protons at τ 9·11. These values, compared with the corresponding ones (−181° and τ 9·18) of IIIa, are consistent with the C/D *cis*-fused configuration on the basis of the ORD and NMR data discussed later in this and the following papers.[26]

In Table 1 are listed the amplitudes of ORD curves in several representative 12-epimeric 11-oxoiminojervanes and 11-oxoetiojervanes with the established configurations. Kupchan and El-Haj[27] have recently deduced from the spectral data the configuration at C_{12} of 12-epimeric 11-oxoetiojervanes (XXXa and XXXb). They interpreted the difference between the amplitudes of negative Cotton effect in the ORD curves of both compounds (−161° for XXXa and −87° for XXXb) in terms of the octant rule for hexahydroindanones advanced earlier by Klyne.[28] The interpretation, considered as confirmatory evidence for their configurational assignment, appears most reasonable, since it has been based on the comparison between the 12-epimers. However, the absolute values may be varied depending on the substituents on the A- and D-rings, even if the B/C and C/D ring junctures are fixed. Therefore, it is desirable to examine the ORD curves of other 11-oxo-C-nor-D-



XXVII 11αH: $R_1 = Ac, R_3 = H$
XXVIIa 11αH: $R_1 = Ac, R_3 = NO$
(XXVII′, 23) 12αH

XXVIII 11βH: $R_1 = Ac, R_3 = H$
XXVIIIa 11βH: $R_1 = Ac, R_3 = NO$
(XXVIII′, 23) 12αH



XXXa 12βH
XXXb 12αH

homosteroids. Here we emphasize that the configuration of all compounds other than XXXa and XXXb, listed in Table 1, has been established regardless of the consideration on the ORD curves due to 11-ketonic group.

As shown in Table 1, the C/D *trans*-fused 11-ketones reveal negative Cotton effects with amplitudes of ca. −175°, while the C/D *cis*-fused, except the β,γ-unsaturated ketones, are at ca. −85°. The difference in amplitude is readily explained by application of the octant rule[28] to the present system, as advanced for XXXa

TABLE 1. THE AMPLITUDE OF COTTON EFFECT IN THE ORD CURVES OF 11-OXOIMINOJERVANES AND 11-OXOETIOJERVANES

C/D ring *trans* (12βH)		C/D ring *cis* (12αH)	
Compound	Amplitude[a]	Compound	Amplitude[a]
IVa	−172°	Va	−82°
XXXIa[b]	−182°	VIIa	−96°
VIa	−169°	VIIIa	−84°
VIb	−174°	VIIIb	−80°
XIIa	−183°	XXXb[c]	−87°
XIIb	−180°	XXXIIb[d]	−82°
XXXa[c]	−161°	X	+333°
XXXIIa[d]	−170°	Xa	+242°
XXXIII[e]	−172°	XIXa	+104°
XXXIV[d]	−178°	XXXVIa[f]	+205°

[a] Solvent, dioxane; temp, 25° ± 2°.

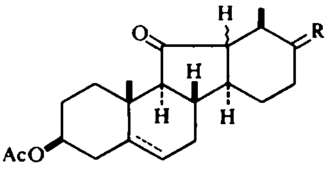
[b] The 5,6-dehydro derivative of IVa (Experimental).

[c] Cited from Ref. 27.

[d] The preparation and configuration of these compounds will be described in detail in the following paper, cf. Ref. 26.

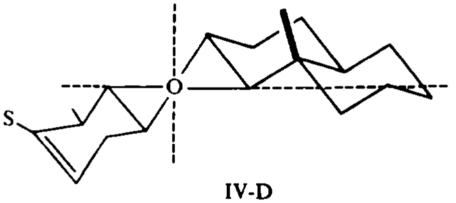
[e] Ref. 16.

[f] The 5β-epimer of XIXa, Ref. 11.

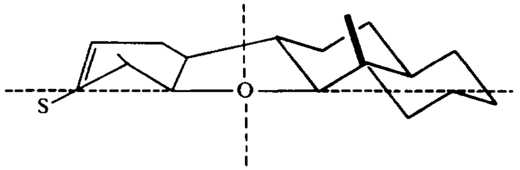


XXXIIa 5αH, 12βH: R = β-C_2H_5, α-H
XXXIIb 5αH, 12αH: R = β-C_2H_5, α-H
XXXII 12βH: R = —OCH_2CH_2O—
XXXIV 12βH: R = H_2

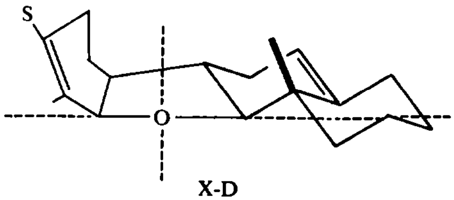
and XXXb by Kupchan and El-Haj;[27] e.g., diagrams IV-D and V-D can be described for compounds IVa and Va, respectively, using the Dreiding model. This result is, therefore, in good accord with the assigned structures of a few compounds in question; II and III exhibit the amplitudes of −164° and −175°, and XXIXa and XXIVc −96° and −82°, as mentioned before. It seems reasonable to conclude from the available data[16,26,27] (ca. 50 compounds) and that the relevant amplitudes in 11-oxoetiojervanes and 11-oxoiminojervanes fall within the limits of −150 ~ −190°, and those of the corresponding 12α-compounds −70 ~ −100°, although the kind and number of functional groups or substituents on the A-, B- and D-rings are not very large in the examples cited. On the other hand, the C/D *cis*-fused β,γ-unsaturated ketones X, XIX and the acetate display strong positive Cottone effects. These enhanced amplitudes, coupled with the UV spectral data (λ_{max} and ε_{max}, 312 mμ and 300 for X, and 310 mμ and 240 for XIX),[11] reflect the strengthened $n - \pi^*$ transitions, pointed out by Moscowitz *et al.*[29] and are consistent with the assigned structures (*cis*-fused C/D linkage, 12αH), as shown in the diagram X-D in which the D-ring enters into a positive quadrant.



