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PLEIADENE SYSTEMS—VI

FURTHER STUDIES IN THE METHYLPLEIADENE SERIES

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Abstract—The reaction of 1-methyl-7,12-dihydropleiadene-7-one (I) with either Ph or Me Grignard reagents affords products resulting from attack of the reagent at the aromatic C-6 position as well as products resulting from addition to the C-7 carbonyl. The unidentified hydrocarbon, m.p. 237°, first reported by Fieser as a reaction product of ketone I with PhMgBr, has been assigned the structure of 6-methyl-1,12-*o*-phenylene-7,12-dihydropleiadene (VII). Reaction of 1,6-dimethyl-7,12-dihydropleiadene (XI) with elemental sulfur gives the 7,12-sulfide XIII as originally proposed by Fieser, rather than the isomeric 1,7-sulfide structure. Sulfide XIII was synthesized in an unambiguous manner; it served also as the precursor, *via* sulfone XVII, for the transient 1,6-dimethylpleiadene (XII), characterized as its dimer and its N-phenylmaleimide adduct.

IN THE course of an early study of the chemistry of some 7,12-dihydropleiadenes, brief mention was made of the fact that a hydrocarbon, m.p. 237°, was obtained by the reaction of PhMgBr with 1-methyl-7,12-dihydropleiadene-7-one (I). An elemental analysis (C, 93·83; H, 5·83) was reported for this hydrocarbon, although it was apparently not further investigated.[1] Since the reported analysis is in good accord with the composition of 1-methyl-7-phenylpleiadene (II), we embarked upon a reinvestigation of this compound in order to determine if it might be the potentially stable pleiadene II or, if not, a dimer of II.

In our hands, the reaction of ketone I with PhMgBr afforded, after workup with ammonium chloride, a mixture of three products, none of which was a hydrocarbon. These products are designated as compounds A, B, and C in the following discussion.

Compound A, m.p. 199–200°, was the major product (45%) isolated. On the basis of its empirical composition ($C_{25}H_{18}O$) and the presence of a strong CO band at 6·06 μ in its IR spectrum, it was assigned the structure of 1-methyl-6-phenyl-7,12-dihydropleiadene-7-one (III). A molecular model of III shows that the Ph substituent is forced out of the plane of the naphthalene ring by the CO group and should therefore add little to the conjugation of the system. In accord with this prediction, the UV spectrum of III shows a max at 340 mμ, as compared with a max at 350 mμ in the spectrum of the unphenylated ketone I. The NMR spectrum of III showed the expected methylene protons at 5·75 τ and the Me group at 7·32 τ. Sodium dichromate oxidation of III afforded a diketone formulated as 1-methyl-7-phenyl-7,12-dihydropleiadene-7,12-dione (IV).

Ketone III apparently arises by way of a 1,4-addition of the Grignard reagent to I to give the partially reduced ketone V, which then undergoes air oxidation during workup and chromatographic separation to give III. 1,4-Additions of Grignard

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reagents to hindered aromatic ketones have been well documented previously.[2] The structure of intermediate V was, indeed, assigned to the second reaction product, compound B (m.p. 140–141°), isolated in very low (2%) yield. Although it was obtained in insufficient amount for complete characterization, it showed CO absorption at 5·99 μ, but gave an UV curve which had no definite max beyond 250 mμ. Most significantly, chloranil oxidation of compound B afforded ketone III.

Compound C, m.p. 175–177°, was obtained in only fair (10%) yield. On the basis of its elemental composition and spectral properties, particularly the lack of CO absorption, it was assigned the structure of the normal Grignard addition product, 1-methyl-7-phenyl-7,12-dihydropleiadene-7-ol (VI).

