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TOTAL SYNTHESIS OF ANTHRASTEROIDS—I
FORMYLATION OF CERTAIN CYCLIC α,β- AND β,γ-UNSATURATED KETONES*

K. WIEDHAUP,† A. J. H. NOLLET, J. G. KORSLOOT‡ and H. O. HUISMAN
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

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Abstract—As part of a study concerning the total synthesis of certain anthraequilenine, anthraestrone and diaza-anthraestrane derivatives, the synthesis and structure proof of the key intermediate *trans*-1β-hydroxy-8β-methyl-4,5-(3'-hydroxy-methylene-4'-oxo-2',3',4',5'-tetrahydrobenzo) hydrindane (VI) is described. The preparation of this system involves a base catalyzed formylation of a cyclic β,γ-unsaturated ketone. The course and the selectivity of this acylation reaction is examined in more detail with the bicyclic model compounds $\Delta^{9(10)}$-octalone-2 and $\Delta^{1(9)}$-octalone-2.

FOLLOWING the initial studies of Nes and Mosettig[1] in 1953 on the transformation of certain steroids into systems with a cyclopentanooctahydroanthracene structure, anthrasteroids have been the subject of many investigations.[2] Interest in this novel class of steroid isomers was stimulated by the hypothesis that their formation from naturally occurring steroids could play an essential role in the biogenesis of carcinogens.[1, 3] The mechanism of the anthrasteroid rearrangement has been thoroughly studied,[2d, 4] and the structure and stereochemistry of the systems thus obtained, all of which feature an aromatic ring B, have been established by chemical transformation ,[1b, 2b–d, 5] by UV[1b, 2b, 4a,6, 7] and NMR[2h, 5] spectroscopy and, in some cases, by total synthesis.[2e–g] More recently a total synthesis of 8-isoanthratestosterone has been reported.[8]

The present investigations aim at the preparation of anthrasteroids that are structurally and stereochemically related to hormonally-active steroidal systems. These studies have resulted in the total synthesis of some anthraequilenine and anthraestrone derivatives as well as a series of diaza-anthraestranes. In this paper we report the synthesis and structure proof of *trans*-1β-hydroxy-8β-methyl-4,5-(3'-hydroxymethylene-4'-oxo-2',3',4',5'-tetrahydrobenzo)hydrindane (VI) which has proved to be a very useful intermediate in the preparation of anthrasteroids and aza-anthrasteroids possessing a ring C/D *trans* configuration.

Following the procedure which has been adapted from Johnson's equilenine synthesis,[9] 6-methoxytetralone-1 (I) was converted stereospecifically to *trans*-1β-hydroxy-8-methyl-4,5-(4'-methoxybenzo)hydrindane (II). Reduction with lithium and t-butanol in liquid ammonia of II[10] afforded the corresponding 2',5'-dihydrodienol ether, III, which was smoothly hydrolyzed with a solution of oxalic acid in aqueous ethanol to the β,γ-unsaturated ketone IV.