IV-D



V-D



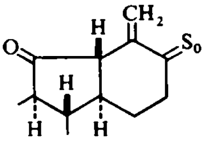
X-D

The CD curves of three 12-epimeric pairs as well as a few compounds under discussion were also measured. These compounds exhibit the following amplitudes [θ] (MeOH) at 24°: IVa and Va, −10,300° (at 312 mμ) and −5000° (309); VIa and VIIIa, −10,200° (314 mμ) and −4400° (309); XXXIIa and XXXIIb, −10,300° (312 mμ) and −4700° (312); II and III, −10,400° (315 mμ) and −9900° (313); Xa, +15,800° (320 mμ). These values are compatible with the result deduced from the ORD curves and support the aforementioned configurational assignment. The CD curves of II, XXXIIa (both C/D *trans*), Va and Xa (both C/D *cis*) were further measured at lower temperatures and revealed the following amplitudes (θ) at 24°, −75° and −186° in a mixture of ether, pentane and ethanol: II, −10,100° (314 mμ), −11,000° (315) and −11,900° (313); XXXIIa, −11,200° (312 mμ), −12,000° (315) and −12,200° (315); Va, −4600° (309 mμ), −4900° (309) and −5100° (311); Xa, +13,300° (320 mμ), +16,400° (320) and +18,600° (320). While the enhanced amplitude at the lower temperature shown by Xa suggests the conformation X-D to be a stable form in the compound, each of the other compounds II, XXXIIa and Va displays nearly equal intensities both at the low and room temperatures, indicating that the respective compound, whether the C/D ring juncture is *trans*- or *cis*-fused, takes a fixed and rigid conformation.

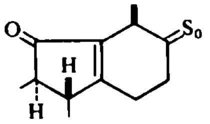
Finally we examined in some detail the hydrogenation product of jervine I over platinum in *acetic acid* and isolated the 12α-epimer (XXIX) of tetrahydrojervine III, although attempts to obtain the corresponding 5,6-dehydro derivative (XXXV) by partial hydrogenation failed: the product in question apparently showed two spots on TLC, but only one spot after treatment with alkali and on subsequent acetylation gave a 70% yield of IIIa in pure form. This yield is nearly equal to that of II obtained by hydrogenation of I in *alkaline ethanol.*[3] The product was separated by acetylation followed by preparative TLC (6 spots): a main fraction accounting for 48% of the material proved to be IIIa (40% in crystalline, pure form). Beside IIIa, the amorphous 12α-epimer XXIXa and XIXa were isolated in 30 and 3·5% yields, respectively, but other fractions could not be characterized. The structure of XXIXa was confirmed by the spectral data and transformation into N-acetyltetrahydrojervine (IIIb) in 80% yield by treatment with alkali. Compound XXIXa is unaffected under the above-mentioned acetylation conditions and, moreover, the relative ratio of each component in the whole product remains unchanged after treatment under the hydrogenation conditions. These facts indicate that III is not produced by epimerization of XXIX but by *trans*-addition of hydrogens.

Many examples have been reported of the *trans*-addition to a fully substituted double bond of cyclic olefins,[30] cyclic α,β-unsaturated ketones[31] and, particularly, steroidal ketons [except Δ^8-11-ketones[32] and 4-methyl-Δ^4-3-ketones (Pd, EtOH)[33]] such as 4-methyl-Δ^4-3-ketones (Pt, AcOH),[34] Δ^8-7-ketones,[35] Δ^8-7,11-diketones[35b, 36] and $\Delta^{8(14)}$-7-ketones.[37] The stereochemistry of hydrogenation is apparently influenced by many factors and various mechanisms have been advanced.[20, 38] One of the most satisfactory postulates, accounting for the *trans*-addition to unconjugated, tetrasubstituted double bonds, is as follows: the relevant double bond migrates to β,γ-position *via* "half-hydrogenated state"[39] and undergoes *cis*-addition from the side opposite to the α-carbon hydrogen.[30a] An alternate explanation, as acceptable as that for the *trans*-addition to α,β-unsaturated ketones, is as follows: the hydrogenation, except in strongly acidic media, involves an enol intermediate formed by 1,4-addition of hydrogens adsorbed on the catalyst to the enone in question or by respective additions of adsorbed hydrogen to the β-carbon and solvent proton to oxygen anion. The resulting enol, after desorption, is submitted to kinetically controlled reketonization,[40] leading in some cases to protonation of the α-carbon from the side opposite to the β-carbon hydrogen.[7, 41]

In the present case, formation of III by the double bond migration mechanism seems very improbable: the hydrogenation process requires an intermediate such as $\Delta^{13(18)}$-12β-11-ketone (XXXVII), which is obtained only by the hydrogen attack to C_{12} from the catalyst attached to the β-side of C_{12}, C_{13} and probably C_{18}. This behaviour on adsorption of the catalyst must hold for the following step, the hydrogen addition to C_{13} and C_{18}, which naturally results in the formation of a 13β-epimer of III. The hydrogenation to III would probably proceed according to the enol mechanism either directly from I or *via* its isomer such as $\Delta^{12(14)}$-13α-11-ketone (XXXVIIIa). In fact, Iselin and Wintersteiner[42] have isolated such an isomer (XXXVIIIb, "Δ^{13}-jervine", C_{13}-configuration undefined) by treatment of I with hydrogen and palladium in 10% aqueous acetic acid. However, the latter route appears also unlikely, because (1) the yield of XXXVIIIb was only 20%, whilst that of III in the pure state was 40% and (2) "hydrogenation in acetic acid yielded a difficulty separable and ill-reproducible mixture of III."[42] On the other hand, the direct hydrogenation of I must involve 1,4-addition of hydrogens to the Δ^{12}-11-ketonic grouping from the rear (α) side and subsequent protonation of C_{12} in the resulting 11-en-11-ol from the front (β) side. The re-ketonization of the postulated enol can be interpreted in terms of the stereo electronic control,[40] in accordance with Wintersteiner's discussion of the closely related enol.[7] The following aspects still require clarification: why does the hydrogen addition to C_{13} take place from the apparently more hindered α-side and why does reduction of the Δ^{12}-11-ketonic group in I undergo mainly *trans*-addition, though that in XVIIIb involves normal *cis*-addition? At the present stage, for want of other reasonable explanations, we prefer to accept the above postulate.