Since Fieser's hydrocarbon, m.p. 237°, must have arisen by way of inadvertent acid dehydration of tertiary alcohol VI during workup, we warmed a solution of alcohol VI in formic acid on the steam bath. The initially purple-red solution became yellow as dehydration took place with the formation of a hydrocarbon, m.p. 240°, which was apparently identical with the hydrocarbon of Fieser. The NMR spectrum of this compound showed, in addition to aromatic protons, one proton at 4·05 τ, two protons centered at 5·41 τ and the expected 3-proton Me signal at 7·31 τ. This data rules out both the pleaidene structure II and pleaidene dimer structures, but it was in accord with the structure of 6-methyl-1,12-*o*-phenylene-7,12-dihydropleiadene (VII), formation of which is readily rationalized by way of the intramolecular cyclization of carbonium ion VIII.*

The reaction of ketone I with MeMgBr was investigated briefly for the purpose of comparison with the Ph Grignard case. The Me Grignard reagent appeared to attack I more sluggishly. In ether solution, only unchanged I was recovered. In refluxing tetrahydrofuran solution there was obtained, in addition to recovered I, a modest yield (19%) of a hydrocarbon, m.p. 100–101°, which was shown to be 1-methyl-7-methylene-7,12-dihydropleiadene (IX) by its spectral characteristics.† Its UV absorption spectrum showed a max at 305 mμ, indicating the presence of increased conjugation over that present (max at 291 mμ) in 1-methyl-7,12-dihydropleiadene.[4] The NMR spectrum of IX showed, in addition to aromatic protons, two ring methylene protons at 5·67 τ, three Me protons at 7·39 τ and two olefinic methylene protons as a pair of doublets ($J = 2$ c/s) at 4·76 τ and 4·33 τ. The proton at 4·33 τ is assigned to the proton *cis* to the naphthalene ring of IX, in keeping with the anticipated stronger deshielding effect of a naphthalene versus a benzene nucleus. The value of the other olefinic proton (4·76 τ) is quite close to that (4·64 τ) recorded for the olefinic proton of α-methylstyrene which lies *cis* to the Ph group.[6]

A second product of the reaction of I with MeMgBr, isolated in under 1% yield, proved to be the known[2] 1,6-dimethyl-7,12-dihydropleiadene-7-one (X). Thus, 1,4-addition of Me Grignard reagent to I was observed in addition to 1,2-addition, but 1,4-addition took place to a much lesser extent than in the Ph Grignard case.

In 1933, Fieser recorded an attempted sulfur dehydrogenation of 1,6-dimethyl-7,12-dihydropleiadene (XI).[7] The product of this reaction was not 1,6-dimethylpleiadene (XII) but rather a S-containing compound, m.p. 217°, assigned the 7,12-

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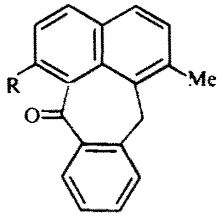
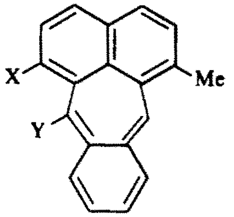
* After the completion of our study (W. S. Lee, Ph.D. dissertation, The Ohio State University, 1964), other workers independently reported the cyclization of the unmethylated analog of VI to the unmethylated analog of VII.[3]

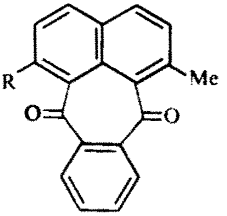
† The synthesis and spectral properties of some closely related analogs of IX were reported recently.[5]



