The **chloroplatinate** of IVb decomposed without melting.

Anal. Calcd. for $C_{10}H_{12}Cl_7N_2Pt$: C, 19.87; H, 2.17; Pt, 32.27. Found: C, 19.94; H, 2.22; Pt, 32.30.

1,2,3,6-Tetrahydro-4,5-dimethyl-2,3′-bipyridine (IVc) was produced in 76% yield, b.p. 108–111° at 0.25 mm.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.56; H, 8.57; N, 14.88. Found: C, 76.40; H, 8.63; N, 15.14.

The **dipicrate** of IVc had m.p. 170–172°.

Anal. Calcd. for $C_{24}H_{22}N_8O_{14}$: C, 44.59; H, 3.43; N, 17.33. Found: C, 44.55; H, 3.61; N, 17.39.

Lithium Aluminum Hydride Reduction of IIa and IIc.—A solution of the N-ethoxycarbonyl compound IIa (0.51 g., 0.0022 mole) in 5 ml. of dry monoglyme was added to a refluxing suspension of lithium aluminum hydride (0.50 g. 0.0132 mole) in 15 ml. of monoglyme during a 2-hr. period. The mixture was then refluxed for 8 hr. and allowed to cool. Excess reducing agent was decomposed with water–monoglyme solution (1:10) and the mixture was filtered. The filter cake was washed with ether, and the filtrate and washings were concentrated to a yellow oil (0.40 g.). This was distilled at 150° (air bath) under a pressure of 6.5 mm. to give 0.107 g. (28%) of **1,2,3,6-tetrahydro-1-methyl-2,3′-bipyridine** (*dl*-N-methylanatabine, Va). This material showed only one peak on gas chromatography; the infrared spectrum showed the N-methyl group (2795 cm.$^{-1}$) and that carbonyl and –NH– groups were absent. The n.m.r. spectrum confirmed the presence of two olefinic protons (δ = 5.63 p.p.m.). and of the N-methyl group (singlet, 2.00 p.p.m.), and showed the pattern characteristic of the 3-pyridyl group. The **dipicrate** prepared from Va in aqueous solution was recrystallized from 0.5% aqueous picric acid (decomposed above 200°, m.p. 222–224°, estimated by introduction of samples into preheated baths; lit.[3c] m.p. 207–208° for *l*-N-methylanatabine).

Anal. Calcd. for $C_{23}H_{20}N_8O_{14}$: C, 43.68; H, 3.19; N, 17.72. Found: C, 44.01; H, 3.45; N, 17.60.

When treated similarly the N-ethoxycarbonyl compound IIc gave **1,2,3,6-tetrahydro-1,4,5-trimethyl-2,3′-bipyridine** (Vb), b.p. 92° at 0.2 mm. (31%); **dipicrate**, m.p. 183–185°.

Anal. Calcd. for $C_{25}H_{24}N_8O_{14}$: C, 45.46; H, 3.66; N, 16.96. Found: C, 45.15; H, 3.88; N, 16.95.

Dehydrogenation of *dl*-Anatabine[3b,4] (IVa).—Synthetic *dl*-anatabine (0.200 g.) was heated with 10% palladium on charcoal (0.030 g.) at 200° for 20 min. in an atmosphere of nitrogen. The mixture was taken up in ether, the solution was filtered, and the solvent was distilled to leave a residue recognizable by its infrared spectrum[15] as 2,3′-bipyridine. This material gave a precipitate with saturated aqueous picric acid which was recrystallized three times from 0.5% aqueous picric acid,[15] m.p. and m.m.p. 161–163° with an authentic sample of 2,3′-bipyridine (lit.[15] m.p. 166–167°).

Comparison of IVa with Natural *l*-Anatabine.—A sample of natural *l*-anatabine was obtained by decomposition of the dipicrate. The natural and synthetic alkaloids were indistinguishable by gas chromatography on two columns. Retention volumes are given relative to nicotine which was used as an internal standard: column 1 at 198°, relative retention volume = 2.15; column 2 at 197°, relative retention volume = 2.85. The alkaloids also showed the same behavior in two paper chromatographic systems: (1) *t*-amyl alcohol–acetate buffer,[4] R_f 0.36; (2) *n*-butyl alcohol–pyridine–water,[8] R_f = 0.22.

Acknowledgment.—We are indebted to the American Tobacco Company for financial support of this work, and for providing a sample of natural *l*-anatabine dipicrate. P. M. Q. also thanks the Committee on the International Exchange of Persons for a Fulbright Travel Scholarship.