XXXVII



XXXVIIIa (13αH)
XXXVIIIb (13ξH)

EXPERIMENTAL

All the m.ps were uncorrected. The homogeneity of each compound was checked by TLC on silica gel (Wakogel B-5) using various solvent systems, and the spots were developed with ceric sulphate in dil H_2SO_4 and/or I_2. The optical rotations, UV and IR spectra were measured at room temp in $CHCl_3$, 99% EtOH and Nujol, respectively, unless otherwise stated. The measurement of CD curves was performed at room temp in MeOH on a Jasco ORD/CD-5 spectropolarimeter. The variable temp CD curves were obtained in a 5:5:2 mixture of ether, pentane and ethanol. The NMR spectra were measured in $CDCl_3$ at 60 and/or 100 Mc and the chemical shifts were given in τ-values, TMS being used as an internal reference. The abbreviations "s, d, br and m" in the NMR spectra denote "singlet, doublet, broad and multiplet," respectively.

Hydrogenation of 3-O,23-O,N-*triacetyl*-22,27-*imino*-17β-*jerv*-5-*ene*-3β,23β-*diol*-11-*one* (XIIa) *to its* 5α,6-*dihydro derivative* (VIa)

Compound XIIa[13b] (200 mg) in AcOH (7 ml) was hydrogenated in the presence of prereduced Adams Pt (100 mg as $PtO_2 \cdot H_2O$) at 26° for 30 min when 8·83 ml of H_2 (1·04 mol) were adsorbed. After removal of the catalyst and solvent by azeotropization with benzene, the residue was dissolved in $CHCl_3$ (20 ml), and the $CHCl_3$ soln was washed with dil NaOHaq and then water, dried over Na_2SO_4 and evaporated to dryness, leaving an amorphous substance (219 mg), which crystallized on trituration with ether, m.p. 240–241°, 160 mg. Recrystallization from ether gave a pure sample of VIa, m.p. 242–243°, which was identical with an authentic specimen prepared by Wintersteiner's procedure;[4,8] $[\alpha]_D$ −38·5°; IR, ν_{max} 1721, 1641 and 1245 cm^{-1}; NMR, τ 9·17 (3H, s, 19-Me).[11]

The following experiment was conducted as additional support for the identification: the sample VIa (70 mg) prepared by the hydrogenation of XIIa was hydrolyzed with 5% KOH in MeOH (4 ml) at 50° for 20 min. The product was poured into water (20 ml) and extracted with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ soln was washed with water (2 × 20 ml), dried and evaporated to leave solid (58 mg), which was crystallized from 95% EtOH, m.p. 269–270°, 48 mg. Recrystallization from EtOH–acetone afforded a pure sample of VIb, m.p. 270–171°; $[\alpha]_D$ −45·0°; IR, ν_{max} 3420, 1728 and 1606 cm^{-1}; NMR, τ 9·18 (3H, s, 19-Me) and 7·86 (3H, s, N-Ac). This sample was identical with an authentic speciment.[4,8]

22,27-Imino-17β-jerv-5-ene-3β,23β-diol (XIII) *and its* 3-O,23-O,N-*triacetyl and* N-*acetyl derivatives* (XIIIa *and* XIIIb)

Compounds XIII and XIIIa were prepared with modification of the procedures mentioned.[12] Compound XIII (400 mg) was acetylated with Ac_2O (4 ml) and Py (8 ml) at room temp overnight. The mixture was poured into ice-water (50 ml), stirred for 2 hr and then filtered. The crude acetate XIIIa was dissolved in $CHCl_3$ (10 ml), washed with water (20 ml), dried and evaporated to give amorphous material, which crystallized on trituration with acetone–ether and amounted to 485 mg. This crystal melted at 164°, partly solidified and melted at 175°. Recrystallization from the same solvent afforded an analytical sample of XIIIa, m.p. 164–165°, resolidified and again melted at 175–176° (lit.[12] 155–156°); $[\alpha]_D$ −25·3° (lit.[12] −75·0° in 95% EtOH); IR, ν_{max} 1747, 1736, 1640 and 1244 cm^{-1}; NMR, τ 9·04 (3H, s, 19-Me), 8·00 and 7·90 (6H and 3H, each s, OAc and NAc), 4·95 (1H, br W_H = 8 c/s, 23-H), and 4·66 (1H, br, 6-H). (Found: C, 73·32; H, 9·50; N, 2·43. Calc. for $C_{33}H_{41}O_5N$: C, 73·16; H, 9·49; N, 2·59%).

