Notes

Terpenes. XIX. Studies in the Synthesis of Diterpenoid Alkaloids

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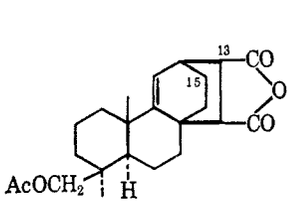
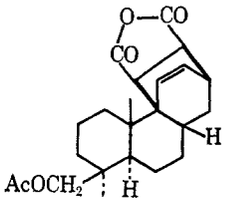
We have earlier described[3] an approach to the synthesis of diterpenoid alkaloids which begins with the readily available and previously synthesized diterpene, podocarpic acid.[4] Thus, podocarpic acid was converted into Diels–Alder adducts I and II and the former adduct was further converted into III (R = CH_3) isomeric with IV (R = CH_3) prepared from maleopimaric acid.[5] Both III and IV gave the same saturated hydrocarbon (V) on hydrogenation. Atisine (VI) has been degraded to the enantiomer of V.[6]



I



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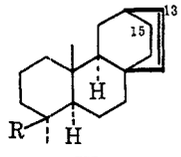
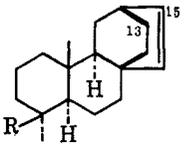
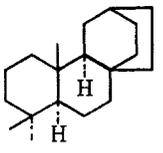


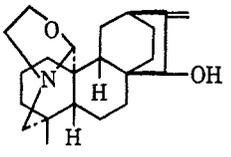
III



IV

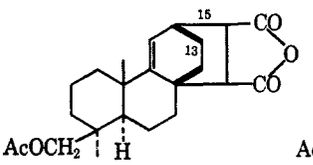


V

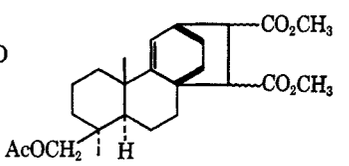


VI

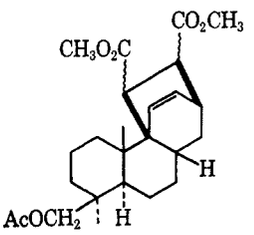
The formation of I is anomalous since it requires reaction of the precursor diene with maleic anhydride from the more hindered topside (β) of the molecule. Thus we were encouraged to determine if the "normal" adduct (VII) was produced in the Diels–Alder reaction. The noncrystalline residue remaining after removal of the crystalline adducts I and II was indeed found to contain VII which was best isolated, in approximately 10% yield, in the form of its epimerized dimethyl ester VIII by chromatography. In addition, a very small amount of the *trans* diester (IX) was also isolated from the chromatography, but this undoubtedly arises by epimerization of X derived from adduct II.



VII

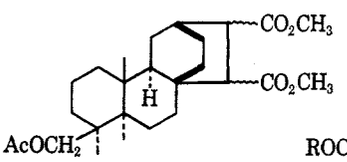


VIII

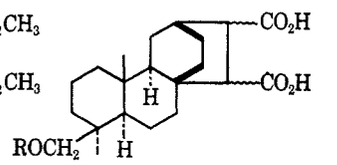


trans IX
cis X

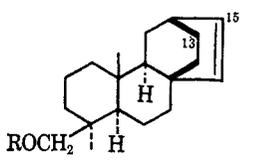
Dimethyl ester VIII was hydrogenated in the presence of platinum on carbon to give XI which was saponified to give XII and the latter on acetylation gave XIII. On oxidative bisdecarboxylation with lead tetraacetate, XIII gave XIV which was saponified to give XV. Of particular significance was the appearance of a high field signal at δ 0.53 in the nmr spectrum of III (R = CH_2OH) and the absence of such a signal in the spectrum of the isomeric XV. Hydrogenation of XV gave the dihydro derivative (XVI), identical in all respects with the product obtained on hydrogenation of III (R = CH_2OH).