Configuration of N,β-Dimethylleucine, a Constituent Amino Acid of Triostin C

JUN-ICHI SHŌJI, KAZUO TORI, AND HIDEO ŌTSUKA

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received December 8, 1964

The configurations of N,β-dimethylleucine derived from triostin C and two synthesized diastereoisomers (Ib and IIb), separated by ion-exchange chromatography, were studied by n.m.r. spectroscopy. The coupling constants obtained from the doublet signal due to the proton on the α-carbon atom of these three compounds were compared with those of the reference compounds, *i.e.*, N-methyl-L-isoleucine, N-methyl-DL-isoleucine (Ia), and N-methyl-DL-alloisoleucine (IIa). The information obtained from the n.m.r. spectra and other facts led to the conclusion that the configurations of N,β-dimethylleucine isomers Ib and IIb and the one derived from triostin C are represented by Fischer projection formulas I (DL), II (DL), and II (L) (R = CH_3), respectively. (These can be called N,γ-dimethyl-DL-isoleucine, N,γ-dimethyl-DL-alloisoleucine, and N,γ-dimethyl-L-alloisoleucine, respectively.)

N,β-Dimethylleucine was first discovered in nature by Sheehan and co-workers[1] from the degradation of ethamycin. They proved that the amino acid belongs to the L-series and that the configuration at the β-carbon atom is identical to that of the ergosterol side chain. As the absolute configuration at C-24 of the ergosterol side chain has been determined to be 24β,[2] the configuration of the N,β-dimethylleucine isolated from etamycin could be deduced. Later, Sheehan and Howell[3] synthesized and resolved β-methylleucine and related compounds to find an approach to clarify the whole configuration of N,β-dimethylleucine.

We also had isolated N,β-dimethylleucine from the degradation product of the antibiotic triostin C.[4] In order to elucidate the configuration at the β-carbon atom of the amino acid, we compared diastereoisomers of N,β-dimethylleucine with similar diastereoisomeric compounds such as N-methylisoleucine and N-methylalloisoleucine by n.m.r. spectroscopy, which was expected to reflect the relative configuration at the α- and β-carbon atoms of the diastereoisomers. Some other properties such as solubility and behavior on chromatography were also used for the comparison. N,β-Dimethylleucine was synthesized and separated into two diastereoisomers (Ib and IIb) by ion-exchange chromatography. A synthetic N-methylisoleucine-N-methylalloisoleucine mixture was also separated in a similar way. The coupling constants, $J_{H\alpha,H\beta}$, of these compounds were measured from the doublet signal of the proton on the α-carbon atom. The configurations of the N,β-dimethylleucine isomers were determined by reference to the relationships between the configurations and the coupling constants of the known compounds.

(1) J. C. Sheehan, H. G. Zachau, and W. B. Lawson, *J. Am. Chem. Soc.*, **80**, 3349 (1958).

(2) (a) W.-Y. Huang and C.-W. Hsu, *Hua Hsueh Hsueh Pao*, **28**, 68 (1962); *Chem. Abstr.*, **59**, 14047 (1963); (b) G. D. Maio and A. Romeo, *Gazz. chim. ital.*, **89**, 1627 (1959).

(3) J. C. Sheehan and M. G. Howell, *J. Org. Chem.*, **28**, 2279 (1963).

(4) H. Ōtsuka and J. Shōji, *J. Antibiotics* (Tokyo), **A16**, 52 (1963).

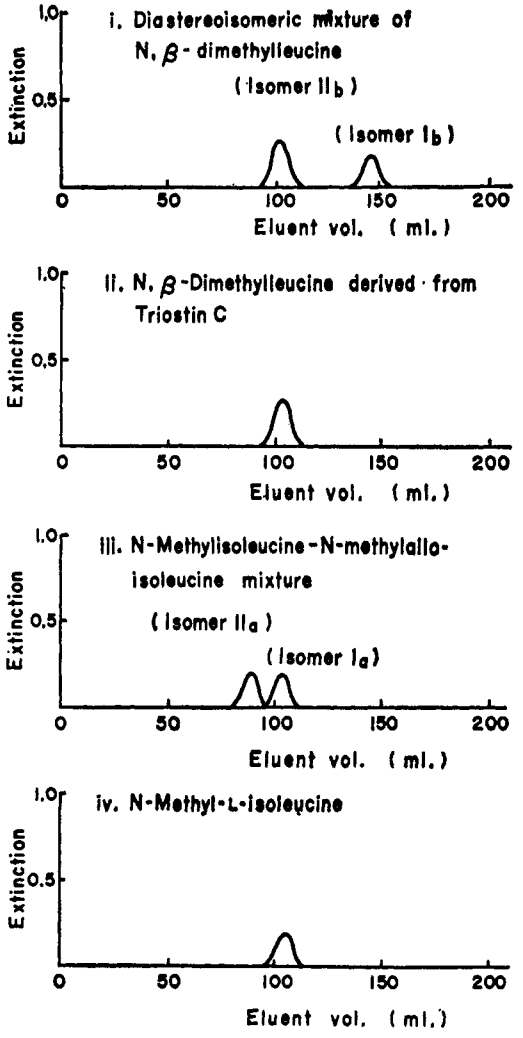


Figure 1.—Elution curves on an automatic amino acid analyzer.