Compound XIIIa (415 mg) was hydrolyzed with 5% KOH in MeOH (10 ml) at 50° for 20 min. After cooling, the mixture was diluted with water (50 ml) and extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ soln was washed with water (2 × 30 ml), dried and evaporated to leave an amorphous substance (355 mg), which was crystallized from acetone–$CHCl_3$, m.p. 253–254°. The crystalline material (329 mg) was recrystallized from the same solvent for analysis, m.p. 253–254°; $[\alpha]_D$ −36·5°. IR, ν_{max} 3420 and 1597 cm^{-1}; NMR, τ 9·04 (3H, s, 19-Me), 7·88 (3H, s, NAc), 5·94 (1H, br W_H = 7 c/s, 23-H), and 4·68 (1H, br, 6-H). (Found: C, 76·15; H, 10·32; N, 3·21. $C_{29}H_{47}O_3N$ requires: C, 76·10; H, 10·35; N, 3·0%).

22,27-Imino-17β-jervane-3β,23β-diol (XIV) *and its* 3-O,23-O,N-*triacetyl derivative* (XIVa).

(a) *From* XIII. Compound XIII[12] (120 mg) in AcOH (16 ml) was hydrogenated over prereduced Adams Pt (65 mg) at 21° for 70 min, until 6·95 ml of H_2 (1·04 mol) had been consumed. After work up an amorphous residue (127 mg) was obtained which on trituration with acetone gave crystalline XIV (95 mg), m.p. 207–208°. Recrystallization from MeOH afforded an analytical sample (71 mg), m.p. 206–207°; $[\alpha]_D$ +15·4°; IR, ν_{max} 3420 cm^{-1}; NMR, τ 9·26 (3H, s, 19-Me). (Found: C, 77·71; H, 11·29; N, 3·41. $C_{27}H_{47}O_2N$ requires: C, 77·64; H, 11·34; N, 3·35%).

The above XIV (50 mg) was treated with Ac_2O (1 ml) and Py (1 ml) at room temp for 19 hr. The product was poured into ice-water (150 ml), stirred for 3 hr and filtered. The ppt was dissolved in $CHCl_3$ (30 ml) and dried over $MgSO_4$. Removal of the solvent left an amorphous substance, which was crystallized from acetone–ether, m.p. 213–214°, 41 mg. Recrystallization from ether afforded an analytical sample of XIVa, m.p. 214–215·5°; $[\alpha]_D$ +57·8°; IR, ν_{max} 1740, 1734, 1645 and 1248 cm^{-1}; NMR, τ 9·26 (3H, s, 19-Me). (Found: C, 72·76; H, 9·81; N, 2·64. $C_{33}H_{53}O_5N$ requires: C, 72·89; H, 9·82; N, 2·58%).

(b) *From* VIb. To freshly-distilled diethylene glycol (DEG, 15 ml) containing Na (0·4 g) and heated to 180° was added anhydrous NH_2NH_2 (8 ml). To the cooled soln, VIb (212 mg) was added and the mixture heated under reflux (at ca. 140°) for 24 hr. The condenser was removed and the soln distilled to remove excess NH_2NH_2, until the temp was raised to 240°. The reaction vessel was equipped with a new condenser and the soln refluxed at the temp (240°) for 13 hr. After cooling, the mixture was poured into water (100 ml), and the ppt collected by filtration and dried over P_2O_5 *in vacuo*. The ppt (166 mg), showing no CO peak in the IR spectrum and only one spot on TLC, was crystallized and then recrystallized from acetone to yield a pure sample of XIV (51 mg), m.p. 199–201°; $[\alpha]_D$ +26·3°; IR, ν_{max} 3400 and 1036 cm^{-1}. This sample proved to be identical with the one prepared from XIII (method a) by comparison of the IR spectra, TLC and the mixed m.p.

The sample of XIV (19 mg) was acetylated with Ac_2O (0·2 ml) and Py (0·4 ml) at room temp overnight. The mixture yielded crystalline substance (14 mg), which on recrystallization from isopropyl ether yielded XIVa (9 mg), m.p. 210–212°; $[\alpha]_D$ +58·2°. The IR spectrum was identical with the sample prepared by the method a.

(c) *From* XVIIa. Compound XVIIa (36 mg) described later was hydrogentated in AcOH (5 ml) in the presence of Adams Pt (34 mg) at room temp for 22 min. The reaction mixture was worked up as usual and the residue crystallized on trituration with isopropyl ether. Recrystallization from the same solvent afforded XIVa (18·5 mg), m.p. 214–215°; $[\alpha]_D$ +59·1°; IR, ν_{max} 1736, 1640, 1248 and 1027 cm^{-1}. This sample proved to be identical with those prepared from XIII and VIb (methods a and b) by comparison of the IR spectra, TLC and mixed m.p.

22,27-Iminojerv-16-ene-3β,23β-diol (XVII) *and its* 3-O,23-O,N-*triacetyl derivative* (XVIIa)

(a) *From* XXVIa. Compound XXVIa[23] (1·01 g) was dissolved in a mixture of AcOH (15 ml) and Ac_2O

(35 ml) containing conc H_2SO_4 (0·5 ml) under cooling, and the mixture was allowed to stand at room temp for 22 hr. The reaction product was poured into ice-water and made slightly alkaline (pH 7·8) with Na_2CO_3, when NaOAc separated out and was removed by filtration. The filtrate was extracted with $CHCl_3$, and the $CHCl_3$ soln was washed with water, dried and evaporated to dryness *in vacuo*. The residue (1·09 g) was partially crystallized from MeOH aq and filtered. The crystalline material (340 mg), m.p. 148–150°, was recrystallized from MeOH aq to give a compound (29 mg) m.p. 161–162°, which showed one spot on TLC but was not further examined. The filtrate obtained on removal of the crystalline compound, m.p. 150°, was evaporated to leave an oily residue, which after being dried over P_2O_5 was chromatographed on acid-washed Al_2O_3 (20 g). Fractions eluted with 100 ml benzene–ether (8 : 2) and with 200 ml benzene–ether (7 : 3) crystallized on removal of the solvent and trituration with acetone and amounted to 350 mg, showing one spot. Recrystallization of the crystals from acetone afforded a pure sample of XVIIa (80 mg), m.p. 200–202°; $[\alpha]_D$ +11·0°; IR, ν_{max} 1745 (shoulder), 1735, 1630, 1245 and 1025 cm^{-1}; NMR, τ 9·23 (3H, s, 19-Me) and 4·44 (1H, br, 16-H). (Found: C, 73·03; H, 9·55; N, 2·75. $C_{33}H_{51}O_5N$ requires: C, 73·16; H, 9·49; N, 2·59%).