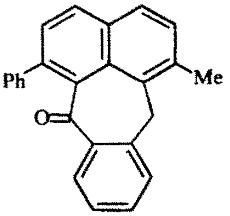
I: R = H
III: R = Ph
X: R = Me



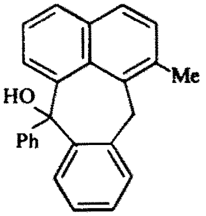
II: X = H; Y = Ph
XII: X = Me; Y = H



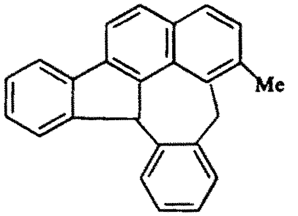
IV: R = Ph
XV: R = Me



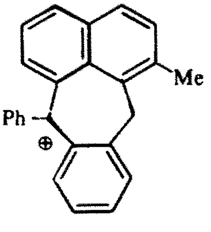
V



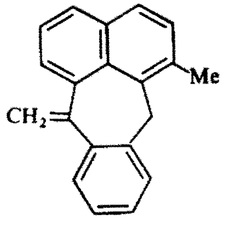
VI



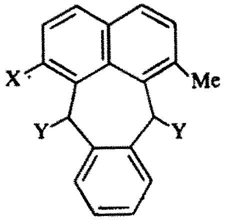
VII



VIII



IX



XI: X = Me; Y = H
XVI: X = Me; Y = OH
XXI: X = H; Y = H

sulfide structure XIII. Since the method of formation of this sulfide did not rule out the isomeric formulation XIV, we decided to reinvestigate the compound in order to distinguish between the two possible structures. Authentic 1,6-dimethyl-7,12-dihydropleiadene-7,12-sulfide (XIII) was prepared from the previously reported[1] 1,6-dimethyl-2,7-dihydropleiadene-7,12-dione (XV) by borohydride reduction of XV to diol XVI, followed by reaction of the latter diol with phosphorus pentasulfide. The resulting sulfide was identical with material prepared by Fieser's method. It thus is quite possible that Fieser was the first to generate a pleiadene (namely, the 1,6-dimethyl derivative XII), which was trapped *in situ* by elemental S to give sulfide XIII.

Peracetic acid oxidation of sulfide XIII afforded the corresponding sulfone XVII. Pyrolysis of sulfone XVII in the presence of N-phenylmaleimide generated 1,6-dimethylpleiadene (XII), which was trapped to give adduct XVIII, m.p. 310–311°. Decomposition of sulfone XVII either photolytically or pyrolytically in the absence of dienophile afforded 1,6-dimethylpleiadene dimer (XIX), m.p. >405°.*

Comparison of the NMR spectrum of 1,6-dimethyl-7,12-dihydropleiadene-7,12-sulfide (XIII) with that of 1-methyl-7,12-dihydropleiadene-7,12-sulfide (XX)[4] revealed

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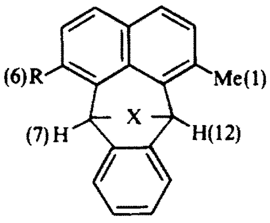
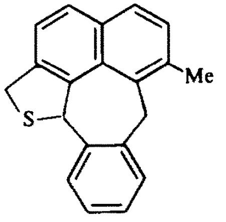
* The stereochemistry of compounds XVIII and XIX was assigned by analogy with the corresponding substances in the unsubstituted pleiadene series.[8]

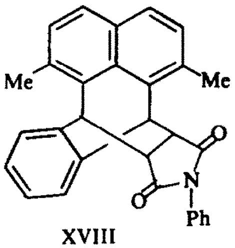
an interesting stereochemical effect. The Me groups of XIII and that of XX appear at practically the same position (7·39 τ and 7·42 τ, respectively). On the other hand, while the C-12 proton of XX appears at exactly the same position (4·38 τ) as the C-7 and C-12 protons of XIII, the C-7 proton of XX appears at much higher field (4·81 τ). It must be concluded, therefore, that the C-12 proton of XX is considerably deshielded by the C-1 Me group as a result of a van der Waals repulsion effect. The magnitude of this effect may be estimated by the same type of analysis which has been reported by other investigators in the octahydrophenanthrene series.[9] From the known van der Waals radii of a Me group (2.0 Å) and of a H atom (1·2 Å),[10] and from the distance of 2·34 Å (estimated by use of Dreiding models) between the Me group and the C-12 hydrogen, the very significant value of 0·86 was calculated[9] for the van der Waals compression factor *c*. It is of interest to note that all four methylene protons of 1-methyl-7,12-dihydropleiadene (XXI)[4] appear at the same position (5·58 τ), no deshielding effect of the Me group being discernible. This difference between the rigid 7,12-sulfide XX and the corresponding hydrocarbon XXI must be attributed to the expected[5] conformational mobility of XXI.