N,β-Dimethylleucine was prepared by the synthetic route explored by Sheehan and Howell[3] from methyl isopropyl ketone. Analytical separation of the diastereoisomeric mixture of N,β-dimethylleucine was effected by an automatic amino acid analyzer. The two peaks which were observed were arbitrarily named isomer Ib (slower moving) and isomer IIb (faster moving) as shown in Figure 1. Preparative separation using a Dowex 50W column afforded pure preparations of the isomers.

These two isomers showed differences in the infrared absorption spectra (KBr disk) (Figure 2) and in solubilities; isomer Ib was less soluble than isomer IIb in water and lower alcohols. In these properties, the isomers Ib and IIb corresponded with Sheehans isomers I and II, respectively, which were reported to have been separated by fractional recrystallization.

The N,β-dimethylleucine derived from triostin C showed a mobility on chromatography[5] (Figure 1) identical with that of isomer IIb and a similar solubility. The n.m.r. spectra of the two samples were identical (Figure 3), indicating their configurational similarity, although isomer IIb was obviously a DL racemate. Their infrared absorption spectra measured

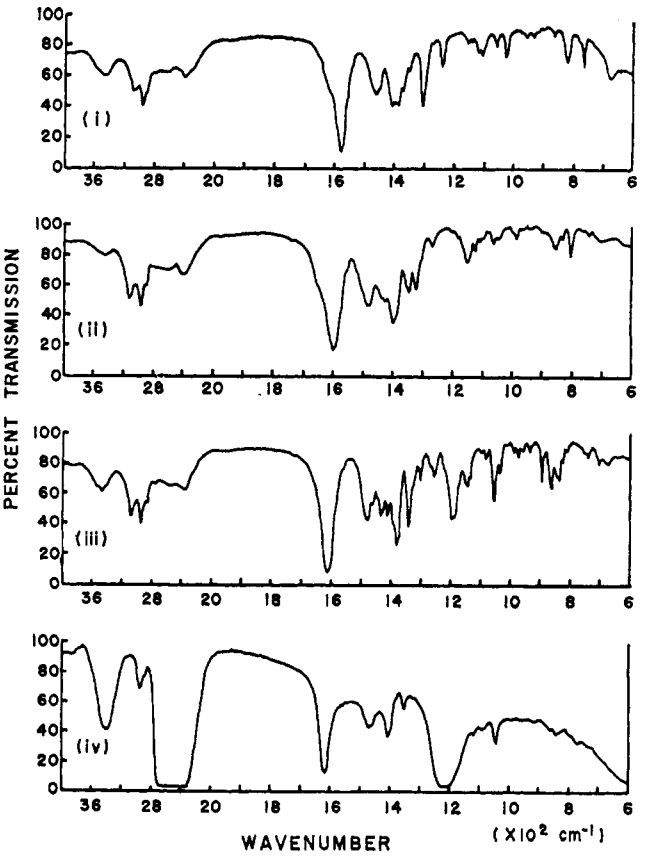


Figure 2.—Infrared absorption spectra of N,β-dimethylleucine: (i) isomer Ib (KBr); (ii) isomer IIb (KBr); (iii) the one derived from triostin C (KBr); (iv) isomer IIb and the one derived from triostin C (D_2O).

on solutions in deuterium oxide were also identical, although those measured on KBr disk were not identical (Figure 2).

A N-methylisoleucine–N-methylalloisoleucine mixture, synthesized from an optically inactive β-methylvaleric acid, was also separated by the automatic amino acid analyzer into two peaks (isomers Ia and IIa, Figure 1) and preparatively on a Dowex 50W column. The slower moving substance had the same mobility on chromatography[5] and the same n.m.r. and infrared (KBr disk) spectra as N-methyl-L-isoleucine. This indicated that the slower moving one (Ia) is N-methyl-DL-isoleucine and the other (faster moving, IIa) is N-methyl-DL-alloisoleucine. The infrared absorption spectra (KBr disk) and solubilities of the above two diastereoisomers were, of course, distinguishable; N-methyl-DL-isoleucine was less soluble than N-methyl-DL-alloisoleucine in water and lower alcohols.