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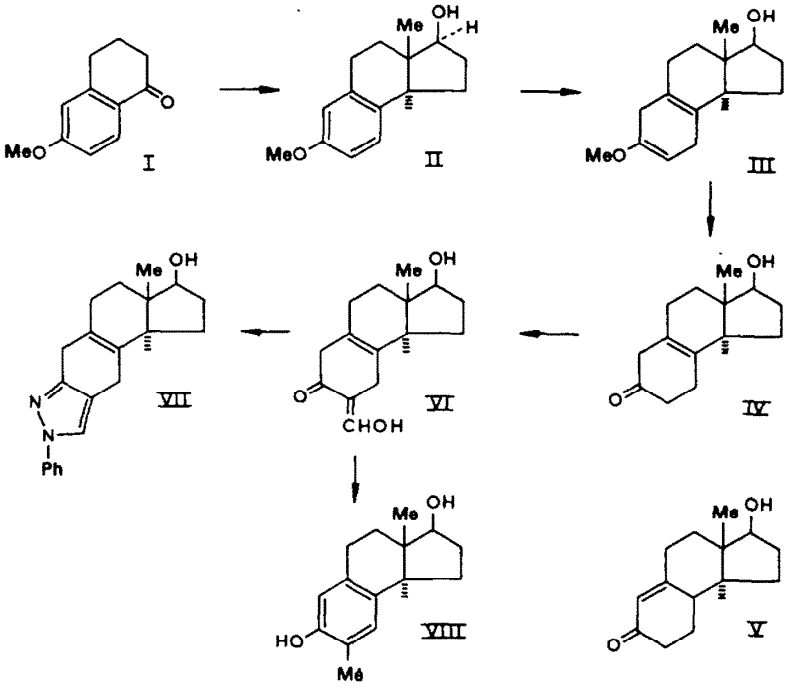
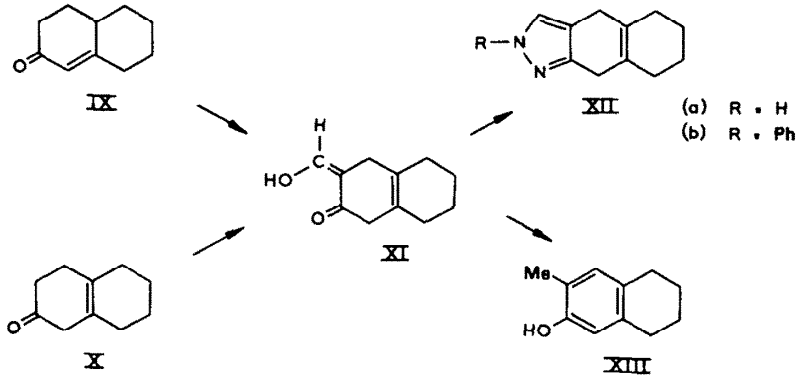
† Present address: Department of Chemistry, Stanford University, Stanford, California.

‡ Present address: Laboratories of N.V. Philips-Duphar, Weesp, The Netherlands.

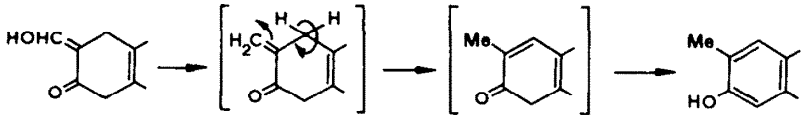


It was initially intended to utilize the α,β-unsaturated isomer V in the subsequent formylation step. However, preliminary studies of the base catalyzed acylation of simple bicyclic analogues with ethylformate strongly suggested ketone IV to be the more expedient starting material for this reaction. Evidence for this choice is presented below.[11]

Formylation of $\Delta^{1(9)}$-octalone-2 (IX) in toluene, using *one* equivalent of sodium methoxide as the condensing agent, resulted in a *single* hydroxymethylene derivative in 70% yield. Unexpectedly, treatment of $\Delta^{9(10)}$-octalone-2 (X) with ethylformate also gave a single hydroxymethylene product in 78% yield which proved to be identical with the compound obtained from IX. The structure of the compound resulting from these reactions has been established to be XI. The tetrasubstituted position of the



endocyclic double bond in this system was suggested by its NMR spectrum, in which a singlet absorption at δ 2·88 accounted for the four methylene protons at C_1 and C_4, while no absorption in the vinyl proton region was observed. The UV absorption (EtOH): 276 ($\varepsilon = 7500$) nm was characteristic of a cyclic α-hydroxymethylene ketone system, *non*-conjugated with a double bond.[12] Additional support for this assignment was obtained by treating XI with hydrazine hydrate and phenylhydrazine to give the corresponding pyrazoles XIIa and XIIb. The NMR and UV spectra of these compounds clearly indicated that the double bond was not conjugated with the heterocyclic system.[12, 13] The most compelling evidence establishing the structure XI resulted from its hydrogenation over Pd–C at room temperature and atmospheric pressure. From this reaction mixture a methyl substituted phenol was isolated in 31% yield.* The latter system proved to be identical with 6-hydroxy-7-methyltetraline (XIII).[14] Barring unusual molecular rearrangements, it is clear that the methyl group in XIII must arise from the hydroxymethylene function in XI.† The



XI XIII

Chart I

attachment of this group at C_7 thus establishes that the direction of formylation of the ketones IX and X occurred at the C_3 position.