XI



XII, R=H
XIII, R=$COCH_3$



XIV, R=$COCH_3$
XV, R=H

Our next goal was construction of the nitrogen containing an E ring such as present in atisine. Chromic anhydride in pyridine converted XV into acid XVII which was further converted into the acyl azide XVIII *via* the intermediate acyl chloride XIX and acyl hydrazide XX following a previously described procedure.[7] Irradiation of XVIII in *n*-hexane gave a mixture of

(1) Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc., Rahway, N. J. 07065.
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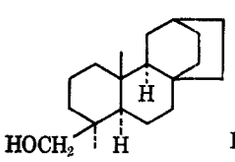
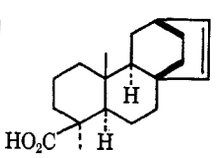
(3) N. N. Girotra and L. H. Zalkow, *Tetrahedron*, **21**, 101 (1965).
(4) E. Wenkert and A. Tahara, *J. Am. Chem. Soc.*, **82**, 3229 (1960).
(5) L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, **29**, 1299 (1964).
(6) W. A. Ayer, C. E. McDonald, and G. G. Iverach, *Tetrahedron Letters*, 1095 (1963).
(7) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962).

products, which after chromatography on alumina yielded lactam XXI in approximately 20% yield. Lactam XXI was readily identified in the separation, since it was the only product which showed only one methyl group singlet (δ 1.13) in its nmr spectrum; other products to be expected[7] from the photolysis reaction would possess two methyl groups (C-4 and C-10).

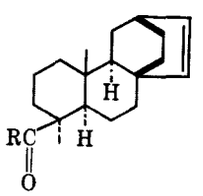
Since Pelletier and Parthasarathy[8] have described the reconversion of the enantiomer of XXII, a degradation product of atisine, into atisine, it is clear that the transformation of XXI into XXII would constitute a total synthesis of atisine. We have, however, not realized this goal because of the limited amount of XXI available and because several syntheses of atisine have already been accomplished.[9-12] Instead we have now concentrated our efforts on using the approach described here for the synthesis of the more complicated alkaloids atidine and ajaconine.



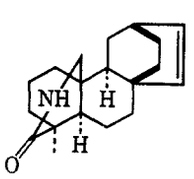
XVI



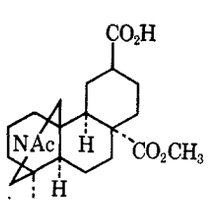
XVII



XVIII, R = N_3
XIX, R = Cl
XX, R = $NHNH_2$



XXI



XXII

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nmr spectra were recorded with a Varian A-60 nmr spectrometer, using TMS as an internal standard (δ = 0).

Preparation of Diels–Alder Adducts I, II, and VII.—A solution of the crude diene mixture (91.2 g), prepared as previously described,[3] and 54 g of maleic anhydride in 230 ml of dry xylene was refluxed for 8 hr in an atmosphere of N_2. After standing at 0° overnight, 6.4 g of I (mp 238–250°) precipitated. Recrystallization from benzene–hexane gave 6 g of pure material (mp 251–252°).[3] After dilution with ether, the filtrate was extracted with water until the aqueous extract was neutral to congo red paper. The organic layer was dried ($MgSO_4$) and evaporated to yield a gummy material which after standing overnight at 0° deposited 18.1 g of crude II, mp 180–190°.[3]

The noncrystalline residue (74 g) containing VII was treated with an excess of methanolic diazomethane and the crude esterified product (78 g) was refluxed in a solution of 150 ml of 20% NaOH and 300 ml of methanol for 10 hr. After addition of water (2 l.) and extraction with ether, the aqueous, alkaline solution was acidified with 6 *N* HCl and extracted with ether. After washing with water, the ether layer was dried ($MgSO_4$) and evaporated to yield a fluffy, yellow solid which was directly treated with methanolic diazomethane to yield 38.4 g of a glassy solid. This material was treated with 170 ml of dry pyridine and 25 ml of acetic anhydride at room temperature for 12 hr and after the usual work-up, 42.5 g of crude VIII was obtained as a brown, viscous oil. Repeated chromatography on Merck acid-washed alumina (activity III) gave 11.1 g of pure VIII: mp 98–100° in the benzene–petroleum ether (bp 60–80°) eluent; λ_{max}^{KBr} 5.75, 5.78, 8.05 μ; nmr (CCl_4) δ 0.90 (s, 3), 1.07 (s, 3), 1.93 (s, 3), 3.65 (s, 3), 3.69 (s, 3), 4.12 (q, 2, J = 11 cps), 6.02 (d, 1, J = 12 cps).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.14; H, 8.53.