N-Methyl-L-isoleucine was synthesized from L-isoleucine by the usual N-methylation procedure of amino acids developed by Quitt, *et al.*[6]

All four possible stereoisomers of N-methylisoleucine and N,β-dimethylleucine are shown in Fisher projection formulas I (L), I (D), II(L), and II (D), R = H and R = CH_3, in Figure 4. Since I (L) and I (D) as well as II (L) and II (D) are optical antipodes and are equivalent in the spatial relation between the α- and β-protons, they can not be distinguished by n.m.r. spectroscopy.

(5) For confirmatory evidence, the mixture of two samples was analyzed on a column of 150-cm. length.

(6) P. Quitt, J. Hellerbach, and K. Vogler, *Helv. Chim. Acta*, **46**, 327 (1963).

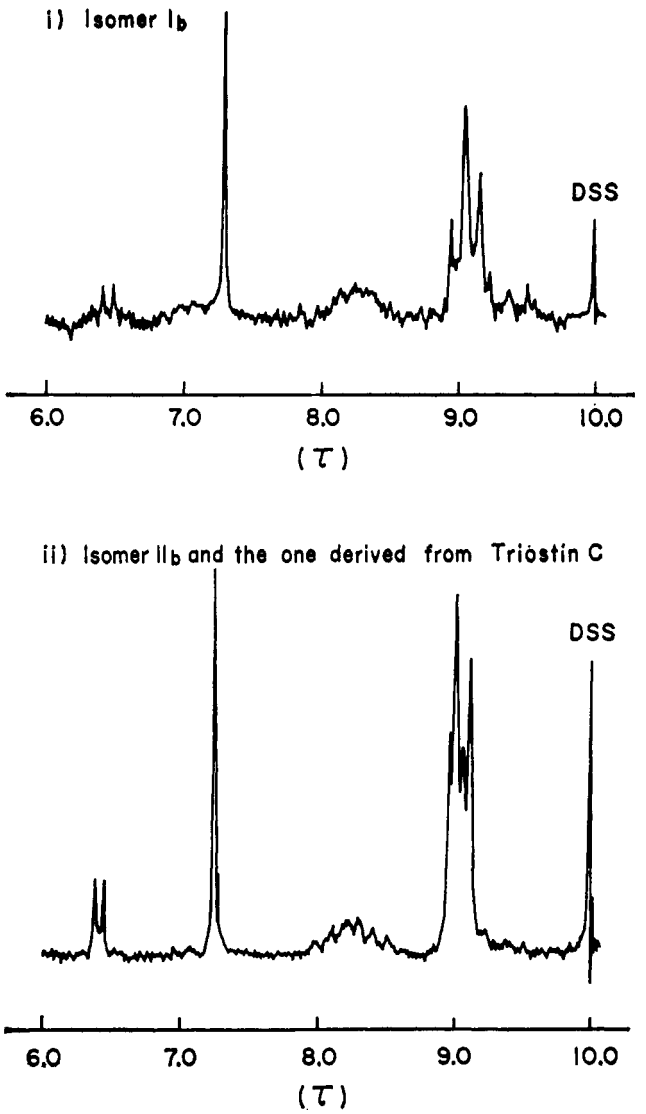


Figure 3.—The n.m.r. spectra of N,β-dimethylleucine.

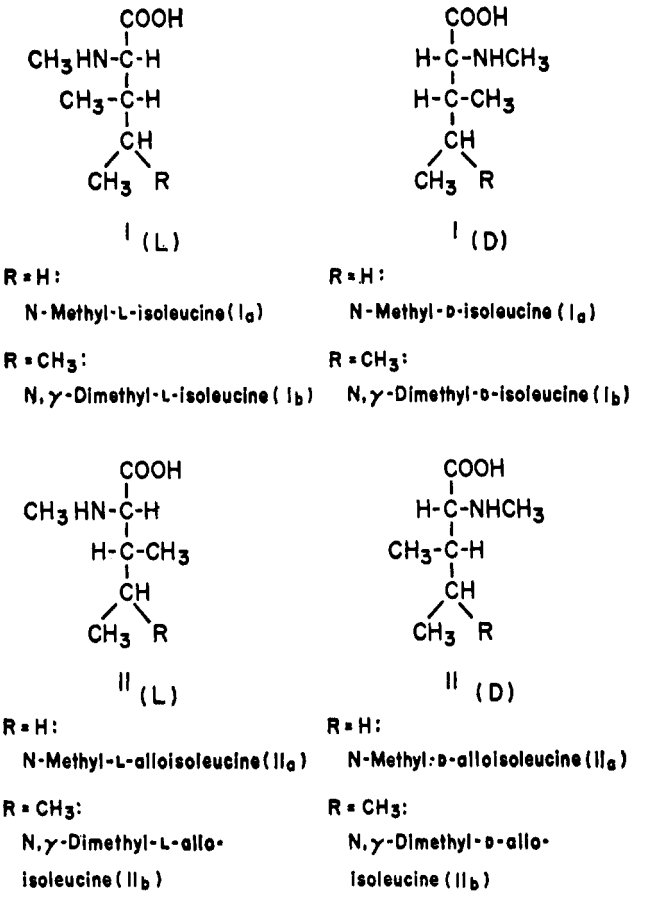


Figure 4.—Fisher projection formulas.