The high degree of specificity observed in the formylation of ketone X in toluene lead us to examine this reaction in t-butanol (using *one* equivalent potassium t-butoxide as base) and ethanol (with *one* equivalent sodium ethoxide). While XI was obtained from these reactions in yields of 64 and 20% respectively, in no instance was it possible to detect the corresponding 1-hydroxymethylene ketone, although traces might have been present. In addition to XI, a mixture of the ketones IX and X (in a ratio of ca. 7:3, as evidenced from spectroscopic data), was isolated from every experiment. That the formylation of the ketones IX and X thus proceeds exclusively (or to a very predominant extent) via the less stable anion B, (Chart II) can be interpreted in terms of steric factors.

* Spectroscopic data indicated the presence of a mixture of isomeric methyldecalones in addition to XIII in the reaction product.

† The unexpected formation of XIII from XI presumably involves an initial reductive fission of the enolic carbon oxygen bond, followed by rearrangement of the exocyclic double bond and enolization of the ketone function (see Chart I). An alternative route involving aromatization of XI to give the corresponding 3-hydroxymethyl substituted phenol, followed by reduction of the hydroxymethyl group seems less likely since no rearrangement was observed when substance XI was treated with Pd–C alone.
(*Beilsteins Handbuch der Organischen Chemie*, VI (erstes Ergänzungswerk) p. 218. Springer Verlag, Berlin (1931).

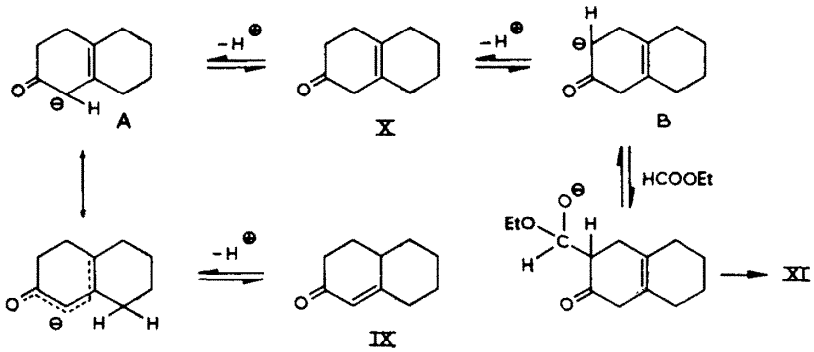


Chart II

The intermediate of the reversible base catalyzed formylation of ketones involves a bulky semi acetale anion,[15] and it well may be anticipated that in the case of the C_1 enolized anion, A, the proximate hydrogen atoms at C_8 of the neighbouring ring will markedly impede the attack of the electrophilic species. No obvious steric interference is to be expected in the formation of the C_3 substituted intermediate (chart II). A similar sterically controlled reaction course has been observed in the oxalylation,[16] and, to a lesser extent in the formylation[11,17] of tetralone-2. The formation of the mesomeric anion A from X under the conditions employed is self-evident from thermodynamic considerations and was verified by the previously noted formation of ketone IX from X, which will proceed by γ-protonation of this anion. It may be assumed that the anionic species A will also be involved in the conversion of the conjugated ketone IX to the hydroxymethylene derivative XI.