(b) *From* Vb. The Wolff–Kishner reduction of Vb[4,8] (186 mg) was carried out as for VIb. The reaction mixture was poured into water (100 ml), the ppt collected by filtration, dried, dissolved in benzene and chromatographed on Al_2O_3 (standard, 3·5 g). Fractions eluted with benzene were evaporated to yield an oily residue (102 mg), which showed one spot on TLC and crystallized on tituration with acetone–n-hexane. Repeated recrystallization from the same solvent afforded a pure sample of XVII (16 mg), m.p. 193–196°; $[\alpha]_D$ −21·7°; IR ($CHCl_3$), ν_{max} 3605, 3500 and 1030 cm^{-1}; NMR, τ 9·225 (3H, s, 19-Me) and 4·44 (1H, br, 16-H).

Compound XVII (11 mg) was treated with Ac_2O (0·2 ml) and Py (0·2 ml) on a water bath for 3 hr and then mixed with water. The whole mixture was extracted with $CHCl_3$ and the $CHCl_3$ soln was washed successively with 1N HCl, 5% NaOH aq and water, dried and evaporated to dryness. The residue was crystallized and recrystallized from isopropyl ether to yield XVIIa (6 mg), m.p. 196–198°. This sample proved to be identical with the above-mentioned (method a) by comparison of the IR spectra (in $CHCl_3$) and TLC.

An attempted Wolff–Kishner reduction of the 11-*carbonyl group of* N-*acetyl*-22,27-*imino*-12α-*jervane*-3β,23β-*diol*-11-*one* (VIIIb)

Compound VIIIb[4,8] (63 mg) was submitted to the Wolff–Kishner reaction as for VIb or Vb. The reaction product was poured into water (50 ml) to give dark-brown, tarry substance, and the whole mixture was extracted with $CHCl_3$ repeatedly. After being washed with water, the $CHCl_3$ soln was shaken with 2N HCl (4 × 100 ml). The acidic aqueous soln was made alkaline with NH_3 and again extracted with $CHCl_3$. The $CHCl_3$ soln after being worked up as usual left an oily residue (21 mg), which resisted crystallization, showed a strong peak at 1725 cm^{-1} on the IR spectrum in $CHCl_3$, and was not further examined.

Hydrogenation of 3-O,23-O,N-*triacetyl*-22,27-*imino*-12α-*jerva*-5,13(17)-*diene*-3β,23β-*diol*-11-*one* (Xa)

Compound Xa (404 mg) in AcOH (12 ml) was hydrogenated in the presence of prereduced Rh-PtO_2 (3 : 1) catalyst[43] (180 mg) at room temp. After 2 days an additional amount (130 mg) was added to the system and the reaction was further continued (1 day), until the unreacted starting material had disappeared on TLC. After removal of the catalyst and the solvent below 60° *in vacuo*, the residue was shaken with water and $CHCl_3$. The $CHCl_3$ soln was washed with 5% $NaHCO_3$ aq and water, dried over Na_2SO_4 and evaporated to dryness, leaving an amorphous substance (402 mg), which showed only 2 spots and was separated by preparative TLC (Wakogel B-5; solvent, ether). A more mobile fraction gave amorphous substance (170 mg), which was crystallized and recrystallized from MeOH aq to yield XIXa (99 mg), m.p. 156–159°, which proved to be identical with an authentic specimen[12,21] by comparison of the IR spectra, TLC and mixed m.p.

A less mobile fraction afforded an amorphous substance (154 mg), which showed the ORD curve with a negative Cotton effect with the following amplitude: $[\phi]^{trough}_{334}$ −4500°, $[\phi]^{peak}_{292}$ +3900°, a = −84°. A part (106 mg) of the substance was refluxed with 5% KOH in MeOH (10 ml) for 1 hr. After removal of the solvent *in vacuo* the residue was mixed with water, extracted with $CHCl_3$, dried and evaporated to leave amorphous material (82 mg), which was crystallized and recrystallized from MeOH–acetone to give VIIIb (60 mg), m.p. 229–232° and $[\alpha]_D$ −13·3°. This sample was identical with an authentic specimen[4,8] (IR spectra in Nujol, TLC and mixed m.p.). This compound (30 mg) was reacetylated with Ac_2O (1 ml) and Py (1 ml) at room temp for 24 hr yielding amorphous material (34 mg), whose IR spectrum in $CHCl_3$ was superimposable over that of the starting compound.

N-*Acetyl-22,27-imino-5β,12α-jervane-3β,23β-diol-11-one* (XXIVb) *and its* 3-O-*acetyl derivative* (XXIVc)

Compounds XXIVb and XXIVc were prepared according to the procedure by Wintersteiner and Moore,[7] and complementary data are reported here. Compound XXIVb; NMR, τ 8·98 (3H, s, 19-Me), 9·26, 9·11 and 8·92 (each 3H, d, J = 7, 7 and 7·5 c/s, 18-Me, 21-Me and 26-Me or *vice versa*), 7·87 (3H, s, NAc), and 5·95 (1H, br W_H = 10 c/s, 3-H). Compound XXIVc; NMR, τ 8·975 (3H, s, 19-Me), 9·265, 9·12 and 8·93 (each 3H, d J = 7, 6·5 and 6·5 c/s, 18-Me, 21-Me and 26-Me or *vice versa*), 7·97 and 7·88 (each 3H, s, OAc and NAc), and 4·98 (1H, br W_H = 7 c/s, 3-H).