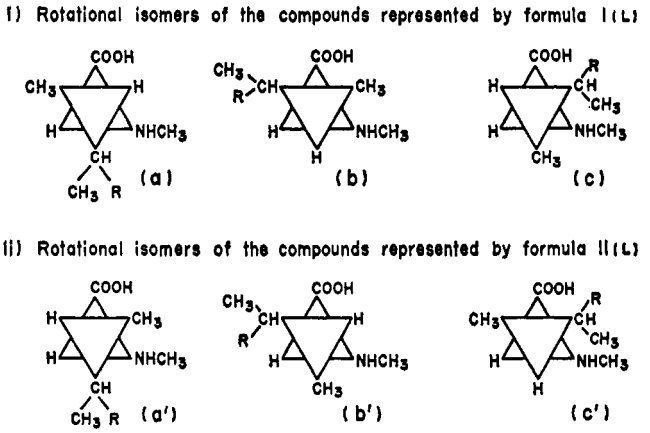


Figure 5.

Although recent n.m.r. studies have demonstrated that coupling constants in the well-known Karplus equation[7] are considerably affected by the environment of the >CH–CH< fragment,[8] in the present case the comparison of $J_{H\alpha,H\beta}$ between the formulas I and II is thought to be reasonable because of the similar structures involved.

The coupling constant to be measured in the present compounds is an average value of those due to the three staggered forms shown in Figure 5. Stability of a rotational isomer is affected by attracting or repelling forces between the substituents at the two adjacent asymmetric carbon atoms. Probably, in the present compounds the repelling force between the carboxyl group at the α-carbon and the ethyl or isopropyl group at the β-carbon is most important to the stability, as an examination with molecular models indicates. Thus the contribution of the rotational isomer a in Figure 5 might be relatively larger because of its more stable form. Then the $J_{H\alpha,H\beta}$ of the formula I can be expected to be larger than that of the formula II.

Table I shows the observed values of $J_{H\alpha,H\beta}$. As expected, the $J_{H\alpha,H\beta}$ obtained from N-methyl-DL-isoleucine, which is equal to the one from N-methyl-L-isoleucine, is larger than that obtained from N-methyl-DL-alloisoleucine. Similarly, the $J_{H\alpha,H\beta}$ obtained from N,β-dimethylleucine isomer Ib is larger than that obtained from the isomer IIb which is equal to that from the one derived from triostin C. The steric effect which seems to produce the $J_{H\alpha,H\beta}$ differences is enhanced as bulkiness of the groups is increased. It is reasonable to note that the difference in $J_{H\alpha,H\beta}$ of isomers Ia and IIa in the N-methylisoleucine pair (0.4 c.p.s.) is smaller than that in $J_{H\alpha,H\beta}$ of isomers Ib

(7) M. Karplus, *J. Chem. Phys.*, **31**, 11 (1959).

(8) (a) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963); (b) R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963); (c) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963); (d) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1163 (1964); (e) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1963–1964); (f) D. H. Williams and N. S. Bhacca, *J. Am. Chem. Soc.*, **86**, 2742 (1964); (g) R. A. Wohl, *Chimia* (Aarau), **18**, 219 (1964).

and IIb in the N,β-dimethylleucine pair (0.8 c.p.s.). Here the groups are ethyl and isopropyl, respectively. Thus, it is concluded that the configurations of the isomers Ib and IIb (optically inactive) can be shown in the formulas I (DL) and II (DL) (R = CH_3), respectively, and that the N,β-dimethylleucine from triostin C (optically active) can be shown in formula II (L) or II (D) (R = CH_3).

TABLE I

COUPLING CONSTANTS OBTAINED FROM THE DOUBLET SIGNAL OF THE α-PROTON

Compound	$J_{H\alpha,H\beta}$, c.p.s.[a]
N,β-Dimethylleucine isomer Ib	4.80 ± 0.08
N,β-Dimethylleucine isomer IIb	4.05 ± 0.08
N,β-Dimethylleucine derived from triostin C	4.00 ± 0.03
N-Methyl-L-isoleucine (Ia)	4.05 ± 0.05
N-Methyl-DL-isoleucine (Ia)	4.05 ± 0.05
N-Methyl-DL-alloisoleucine (IIa)	3.68 ± 0.06

[a] Averages of six measurements.