As anticipated from the results of the model experiments, acylation of the tricyclic β,γ-unsaturated ketone IV with ethylformate and sodium methoxide in toluene afforded the single product VI in 65% yield. Its structure was confirmed by the NMR and UV spectra (EtOH): 277 (ε = 8100) nm which were fully comparable to those of the bicyclic analogue XI. Condensation of VI with phenylhydrazine yielded the expected heterocyclic derivative VII. Furthermore, conforming to the observed behaviour of XI, catalytic hydrogenation of VI over Pd–C afforded the methyl substituted phenol VIII in a yield of 34%. In the NMR spectrum singlets for the angular and aromatic methyl groups were found at δ 0·63 and δ 2·18 respectively. As required by structure VIII the display of two sharp singlet bands at δ 6·55 and δ 6·70, consistent with the absence of aromatic vicinal coupling, confirmed the attachment of the methyl group to be at $C_{3'}$.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were measured on an Unicam SP 200 spectrophotometer. UV spectra were determined on a Zeiss RPQ 20 A self-recording spectrophotometer and the NMR spectra on a Varian A-60 spectrometer with $CDCl_3$ as a solvent and TMS as an internal reference.

(±)-*trans*-1β-*Hydroxy*-8β-*methyl*-4,5-(4'-*oxo*-2',3',4',5'-*tetrahydrobenzo*) *hydrindane* (IV). To a soln of III* (14·5 g) in 150 ml EtOH, oxalic acid dihydrate (15·0 g), dissolved in a mixture of 250 ml EtOH and 50 ml water was added under stirring at 25° in 30 min. After stirring this soln for 2 hr, it was poured into a 100 ml sat. NaCl aq. The resulting mixture was neutralized with a calculated amount of $NaHCO_3$ and extracted with ether. The organic layer was washed with sat. NaCl aq and dried ($MgSO_4$). Evaporation

* Prepared from the corresponding methoxy ether II according to the procedure described by Chinn and Dryden.[10] The latter system was synthesized, with some alterations, following the procedure of Banerjee *et al.*;[9] however, the Stobbe condensation was carried out according to a recently published method.

of the solvent gave 12·5 g (91%) of IV as a colourless viscous oil. The UV spectrum of the crude material (EtOH): 234 (ε = 750) nm indicated the presence of less than 5% of the conjugated isomer[10] and showed further no significant absorption. ν_{max}^{liq} at 3450, 1708, 1380, 1070 and 1050 cm^{-1}. The NMR spectrum showed a singlet at δ 0·75 (3p, Me) and a triplet at δ 3·78 (1p, 1-H).

(±)-*trans*-1β-*Hydroxy*-8β-*methyl*-4,5-(3'-*hydroxymethylene*-4'-*oxo*-2',3',4',5'-*tetrahydrobenzo*) *hydrindane* (VI). Sodium methoxide (1·73 g; 0·032 mole) was freshly prepared by adding Na to dry MeOH, evaporating the resulting soln to dryness and heating the remaining alkoxide at 180° and 15 mm for 2 hr. The powdered alkoxide was added to a soln of 3·88 g (0·052 mole) over P_2O_5 dried and distilled ethyl formate in 50 ml dry toluene. The resulting suspension was stirred at 0° under N_2 for 45 min. A soln of 4·80 g (0·022 mole) of IV in 40 ml dry toluene was added dropwise under vigorous stirring at 0° in 1 hr. After stirring the mixture at room temp (N_2) for an additional 15 hr, water was added and the organic layer extracted with water. The aqueous solns were combined, washed with ether, cooled to 0° and cautiously acidified with dil HCl aq (pH 5). The yellow ppt was filtered off and dried to yield 3·55 g (65%) of VI, m.p. 156–158°, after recrystallization from EtOH–water 162–165°. (Found: C, 72·66; H, 8·13; $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%); UV (EtOH): 277 (ε = 8100) nm; IR (KBr): 3140, 1680, 1600, 1210 and 1040 cm^{-1}. NMR signals were displayed at δ 0·76 (s 3p, Me), δ 2·90 (s 4p, 2'-H_2 and 5'-H_2), δ 8·22 (s 1p, =CHOH). Working up of the toluene layer of the reaction mixture afforded 1·25 g of a colourless oil of which spectroscopic data (IR (liq): 3450, 1710, 1660, 1610, 1450 and 1050 cm^{-1}) indicated the presence of the starting ketone IV and its conjugated isomer V.