3-O,23-O,N-*Triacetyl-22,27-iminojerva-5,16-diene-3β,23β-diol-11-one* (XXXIa)

Diacetyldihydrojervine (IIa) was submitted to acetolysis essentially under the same conditions as IIIa[4] or XXVIa: to a soln of IIa (1·00 g) in Ac_2O (35 ml) and AcOH (10 ml) was added AcOH (5 ml) containing conc H_2SO_4 (0·5 ml) under ice-cooling and the whole soln was allowed to stand at room temp for 22 hr. The reaction mixture was poured into crushed ice, made slightly alkaline by addition of Na_2CO_3 and extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ soln was washed with sat NaClaq (2 × 100 ml), dried and evaporated to dryness, leaving yellow resinous material (654 mg), which crystallized on trituration with acetone. Recrystallization from acetone afforded XXXIa (143 mg), m.p. 204–206°, and an additional amount (34 mg) of XXXIa, m.p. 202–204°, was recovered from the mother liquor. Further recrystallization from EtOHaq gave an analytical sample, m.p. 204–205°; $[\alpha]_D$ − 123·5°; IR, ν_{max} 1740, 1727 and 1247 cm^{-1}; NMR, τ 8·94 (3H, s, 19-Me), 4·43 (1H, m, 16-H) and 4·54 (1H, m, 6-H). (Found: C, 71·66; H, 8·56; N, 2·71. $C_{33}H_{47}O_6N$ requires: C, 71·58; H, 8·56; N, 2·71%).

The structure of XXXIa was confirmed by transformation into VIa: XXXIa (43 mg) in AcOH (6 ml) was hydrogenated over prereduced Adams Pt (40 mg) at 19° for 29 min, when 3·9 ml of H_2 (2·1 mol) had been consumed. The mixture gave a crystalline substance (43 mg) after being worked up as usual. Two recrystallizations from ether afforded a pure sample of VIa (27 mg), needles, m.p. 242–243°, which was identical with an authentic sample[4, 8] in all respects.

Hydrogenation of jervine (I)

Jervine (I, 1·50 g), m.p. 242–243°, dissolved in AcOH (100 ml) was hydrogenated in the presence of prereduced Pt (1·00 g) at room temp for 48 hr, until 137 ml H_2 (1·54 moles) had been consumed. In order to attain the uptake of 2 moles of H_2 the new catalyst (0·50 g) and AcOH (30 ml) had to be added, and the hydrogenation was continued for further 80 hr, until 184 ml H_2 (2·22 moles) had been absorbed. After removal of the catalyst by filtration and the solvent by azeotropization with benzene below 50° under diminished pressure, the residue was dissolved in $CHCl_3$ (40 ml), washed with 5% Na_2CO_3 (2 × 30 ml) and water (3 × 30 ml) and evaporated to leave an amorphous substance (A, 1·55 g), which showed two strong spots (R_f 0·25 and 0·16) and one very weak (0·28) on TLC (acetone: ether 2:1).

A part (100 mg) of substance A was refluxed with 5% KOH in MeOH (5 ml) for 40 min. The soln was evaporated and the residue was mixed with water (10 ml) and shaken with $CHCl_3$ (2 × 10 ml). The $CHCl_3$ soln was washed with water (2 × 10 ml), dried and evaporated to give an amorphous material (B, 94 mg), which showed practically one spot: the spot of R_f 0·25 was intensified but those with R_f 0·16 and 0·28 disappeared and remained unchanged, respectively. Acetylation of B (84 mg) with Ac_2O (1 ml) and Py (1 ml) at room temp for 12 hr afforded a crystalline residue (92 mg) on trituration with acetone. Recrystallization from acetone gave IIIa (35 mg), m.p. 216–217°, which was identical with an authentic sample.[4] The semi-crystalline material (56 mg) recovered from the mother liquor gave one strong (R_f 0·40) and five weak spots (R_f 0·23, 0·50, 0·57, 0·75 and 0·85) on TLC (benzene: ether 1:2) and was separated by preparative TLC, using ten plates (20 × 20 cm^2) and Wakogel-B (each plate 10 g). Each fraction showing weak spots afforded amorphous substances amounting to 4, 2, 2, 5 and 7 mg, respectively, but were not further examined. A main fraction with R_f 0·40 gave crystals (36 mg), which on recrystallization from acetone afforded IIIa (20 mg), m.p. 215–217°, in pure state.

A part (516 mg) of substance A was treated with Ac_2O (5 ml) and Py (6 ml) at room temp for 21 hr. The reaction mixture was poured into ice-water (300 ml), stirred for 1 hr, and the ppt was dissolved in $CHCl_3$ (30 ml). The $CHCl_3$ soln was washed with water (30 ml), dried over Na_2SO_4, evaporated and again dried over P_2O_5 in a desiccator to give amorphous material (C, 505 mg). This material showed two strong (R_f 0·40 and 0·30) and four weak spots (R_f 0·80, 0·57, 0·50 and 0·23) on TLC (benzene:ether 1:2). The spot with R_f 0·30 could not be detected in the acetylation of substance B. These fractions were separated by preparative TLC, using 25 plates. Each fraction was eluted with acetone, dissolved in $CHCl_3$ after removal of the solvent, and the $CHCl_3$ soln worked up as usual. An amorphous material (240 mg) with R_f 0·40 crystallized on trituration with MeOH and was recrystallized from MeOH to give IIIa; the 1st crop (170 mg), m.p. 214–217°, and the 2nd (17 mg), m.p. 208–212°. An additional amount (11 mg) of IIIa was recovered from the mother liquor on recrystallization from acetone–ether; IR, ν_{max} 1737 and 1668 cm^{-1}, ν_{max} ($CHCl_3$) 1729 and 1638 cm^{-1}; NMR, τ 9·18 (3H, s, 19-Me, lit.[23] 9·17), 9·19 and 8·99 (each d J = 6·5 c/s, 26-, 21- and probably 18-Me), and 5·38 (1H, br W_H = 16 c/s, 3-H).