This conclusion can be also supported by the observation of solubilities and behavior on chromatography of these amino acids; lower solubilities and mobilities were observed in the compounds represented by the formula I than in the formula II whether R = H or R = CH_3.

The optical rotation of the N,β-dimethylleucine from triostin C was measured in water at neutral and acid pH: $[\alpha]^{25.5}D$ +28.4 ± 2° (*c* 0.937, water) and $[\alpha]^{25.5}D$ +41.9 ± 2° (*c* 1.049, 5 *N* HCl). The positive rotation shift on acidification[9] indicated that the amino acid belongs to the L-series. Thus, it is concluded that the configuration of the N,β-dimethylleucine derived from triostin C is as shown in formula I (L) (R = CH_3). The amino acid can therefore also be called N,γ-dimethyl-L-alloisoleucine. This conclusion is in agreement with that obtained for the N,β-dimethylleucine from etamycin, which had been deduced by a comparison of optical rotational data of the chemical degradation products of the amino acid and the ergosterol side chain.

Experimental

All melting points were uncorrected and were determined using a micro melting point apparatus. When a sample sublimed, a sealed capillary was used. The optical rotation values reported were obtained with a Rudolph high-precision polarimeter. A Hitachi automatic amino acid analyzer was used for amino acid analysis. In the experiments listed in Figure 1, a column of IR-120 Type III (0.9 × 50 cm.) with 0.2 *M* citrate buffer, pH 3.25, was used. Infrared absorption spectra were recorded with a Nihon Bunko Model DS-201B spectrophotometer. The n.m.r. spectra were taken with a Varian A-60 spectrometer on solutions in deuterium oxide containing about 1% of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal reference at normal probe temperature. Calibration of the spectrometer was checked by the usual side-band technique.

Separation of N,β-Dimethylleucine Isomers.—A crude preparation of a diastereoisomeric mixture of N,β-dimethylleucine (255 mg.) was chromatographed on a column of Dowex 50 W × 4, 200–400 mesh (1.4 × 80 cm.), which was equilibrated with 0.2 *M* pyridine–acetic acid buffer, pH 3.18. The elution was carried out with the same buffer and the fractions were detected with ninhydrin. The isomer IIb (faster moving) was eluted in the fraction 140–190 ml. and the isomer Ib (slower moving) was appeared in the fraction 210–250 ml. These fractions were lyophilized, and solution and lyophilization were repeated to ensure complete removal of the pyridine acetate. The isomer IIb was crystallized as colorless needles from methanol, which did not melt nor decompose up to 300°.

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.33; H, 10.74; N, 8.66.

The isomer Ib was crystallized from water–acetone as colorless needles which did not melt nor decompose up to 300°.

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.76; H, 10.86; N, 8.89.

N-Methylisoleucine–N-Methylalloisoleucine Mixture.—To 4 g. of β-methylvaleric acid, b.p. 187–193°, which was synthesized from diethyl malonate and *sec*-butyl bromide, dry bromine (6 g.) and phosphorus trichloride (0.1 ml.) were added. The mixture was heated gradually up to 160° during 6 hr. From the reaction mixture, 3.99 g. of α-bromo-β-methylvaleric acid, b.p. 129–131° (15 mm.), was obtained by distillation.

To the above product, 15 ml. of methylamine (40% aqueous solution) was added. After standing for 1 week at room temperature, the mixture was evaporated to dryness, and the residue was crystallized from water–acetone to give the crude preparation of N-methylisoleucine–N-methylalloisoleucine mixture (1.5 g.).

The above preparation was recognized to contain a ninhydrin-positive impurity in small amount by thin layer chromatography, but further recrystallization was not carried out before chromatography because some fractionation of the diastereoisomers was suspected.

Separation of N-Methylisoleucine Isomers.—The crude preparation of N-methylisoleucine–N-methylalloisoleucine mixture (100 mg.) was chromatographed on a column of Dowex 50 W × 4, 200–400 mesh (1.6 × 130 cm.), which was equilibrated with 0.2 *M* pyridine–formic acid buffer, pH 2.80. The column was eluted with the same buffer and followed by the same procedure as described above. N-Methyl-DL-alloisoleucine and N-methyl-DL-isoleucine were eluted in the fractions 540–600 ml. and 640–700 ml., respectively. After lyophilization, N-methyl-DL-alloisoleucine was crystallized from methanol–acetone as colorless needles, which did not melt nor decompose up to 300°.

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.96; H, 10.41; N, 9.42.

N Methyl-DL-isoleucine was crystallized from water–acetone as colorless needles which did not melt nor decompose up to 300°.