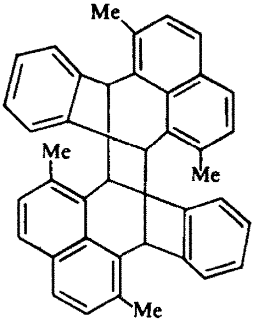
XIII: R = Me; X = S
XVII: R = Me; X = SO_2
XX: R = H; X = S



XIV



XVIII



XIX

EXPERIMENTAL*

Reaction of 1-*methyl*-7,12-*dihydropleiadene*-7-*one* (I) *with* PhMgBr

To a soln of 1-methyl-7,12-pleiadene-7-one[4] (0·500 g) in dry ether (50 ml) was added 3M PhMgBr (3 ml), and the mixture was stirred for 5 hr at room temp. The resulting reaction mixture was hydrolyzed with NH_4Claq (50 ml). After adding benzene (100 ml) to the hydrolysis mixture, the organic layer was separated, washed with water and dried. The residue obtained on evaporation was chromatographed

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* M.ps are uncorrected. The UV spectra were determined in 95% EtOH soln. Chromatography was carried out using Woelm neutral alumina of the activity grade indicated. Analyses were performed by Midwest Microlab, Inc., Indianapolis and by Dr. A. Bernhardt, Mulheim.

on alumina using benzene as a developer. The column gave a blue band followed by a pale, light green-blue band.

(a) *α,β-Dihydroketone* V. The eluent soln from the blue band (1st band) gave white crystals (about 15 mg, 2%, crystallization from benzene–Skelly Solve F) m.p. 140–141°. Elemental analysis was not carried out due to lack of material, but chloranil oxidation gave the fully aromatic ketone III.

(b) 1-*Methyl-6-phenyl-7,12-dihydropleiadene-7-one* (III). The second pale, light green-blue band from above column afforded colorless crystals (0·288 g, 44·5%, crystallization from benzene–Skelly Solve F), m.p. 190–220°; λ_{max} 340 mμ (log ε = 4·99). (Found: C, 90·02; H, 5·46. Calc. for $C_{25}H_{18}O$: C, 89·79; H, 5·43%.)

(c) 1-*Methyl-7-phenyl-7,12-dihydropleiadene-7-ol* (VI). The third fraction eluted after the pale, light green-blue band, gave colorless crystals (0·07 g, 9·9%, crystallization from benzene–Skelly Solve F), m.p. 175–177°. (Found: C, 89·20; H, 5·96. Calc. for $C_{25}H_{20}O$: C, 89·25; H, 5·99%.)

1-*Methyl-6-phenyl-7,12-dihydropleiadene-7,12-dione* (IV)

To a soln of III (0·200 g) in glacial AcOH (25 ml) was added sodium dichromate (0·320 g). After refluxing for 3 hr, the mixture was poured into cold water (200 ml). The ppt was washed with water, dissolved in CH_2Cl_2, and dried over $MgSO_4$. Chromatography on alumina (CH_2Cl_2 eluent) yielded white crystals (0·156 g, 74·8%), m.p. 205°. (Found: C, 86·05; H, 4·56. Calc. for $C_{25}H_{16}O_2$: C, 86·18; H, 4·63%.)

6-*Methyl*-1,12-o-*phenylene*-7,12-*dihydropleiadene* (VII)

A soln of VI (0·50 g) in formic acid (10 ml) was warmed on the steam bath for 20 min, during which time the initially purple-red soln became pale yellow. The cooled soln was filtered, and the crystalline ppt was recrystallized from benzene–EtOH to give VII (0·40 g) as white needles, m.p. 240°. (Found: C, 94·00; H, 5·61. Calc. for $C_{25}H_{18}$: C, 94·30; H, 5·70%.)