An amorphous material (XXIXa) with R_f 0·30 amounted to 149 mg but resisted crystallization; $[\alpha]_D$ −8·9°; IR, ν_{max} 1737 and 1680 cm^{-1}, ν_{max} ($CHCl_3$) 1731 and 1635 cm^{-1}; NMR, τ 9·11 (3H, s, 19-Me), 9·08 and 9·01 (each d J = 7 and 6 c/s, 26-, 21- and probably 18-Me), and 5·28 (1H, br W_H = 15 c/s, 3-H). Compound XXIXa (10 mg) was recovered quantitatively after further treatment with Ac_2O (0·1 ml) and Py (0·12 ml) at room temp for 21 hr. Compound XXIXa (30 mg) was refluxed with 5% KOH in MeOH (5 ml) for 40 min. The reaction product was worked up as usual and yielded an amorphous substance (26 mg). This was crystallized and recrystallized from acetone–ether to give IIIb (20 mg), m.p. 258–260°, which was identical with an authentic specimen;[4] $[\alpha]_D$ −3·0°; IR, ν_{max} 3630, 1731, 1670 cm^{-1}; NMR, τ 9·19 (3H, s, 19-Me), 9·19 and 8·99 (each d J = 6·5 c/s, 21-, 26- and probably 18-Me).

An amorphous material (35 mg) with R_f 0·50 from substance C was again separated into two fractions by preparative TLC under the same conditions. A more mobile part (10 mg) resisted crystallization and was not further examined. A less mobile part (17 mg) crystallized on trituration with ether. Recrystallization from 40% EtOH aq and then 50% EtOH aq afforded XIXa (6 mg), m.p. 163–164°, which was identical with an authentic sample.[11, 19] Other fractions with R_f 0·23, 0·57 and 0·80 gave oily amorphous substances, amounting to 19, 9 and 46 mg, respectively, but could not be characterized.

Substance A (150 mg) in AcOH (15 ml) was treated under the same conditions (prereduced Pt 150 mg, room temp, and 72 hr) as the hydrogenation of I. The reaction mixture was worked up as usual and gave an amorphous substance (D, 141 mg), which showed the same behaviour on TLC as substance A. A part (131 mg) of substance D was acetylated with Ac_2O (1·5 ml) and Py (1·5 ml) at room temp for 21 hr and then worked up as usual to yield an amorphous substance (E, 145 mg). This material E exhibited practically the same behaviour on TLC as C and, in fact, was separated in the same manner as C. The amorphous substance yielded fractions with R_f 0·23, 0·30, 0·40, 0·50, 0·57 and 0·80 amounted to 6, 47, 61, 9, 2 and 13 mg, respectively, indicating that the relative ratio of each component in the product E was essentially the same as that of C. Identity of each substance with the corresponding of C was further checked by comparison of the IR spectra.

The ORD curves

The measurement of ORD curves was performed at room temp (25 ± 2°) in dioxan on a Jasco ORD/UV-5 spectropolarimeter. The compounds described below exhibited the curves of negative Cotton effects with the following $[\phi]$ values at trough and peak and amplitudes, respectively: II, −10,200° (332 mμ), +6200° (293) and −164°; IIa, −10,600° (333), +8000° (290) and −186°; III, −9300° (334), +8200° (293) and −175°; IIIa, −9300° (334), +8800° (293) and −181°; IVa, −9700° (334), +7500° (292) and −172°; Va, −2700° (331), +5500° (288) and −82°; VIa, −10,700° (335), +6200° (294) and −169°; VIb, −9200° (336), +8200° (293) and −174°; VIIa, −5300° (333), +4300° (291) and −96°; VIIIa, −4500° (334), +3900° (291) and −84°; VIIIb, −4200° (334), +3800° (293) and −80°; XIIa, −12,000° (333), +6300° (292) and −183°; XIIb, −11,200° (334), +6800° (293) and −180°; XXIVb, −4900° (334), +3300° (293) and −82°; XXIXa, −3800° (332), +5800° (292) and −96°; XXXIIa,[26] −9900° (334), +7100° (293) and −170°; XXXIIb,[26] −4500° (334), +3700° (293) and −82°; XXXIII,[16] −10,900° (332), +6300° (291) and −172°;[16] XXXIV,[26] −12,200° (334), +5600° (292) and −178°.

The compounds described below revealed the ORD curves of large positive Cotton effects with the following $[\phi]$ values at peak and trough and amplitudes, respectively: X, +12,200° (339 mμ, −21,100° (287) and + 333°; Xa, + 12,100° (339), − 12,100° (289) and + 242°; XIXa, + 6700° (341), − 3700° (298) and + 104°; XXXVIa, + 14,800° (333), − 5700° (291) and + 205°.

Acknowledgements—The authors wish to express their thanks to Dr. M. W. Klohs, Riker Laboratories, for generously providing them with a large amount of crude jervine. They are also indebted to Dr. K. Kuriyama, Shionogi and Company, Ltd., for helpful discussion on the ORD curves and measurement of the CD curves, and to Takeda Chemical Industries, Ltd., for measurement of the NMR spectra (100 Mc) of samples XXVIIa and XXVIIIa.