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.78; H, 10.50; N, 9.59.

N-Methyl-L-isoleucine.—To L-isoleucine (1.31 g., 10 mmoles) in 5 ml. of 2 *N* sodium hydroxide, freshly distilled benzaldehyde (1.06 g., 10 mmoles) was added dropwise under a nitrogen atmosphere, and the whole was stirred for 40 min. at 15°. Sodium borohydride (0.114 g., 3 mmoles) was added and stirring was continued for 30 min. Then the addition of benzaldehyde and sodium borohydride was repeated again. The reaction mixture was extracted with two 20-ml. portions of ether, and the aqueous portion was neutralized by dilute hydrochloric acid. The resulting crystalline precipitate was collected (1.925 g., 8.7 mmoles). Recrystallized N-benzyl-L-isoleucine was obtained as colorless needles from 220 ml. of dimethylformamide–water (1:1, v./v.): m.p. 258.5–259.5°, $[\alpha]^{25.5}D$ +29.2 ± 2° (*c* 1.014, 5 *N* HCl).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.66; H, 8.80; N, 6.68.

A 1.105-g. (5 mmoles) portion of the above product was suspended in a mixture of formic acid (0.56 ml., 15 mmoles) and 38% formalin (0.5 ml., 6 mmoles) and warmed for 1.5 hr. at 100°. As the reaction mixture was evaporated and dried, N-benzyl-N-methyl-L-isoleucine crystallized gradually (0.915 g., 4.05 mmoles). For analysis, recrystallization from acetone–ether was carried out to give fine colorless needles: m.p. 168.5–169.0°, $[\alpha]^{26.5}D$ +41.7 ± 2° (*c* 1.103, 5 *N* HCl).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.24; H, 8.93; N, 6.23.

N-Benzyl-N-methyl-L-isoleucine (0.870 g., 2.7 mmoles) was hydrogenated in the presence of 5% palladium on charcoal in 90% acetic acid solution to give N-methyl-L- isoleucine (0.523 g., 3.6 mmoles). Recrystallization from water–acetone gave colorless needles which did not melt nor decompose up to 300°: $[\alpha]^{26.5}D$ +44.6 ± 2° (*c* 0.997, 5 *N* HCl).

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.17; H, 10.51; N, 9.56.

(9) (a) O. Lutz and B. Jirgensons, *Chem. Ber.*, **63**, 448 (1931); (b) P. A. Plattner and U. Nager, *Helv. Chim. Acta*, **31**, 2192 (1948).

Acknowledgment.—The authors are indebted to Dr. M. Ebata and Mr. Y. Takahashi for a help in part of the amino acid analysis by the automatic amino acid analyzer. Thanks are also due to Dr. Y. Arata of the University of Electrocommunications for his helpful advice.

The Synthesis of a 13,14-Seco Steroid Analog[1]

MASATO TANABE AND DAVID F. CROWE

Life Sciences Research, Stanford Research Institute, Menlo Park, California

Received March 15, 1965

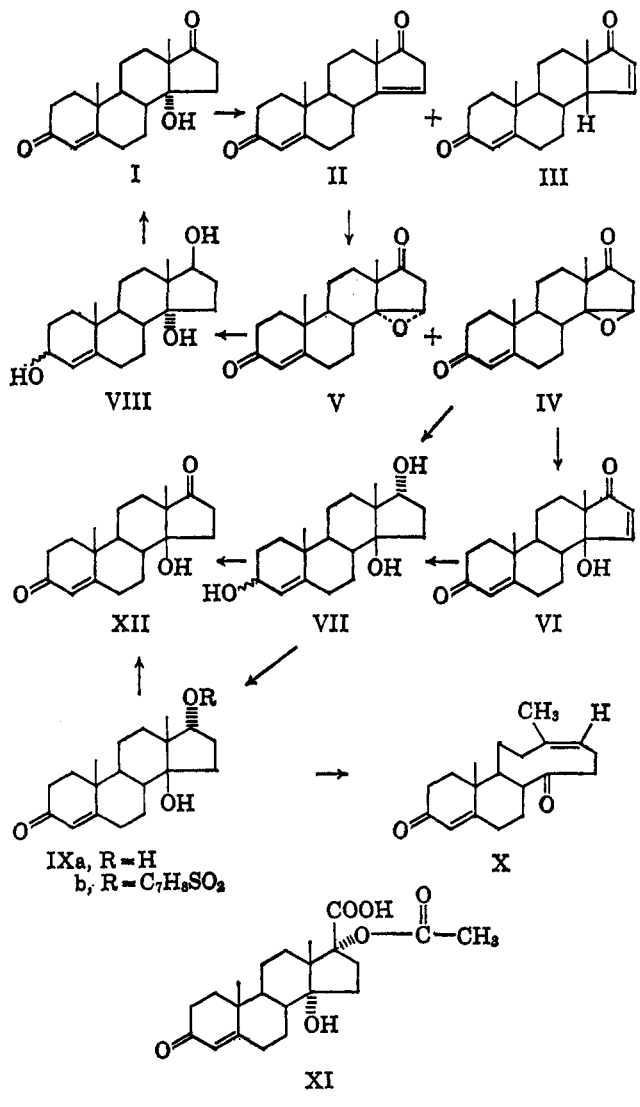
Reaction of 17α-tosyloxy-4-androsten-14β-ol-3-one (IXb) with sodium hydride in tetrahydrofuran yields 13,14-seco-4-*cis*-13(17)-androstadiene-3,14-dione (X). The preparation and reactions of 14β-hydroxyandrostanes are also described.