Repetition of the Diels–Alder reaction with 278 g of crude diene and 158 g of maleic anhydride in 700 ml of xylene gave 35 g of I (9.4%), 36.5 g of II (9.8%), 41.4 g of VIII (9.9%), and 3.4 g of IX (0.8%). The *trans*-dimethyl ester IX was obtained during the chromatographic purification of VIII and was eluted after VIII in benzene. Diester IX was identical in all respects with a sample prepared[3] from X by saponification with sodium hydroxide followed by treatment of the product with diazomethane and acetic anhydride in pyridine: mp 155–156°; nmr (CCl_4) δ 0.92 (s, 3), 1.95 (s, 3), 3.50 (s, 3), 3.64 (s, 3), 4.04 (q, 2, J = 11 cps), 6.24 and 6.26 (these correspond to two lines of the AB part of an ABX system, but since the other lines are not visible a first-order analysis is not possible).

Preparation of XI.—Alkene VIII (3.3 g) was hydrogenated in 40 ml of acetic acid in the presence of 1.4 g of 5% Pt–C at atmospheric pressure and room temperature. The catalyst was removed by filtration and washed with acetic acid. Addition of water to the combined filtrate gave a gummy precipitate which solidified after standing at 0° ovrenight. After drying, 3.2 g of XI was obtained: mp 78–80°; nmr (CCl_4) δ 0.93 (s, 3), 0.98 (s, 3), 1.97 (s, 3), 3.69 (s, 6), 4.02 (q, 2 J = 11 cps).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.92; H, 8.76.

Preparation of XII and XIII.—A suspension of 6.83 g of XI in 70 ml of methanol and 75 ml of 10% NaOH was refluxed for 7 hr, then diluted with 250 ml of water and acidified with 6 *N* HCl and finally extracted with ether. After washing with water, the ether extract was dried ($MgSO_4$) and evaporated to yield 5.81 g of XII which was recrystallized from methanol to give mp 258–262°; λ_{max}^{KBr} 2.90, 3.16, 5.82–6.00 (broad) μ.

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.26; H, 8.89.

A solution of XII (5.66 g) in 30 ml of pyridine and 6 ml of acetic anhydride was allowed to stand at room temperature for 9 hr. After addition of ether (450 ml), the solution was extracted with cold, aqueous, 5% HCl, dried ($MgSO_4$) and evaporated to yield 6.6 g of crude product, whose infrared spectrum indicated the presence of a mixed anhydride of XIII and acetic acid. A solution of this material in 110 ml of dioxane and 55 ml of water was refluxed for 5.5 hr, diluted with water, and extracted with ether. After washing with water and drying ($MgSO_4$), evaporation of the ether extract gave 6.27 g of XIII which on recrystallization from methanol–ethyl acetate gave mp 107–110°; λ_{max}^{KBr} 3.0–3.5 (broad), 5.85–6.00 (broad), 8.1 μ.

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.75; H, 8.53.

Preparation of XIV and XV.—Dry lead tetraacetate (2.9 g) was added to a well-stirred solution of 2.66 g of XIII in 50 ml of dry pyridine maintained at 70° in a nitrogen atmosphere. After 10 min, an additional 1.8 g of lead tetraacetate was added and the solution was refluxed for 70 min. After removal of the pyridine, the dark brown residue was exhaustively extracted with ether. After washing with water and 5% aqueous HCl, the ether extract was dried ($MgSO_4$) and evaporated to yield 2.2 g of crude XIV as a viscous, brown gum: λ_{max}^{film} 5.85, 8.15, 14.1, 14.4 μ.

A solution of 2.2 g of the above crude XIV in 25 ml of 10% aqueous NaOH and 150 ml of methanol was refluxed for 4 hr, then diluted with water (500 ml), and extracted with ether. After drying ($MgSO_4$), the ether was evaporated and the residue was chromatographed on 65 g of Merck acid-washed alumina (actually III). The product (XV) was eluted in 1:1 benzene–petroleum ether (bp 60–80°) in an over-all yield of 45% from XIII: mp 152–153°; λ_{max}^{KBr} 3.0, 9.8, 14.1, 14.4 μ; nmr ($CDCl_3$) δ 0.93 (s, 3), 0.97 (s, 3), 3.60 (q, 2 J = 11), 6.02 and 6.10 (see discussion of nmr of IX).