REFERENCES

[1] For stereochemistry of jervine, see: G. N. Reeke, Jr., R. L. Vincent and W. N. Lipscomb, *J. Am. Chem. Soc.* **90**, 1663 (1968), and S. M. Kupchan and M. I. Suffness, *Ibid.* **90**, 2730 (1968).

[2] W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.* **170**, 635 (1947).

[3] R. Anliker, H. Heusser and O. Jeger, *Helv. Chim. Acta* **35**, 838 (1952).

[4] O. Wintersteiner, M. Moore and B. M. Iselin, *J. Am. Chem. Soc.* **76**, 5609 (1954).

[5] K. Saito, H. Suginome and M. Takaoka, *Bull. Chem. Soc. Japan* **11**, 172 (1936).

[6] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **148**, 51 (1943).

[7] O. Wintersteiner and M. Moore, *Tetrahedron* **21**, 779 (1965).

[8] O. Wintersteiner and M. Moore, *Ibid.* **20**, 1947 (1964).

[9] T. Masamune, A. Murai, H. Ono, K. Orito, S. Numata and H. Suginome, *Tetrahedron Letters* 255 (1969).

[10] H. O. House and G. A. Rasmussen, *J. Org. Chem.* **28**, 31 (1963).

[11] T. Masamune, M. Takasugi, M. Gohda, H. Suzuki, S. Kawahara and T. Irie, *Ibid.* **29**, 2282 (1964).

[12] T. Masamune, K. Orito and A. Murai, *Bull. Chem. Soc. Japan* **39**, 2503 (1966).

[13] [a] T. Masamune, K. Orito and A. Murai, *Tetrahedron Letters* 251 (1969);
[b] T. Masamune and K. Orito, *Tetrahedron* **25**, 4551 (1969).

[14] S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.* **86**, 701 (1964).

[15] W. F. Johns and I. Laos, *J. Org. Chem.* **30**, 123 (1965).

[16] T. Masamune, A. Murai and S. Numata, *Tetrahedron* **25**, 3145 (1969).

[17] Cf. F. Johnson and S. K. Malhotra, *J. Am. Chem. Soc.* **87**, 5492 (1965).

[18] H. Suginome, N. Sato and T. Masamune, *Tetrahedron Letters* 3353 (1969).

[19] O. Wintersteiner and M. Moore, *J. Org. Chem.* **29**, 262 (1964).

[20] [a] R. L. Augustine, *Catalytic Hydrogenation*, p. 59. Dekker, New York (1965).
[b] R. N. Rylander, *Catalytic Hydrogenation over Platinum Metals* p. 100. Academic Press, New York (1967).

[21] H. Mitsuhashi and N. Kawahara, *Tetrahedron* **21**, 1215 (1965).

[22] T. Masamune, M. Takasugi and Y. Mori, *Tetrahedron Letters* 489 (1965).

[23] T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki and Y. Mori, *Tetrahedron* **23**, 1591 (1967).

[24] H. Suginome, N. Sato and T. Masamune, *Tetrahedron Letters* 1557 (1967); *Bull. Chem. Soc. Japan* **42**, 215 (1969).

[25] H. Conroy, *Advances in Organic Chemistry* Vol. II, p. 311. Interscience, New York (1960).

[26] T. Masamune, A. Murai and K. Nishimura, unpublished results (the following paper in this series).

[27] S. M. Kupchan and M. J. Abu El-Haj, *J. Org. Chem.* **33**, 647 (1968).

[28] W. Klyne, *Tetrahedron* **13**, 29 (1961); P. M. Bourne and W. Klyne, *J. Chem. Soc.* 2044 (1960).

[29] A. Moscowitz, K. Mislow, M. A. W. Glass and C. Djerassi, *J. Am. Chem. Soc.* **84**, 1945 (1962).

[30] [a] S. Siegel and G. V. Smith, *Ibid.* **82**, 6082, 6087 (1960),
[b] J. F. Sauvage, R. H. Baker and A. S. Hussey, *Ibid.* **82**, 6090 (1960).

[31] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956); R. Howe and F. J. McQuillin, *Ibid.* 1194 (1958).

[32] C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.* **75**, 3496 (1953).

[33] Y. Mazur and F. Sondheimer, *Ibid.* **80**, 5220 (1958).

[34] G. D. Meakins and O. R. Rodig, *J. Chem. Soc.* 4679 (1956).

[35] [a] H. E. Stavelv and G. N. Bollenback, *J. Am. Chem. Soc.* **65**, 1290 (1943); C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *Ibid.* **74**, 1712 (1952).
[b] J. Elks, R. M. Evans, A. G. Long and G. M. Thomas, *J. Chem. Soc.* 451 (1954).

[36] [a] C. Dorée, J. F. McGhie and F. Kurzer, *J. Chem. Soc.* 988 (1948),
[b] P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas, *Ibid.* 2921 (1953),
[c] Refs. cited in Ref. 32.

[37] O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.* **65**, 1507 (1943).

[38] For a recent review, see: S. Siegel, *Advances in Catalysis* Vol. 16, p. 123. Academic Press, New York (1966).

[39] J. Horiuchi and M. Polanyi, *Trans. Farad. Soc.* **30**, 1164 (1934).

[40] E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.* **78**, 6269 (1956); H. E. Zimmerman and A. Mais, *Ibid.* **81**, 4305 (1959), and previous papers cited there.

[41] F. J. McQuillin and W. O. Ord, *J. Chem. Soc.* 2902 (1959); F. J. McQuillin, W. O. Ord and P. L. Simpson, *Ibid.* 5996 (1963).

[42] B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.* **77**, 5318 (1955).

[43] [a] S. Nishimura, *Bull. Chem. Soc. Japan* **33**, 566 (1960),
[b] Ref. 20b, p. 23.