A previous attempt designed to obtain a 13,14-seco steroid by fragmentation of the C-13–C-14 bond in 3,5-cyclo-6β-methoxy-17β-tosyloxyandrostan-14α-ol under base-catalyzed conditions was unsuccessful. The only product isolated was 3,5-cyclo-6β-methoxy-14-androsten-17α-ol.[2] The origin of this alcohol was presumed to be *via* an intermediate 14α,17α-oxide, the product of the internal displacement reaction of the 14α-alkoxide ion with the 17β-tosylate function as the leaving group.

Placement of the participating C-14 hydroxyl group β or *cis* to the angular methyl group at C-18 should sterically prevent 14β,17β-oxide formation by the internal displacement reaction of the C-14 β-alkoxide ion. Corey[3] has recently reported on the formation of two bicyclononenone derivatives related to *dl*-caryophyllene and *dl*-isocaryophyllene by the fragmentation of tricyclic 1,3-diol monotosylate precursors. In these fragmentation reactions the participating hydroxyl groups were oriented *cis* to angular methyl groups.

The aim of the present investigation was to prepare and study the behavior of a 14β-hydroxy-17α-tosyloxyandrostane derivative under base-catalyzed conditions. A steroid derivative with this stereochemical arrangement of participating groups in the internal elimination reaction should lead to a 13,14-seco derivative. The method of Sondheimer[4] offered a convenient means for the inversion of a 14α-androstanol to its 14β epimer. Steroidal 14α-hydroxy derivatives are available by microbiological and chemical methods,[5] and the inversion process to a 14β-hydroxy derivative involved a four-step route (see Scheme I). The *p*-toluenesulfonic acid catalyzed dehydration of 4-androsten-14α-ol-3,17-dione (I) in toluene yielded 4,14-androstadiene-3,17-dione (II) and 4,15-androstadiene-3,17-dione (III). The origin of the latter 14-iso derivative III is similar to the reported formation of 14-iso-15-dehydroestrone 3-methyl ether from 15-dehydroestrone 3-methyl ether.[6] Treatment of the β,γ-unsaturated ketone II with *m*-chloroperbenzoic acid in chloroform yielded a mixture of approximately equal quantities of the 14β,15β- (IV) and 14α,15α-oxides (V).[7]

SCHEME I



(1) Acknowledgment is made for support of this work by Public Health Service Research Grant AM-05183 from the National Institute of Arthritis and Metabolic Diseases. A portion of this work was published in preliminary form in *Tetrahedron Letters*, 2955 (1964).

(2) M. Tanabe and D. F. Crowe, *J. Org. Chem.*, **28**, 3197 (1963).

(3) E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964).

(4) F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, **82**, 3209 (1960).

(5) (a) A. F. St. Andre, *et al.*, *ibid.*, **74**, 5506 (1962); (b) S. H. Eppstein, *et al.*, *ibid.*, **80**, 3382 (1958).

(6) W. S. Johnson and W. F. Johns, *ibid.*, **79**, 2005 (1957).

(7) Sondheimer and co-workers[4] report only the isolation of the 14β,15β-oxide from perbenzoic acid treatment of 3β-acetoxy-14-androsten-17-one. Substituents at C-17 influence the stereochemical course of the peracid oxidation of Δ^{14} steroids. A cortical side-chain material blocked with bismethylenedioxy groups gives the 14α,15α-oxide: F. Bohlmann, V. Hint, and B. Diedrich, *Ber.*, **96**, 1316 (1963). Peracid treatment of 14-dehydroprogesterone is reported to yield the 14α,15α-oxide: H. Hasegawa, Y. Sato, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **9**, 409 (1961); H. Ishii, *ibid.*, **10**, 354 (1962). In the cardenolide series α oxidation is also reported: P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **45**, 1041 (1962).