(8) S. W. Pelletier and P. C. Parthasarthy, *Tetrahedron Letters*, 205 (1963).
(9) W. Nagata, *et al.*, *J. Am. Chem. Soc.*, **85**, 2342 (1963).
(10) S. Masamune, *ibid.*, **86**, 290 (1964).
(11) Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 2437 (1964).
(12) A. Tahara and K. Hirao, *ibid.*, 1453 (1966).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.01. Found: C, 83.12; H, 11.03.

Preparation of XVI.—Hydrogenation of XV (17 mg) in 2.5 ml of ethyl acetate in the presence of 5 mg of 5% Pt–C at room temperature and atmospheric pressure gave a quantitative yield of XVI, mp 146–148°, identical in all respects with the same compound prepared from III (R = CH_2OH) as previously described.[3]

Preparation of XVII.—A solution of 2.49 g of XV in 48 ml of anhydrous pyridine was added to a mixture of 3.8 g of chromic anhydride in 42 ml of anhydrous pyridine and the mixture was stirred at room temperature for 13 hr. The brown precipitate was removed by filtration and washed with pyridine. The pyridine wash was combined with the filtrate and 250 ml of ice water was added and the entire mixture was extracted with ether. The ether extract was washed with cold 5% HCl, then water, and finally dried over $MgSO_4$. Evaporation gave 2.37 g of semicrystalline product (λ_{max} 3.0–3.5 μ broad). An ether solution (50 ml) of this product was extracted with 10% NaOH and the alkaline layer, after extraction with ether, was acidified with 5% cold HCl. The ether extract of the acidified solution was washed with water, then dried over $MgSO_4$, and evaporated to give 0.74 g of acidic product, mp 170–185°. The ether solutions containing the neutral products on drying and evaporation gave 1.57 g of semicrystalline material which was dissolved in 15 ml of anhydrous tetrahydrofuran and this solution was added dropwise to 0.20 g of lithium aluminum hydride in 10 ml of tetrahydrofuran. After refluxing for 4 hr, the tetrahydrofuran solution was stirred at room temperature for 12 hr, wet ether was then added, followed by a 20% aqueous NH_4Cl solution, and finally the entire solution was extracted with ether. After drying and evaporation 1.55 g of semicrystalline material was isolated from the ether solution. This material was oxidized with chromic anhydride (2.5 g) in pyridine as described above to give 0.24 g of acidic product.

The combined acid fractions were recrystallized twice from methanol to give 0.76 g of pure XVII: mp 203–205°; λ_{max}^{KBr} 3.0–4.0, 5.90, 14.1, 14.5 μ.

Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.30; H, 9.70.

Preparation of XXI.—Thionyl chloride (2.5 ml) was added to a solution prepared by adding 4 drops of pyridine and 0.76 g of XVII to 25 ml of dry ether. After standing at room temperature for 3 hr, the pyridine hydrochloride was removed by filtration and washed with dry ether. The combined ether filtrates were evaporated to give 0.80 g of crude XIX, mp 95–102°, which was directly used without further purification. Acid chloride XIX (0.80 g) in 50 ml of dry ether was added to 10 ml of ethanol containing 3 ml of 95% hydrazine at 0°. The mixture was vigorously stirred for 5 min, then poured into 150 ml of water and extracted with ether. After washing with water and drying ($MgSO_4$), the ether extract was evaporated to give 0.726 g of XX, mp 180–186°. Recrystallization from ethyl acetate gave the analytical sample: mp 185–187°; λ_{max}^{KBr} 2.97, 3.15, 6.15, 10.10, 14.6 μ; nmr ($CDCl_3$) δ 0.87 (s, 3), 1.20 (s, 3), 3.85 (s, broad), 6.02 and 6.10 (these correspond to two lines of the AB part of an ABX system but, since the other lines are not visible a first-order analysis is not possible.)

Anal. Calcd for $C_{19}H_{30}NO_2$: C, 75.45; H, 10.00. Found: C, 74.94, H, 9.95.