Reaction of 1-*methyl-7,12-dihydropleiadene-7-one* (I) with MeMgBr

To a soln of I (0·867 g) in dry THF (50 ml) was added MeMgBr (3M, 10 ml). The mixture was allowed to reflux (58°) for 24 hr, cooled to room temp, and hydrolyzed with NH_4Cl aq.

The organic product was taken up in benzene. The dried and concentrated benzene soln was placed on an alumina column and developed with benzene. A purple-blue band, followed by a sky-blue band was observed.

(a) 1-*Methyl-7-methylene-7,12-dihydropleiadene* (IX). The fraction from the purple-blue band gave IX as white crystals (0·16 g, 18·6%, crystallization from benzene–EtOH), m.p. 100–101°; the IR spectrum possessed a strong band at 11·15 μ characteristic of an α,α-disubstituted olefin; λ_{max} 305 mμ (log ε = 4·11). (Found: C, 93·77; H, 6·37. Calc. for $C_{20}H_{16}$: C, 93·71; H, 6·29%.)

(b) 1,6-*Dimethyl-7,12-dihydropleiadene-7-one* (X). The sky-blue band was cut arbitrarily into two fractions. The first fraction yielded colorless needles (about 5 mg, < 1%, crystallization from benzene–Skelly Solve F), m.p. 172–174°, identical with an authentic sample, m.p. 174° (reported[1] 174°).

The second fraction of the sky-blue band yielded unchanged ketone I.

1,6-*Dimethyl-7,12-dihydropleiadene-7-one* (X) *and* 1,6-*dimethyl-7,12-dihydropleiadene-7,12-dione* (XV)

Monoketone X was prepared in several steps from 2,7-dimethylnaphthalene as described by Fieser and Fieser,[1] except that the intermediary α-(2,7-dimethyl-1-naphthyl)-*o*-toluic acid was cyclized using HF, as described for the corresponding monomethyl acid.[4] An overall yield of 38% of X from 2,7-dimethylnaphthalene was obtained; m.p. 174° (reported[1] 174°).

Oxidation of monoketone X to diketone XV (76% yield) was carried out as described by Fieser and Fieser;[1] m.p. 245–246° (reported[1] 241°).

1,6-*Dimethyl-7,12-dihydropleiadene* (XI)

To a suspension of LAH (2 g) in dry ether (250 ml) was added $AlCl_3$ (2·5 g) dissolved in ether (30 ml). The mixture was refluxed for 48 hr in a Soxhlet apparatus containing X (2·50 g). After the cautious introduction of water (100 ml) into the reaction flask, the 2-phase system was poured into conc HCl aq (100 ml). The organic layer was diluted with benzene (100 ml) and the dried and concentrated extract was chromatographed on alumina (benzene eluent). Crystallization from benzene–EtOH yielded XI as white needles (1·79 g, 75·5%), m.p. 130–131° (reported,[1] 133°). The above synthesis of XI was more convenient than the ordinary reported method using a high-press copper chromite reduction.

1,6-*Dimethyl*-7,12-*dihydropleiadene*-7,12-*sulfide* (XIII)

Method A. A mixture of 1,6-dimethyl-7,12-dihydropleiadene (1·000 g) and powdered S (0·249 g) was placed in a small distilling flask with a condenser. The flask was immersed in a salt bath at 180°, and the temp was raised rapidly. Evolution of H_2S began at about 200°, and became brisk around 260°. Heating was continued at 260° ± 5° for 7 to 8 min or until gas evolution was no longer observed. The reaction mixture was dissolved in benzene and the dark red soln was decolorized with charcoal. The concentrated soln was chromatographed on alumina (benzene eluent). Crystallization from benzene–Skelly Solve F gave orange needles (0·309 g, 28·1%), m.p. 220° (reported[5] 217°).