The acid hydrazide XX (0.87 g) was dissolved in 28 ml of acetic acid and after cooling to 0°, a saturated solution of 0.69 g of sodium nitrite in water was added and the mixture was vigorously shaken for 3 min. After dilution with ice–water, the solution was exhaustively extracted with *n*-hexane, which in turn washed with ice–water and 5% $NaHCO_3$ and finally dried ($MgSO_4$). The *n*-hexane solution (~480 ml) of XVIII was irradiated in a nitrogen atmosphere, by immersion of a 200-w Hanovia lamp in a quartz tube into the solution, at 15–20° for 10 hr. After filtration, to remove a small amount of insoluble material, the hexane solution was evaporated at room temperature with a rotary evaporator to give 0.79 g of partially crystalline material which was chromatographed on 11 g of Merck acid-washed alumina (activity III). The chloroform–benzene (1:3) eluent yielded 0.16 g of lactam XXI: mp 242–245°; λ_{max}^{KBr} 3.12, 6.05, 14.3 μ; nmr ($CDCl_3$) δ 1.13 (s, 3), 3.38 (q, 2, J = 12 cps), 6.08 and 6.14 (see discussion of nmr of XX).

Anal. Calcd for $C_{19}H_{27}NO$: C, 79.95; H, 9.54. Found: C, 79.64; H, 9.49.

Two other products were obtained in small amounts from the chromatography column, but these were shown not to be the desired lactam XXI by the presence of two methyl groups in each of their nmr spectra.

Registry No.—VIII, 10034-00-1; IX, 10034-01-2; XI, 10034-02-3; XII, 10034-03-4; XIII, 10060-18-1; XIV, 10034-04-5; XV, 734-02-1; XVII, 10034-06-7; XX, 10034-07-8; XXI, 10034-08-9.

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Terpenes. XX. The Synthesis of Postulated Tetracarbocyclic Diterpenoids[1]

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In 1955[3] Wenkert first postulated the biogenesis of tetracarbocyclic diterpenes and diterpenoid alkaloids from pimarene-type precursors *via* bridged carbonium ions. Since this postulation a number of new tetracarbocyclic diterpenes (atisirene,[4] hibaene,[5] kaurene[6]) and one pentacarbocyclic diterpene (trachylobane[7]) have been found in nature, the biogenesis of which are readily accommodated by Wenkert's postulation.

Extension of Wenkert's postulation to include precursors of the isopimarene type would lead to the tetra- and pentacarbocyclic diterpenes shown in Scheme I,[8,9] and indeed *in vitro* syntheses of isohibaene and isohibane from isopimaradiene precursors have been accomplished.[10]

Of this group, only diterpenoids possessing the phyllocladene skelton have thus far been encountered in nature; this may be because the cyclization depicted in Scheme I must involve ring C in a nonchair conforma-

(1) Terpenes XX. Terpenes XIX: L. H. Zalkow, N. N. Girotra, and V. B. Zalkow, *J. Org. Chem.*, **32**, 806 (1967).

(2) Department of Chemistry, Simon Frazer University, Burnaby 2, British Columbia, Canada.

(3) E. Wenkert, *Chem. Ind.* (London), 282 (1955); see also W. B. Whalley, *Tetrahedron*, **18**, 43 (1962).

(4) A. H. Kapadi, R. R. Sobti, and S. Dev, *Tetrahedron Letters*, 2729 (1965).

(5) Y. Kitahara and A. Yoshikoshi, *ibid.*, 1771 (1964); P. R. Jefferies, R. S. Rosich, D. E. White, and M. C. Woods, *Australian J. Chem.*, **15**, 521 (1962).

(6) L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmhurst, *Tetrahedron Letters*, 8 (1959); C. Djerassi, *et al.*, *J. Am. Chem. Soc.*, **83**, 3720 (1961).

(7) G. Ourisson, *et al.*, *Bull. Soc. Chim. France*, 2882, 2888, 2894, 2903 (1965).

(8) We do not wish to enter into the controversy regarding classical and nonclassical carbonium ions and simply wish to indicate that the isopimarene carbonium ion generated by protonation of the Δ^8 double bond (A) can give rise to the various diterpenoids *via* some intermediate such as B.

(9) Only relative configurations are indicated in Scheme I.

(10) (a) E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Am. Chem. Soc.*, **86**, 2218 (1964); (b) W. Herz, D. Melchior, R. N. Mirrington, and P. J. S. Pauwels, *J. Org. Chem.*, **30**, 1873 (1965). For a similar synthesis of hibaene, see W. Herz, A. K. Pinder and R. N. Mirrington, *ibid.*, **31**, 2257 (1966).