Method B. To a soln of 1,6-dimethyl-7,12-dihydropleiadene-7,12-dione (0·880 g) in benzene (100 ml) was added EtOH (200 ml), followed by $NaBH_4$ (2 g). The mixture was heated gently until dissolution of the reagent was complete. It was then allowed to stand overnight at room temp. To the reaction mixture was added water (100 ml) and the resulting soln was heated on a steam bath for 30 min. The organic layer containing a suspension of white crystals was separated from aqueous layer, followed by addition of sufficient benzene to dissolve the crystals completely. The organic solution was dried and evaporated. The solid residue was crystallized from acetone–Skelly Solve F to give diol XVI as white crystals, (0·715 g, 80·0%), m.p. 189–190°. Only erratic analyses for this compound were obtained, the results being suggestive of partial dehydration during drying. It was, therefore, converted directly to sulfide XII as described below.

A mixture of the above diol XVI (0·50 g) P_2S_5 (1 g) and CS_2 (100 ml) was stirred for 48 hr at room temp. The resulting reaction mixture was filtered with suction through a Celite mat. The solvent was evaporated and the residue was chromatographed on grade I alumina (benzene eluent). Crystallization from benzene–Skelly Solve F gave XIII as colourless prisms (0·34 g, 70·5%), m.p. 222–223°. IR and NMR spectra showed this compound to be identical with that obtained in Method A. (Found: C, 83·13; H, 5·76; S, 11·25. Calc. for $C_{20}H_{16}S$: C, 83·31; H, 5·59; S, 11·10%.)

1,6-*Dimethyl*-7,12-*dihydropleiadene*-7,12-sulfone (XVII)

To a soln of XIII (0·400 g) in benzene (5 ml) was added glacial AcOH (10 ml), and commercial 40% peracetic acid (8 ml). The mixture was stirred overnight at room temp. Water (50 ml) was added to the resulting reaction mixture and the product was extracted with $CHCl_3$. The organic soln was dried and the solvent was evaporated; the residue was chromatographed on alumina using a 1:1 mixture of benzene and $CHCl_3$ as eluent. Crystallization from $CHCl_3$–Skelly Solve F gave colorless plates (0·36 g, 79·8%), m.p. 220–230° (dec). (Found: C, 74·85; H, 5·07; S, 10·06. Calc. for $C_{20}H_{16}SO_2$: C, 74·99; H, 5·03; S, 9·99%.)

Diels–Alder adduct (XVIII) *from sulfone* XVII *and* N-*phenylmaleimide*

A mixture of XVII (0·100 g) and N-phenylmaleimide (0·200 g) was heated in an open test tube in a salt bath at 220–240° (ca. 8 min), until evolution of SO_2 was complete. The resulting brown solid was washed with cyclohexane to remove excess N-phenylmaleimide, and the residual solid was chromatographed on alumina (benzene eluent). Crystallization from benzene–Skelly Solve F yielded colorless prisms (0·070 g, 51·3%), m.p. 310–311°. (Found: C, 83·69; H, 5·41; N, 3·10. Calc. for $C_{30}H_{23}NO_2$: C, 83·89; H, 5·40; N, 3·26%.)

Dimer XIX *of* 1,6-*Dimethylpleiadene* (XII)

(a) *Photolysis of sulfone* XVII. A soln of XVII (0·120 g) in benzene (180 ml) was irradiated with a Hg arc at 20° under a N atm (1 atm) for 1 hr. The resulting soln was concentrated and chromatographed on grade I alumina (benzene eluent). A bright fluorescent band was eluted from the column. The solid residue formed on evaporation of the eluate of this fraction crystallized from benzene–EtOH yielding XIX as pale yellow needles (0·024 g, 12·5%), m.p. >405°. (Found: C, 93·73; H, 6·54. Calc. for $C_{40}H_{32}$: C, 93·71; H, 6·29%.)

(b) *Pyrolysis of sulfone* XVII. Sulfone XVII (0·100 g) was heated in an open test tube at 220–240° until the evolution of SO_2 was complete (about 8 min). The brown solid which formed was dissolved in benzene and decolorized with charcoal. The concentrated soln was chromatographed and crystallized as described in Method A to give yellow needles (0·022 g, 13·8%), m.p. >405°. This product was found to be identical (IR spectrum) with the compound obtained from the photolysis of sulfone XV.

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