(±)-A-*Nor*-2-*phenyl*-2,3-*diaza*-*anthraestra*-1(6),3,8-*triene*-17-*ol* (VII). A soln of 0·50 g of VI and 0·50 ml freshly distilled phenylhydrazine in 10 ml EtOH was refluxed for 15 hr. After evaporating the solvent, the residual material was taken up in ether and the resulting soln washed with dil HCl aq, with 3% NaOH aq, H_2O and dried ($MgSO_4$). Evaporation of the solvent afforded 0·52 g of a yellow semisolid material which was dissolved in a small amount of ether and treated with n-hexane until persisting turbidity of the soln. The VII (0·35 g; 54%) crystallized from this mixture after standing for a few days. Recrystallization from benzene yielded the pure product, m.p. 186–189°. (Found: C, 78·65; H, 7·52; O, 5·08; N, 8·73; $C_{21}H_{24}ON_2$ requires: C, 78·71; H, 7·55; O, 4·99; N, 8·74%); UV (EtOH): 270 (ε = 19,500) nm; IR (KBr): 3440, 1600, 1580, 1510, 1380, 1260, 1040 and 750 cm^{-1}. The NMR spectrum showed absorptions at δ 0·79 (s 3p, Me), δ 3·22 (s 4p, 7-H_2 and 10-H_2) and δ 3·82 (t 1p, 17-H).

(±)-*trans*-1β-*Hydroxy*-8β-*methyl*-4,5-(3'-*methyl*-4'-*hydroxybenzo*) *hydrindane* (VIII). Compound VI (0·5 g) dissolved in 20 ml MeOH was hydrogenated until saturation over 0·2 g Pd–C (10%). The mixture was filtered and the filtrate evaporated to dryness. The remaining oil was taken up in ether and the resulting soln was repeatedly extracted with 10% KOH aq. Acidification with HCl aq of the alkaline soln afforded VIII (0·16 g; 34%), m.p. 67–70°, after sublimation 72–74°. (Found: C, 77·00; H, 8·59; $C_{15}H_{20}O_2$ requires C, 77·55; H, 8·68%); UV (EtOH): 212 (ε = 11,500) and 283 (ε = 4400) nm; IR (KBr): 3460, 1615, 1580, 1500 and 1060 cm^{-1}. The NMR spectrum showed signals at δ 0·63 (s 3p, angular Me), δ 2·18 (s 3p, PhMe), δ 6·55 (s 1p, Ph–H) and δ 6·70 (s 1p, Ph–H).

The ethereal soln (see above), after washing with 10% KOH aq, water, sat NaCl aq, drying ($MgSO_4$) and evaporation of the solvent yielded 0·25 g of a colourless oil that presumably consisted of a mixture of saturated methyl ketones as was indicated by its spectra (IR, $CHCl_3$; 3500, 1705, 1460 and 1260 cm^{-1}). No change in the spectra was observed upon refluxing this mixture with HCl aq in EtOH.

Formylation of $\Delta^{1(9)}$-*octalone*-2 (IX). Under the conditions outlined for the preparation of VI, 2·00 g (0·013 mole) of ketone IX* dissolved in 15 ml anhyd toluene was added dropwise at 0° to a suspension of 1·0 g (0·018 mole) freshly prepared MeONa and 1·85 g (0·025 mole) ethyl formate in 10 ml toluene. Following the earlier described procedure, 1·65 g (70%) of XI was isolated, m.p. after recrystallization from EtOH–water 90–91°. (Found: C, 74·05; H, 7·96; $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92%); UV (EtOH): 276 (ε = 7500) nm; IR (KBr): 3280, 1700, 1610, 1430, 1390, 1318, 1190 and 1170 cm^{-1}. The NMR spectrum displayed absorptions at δ 2·88 (s 4p, 1-H_2 and 4-H_2) and δ 8·78 (s 1p, =CHOH).

Working up of the toluene layer of the reaction mixture afforded 0·45 g of a colourless oil of which the spectroscopic data indicated the presence of ca. 70% IX and 30% X. UV (EtOH): 236 (ε = 10,600) nm;† IR (liq): 1710, 1670, 1620, 1455, 1200 and 860 cm^{-1}.

Formylation of $\Delta^{9(10)}$-*octalone*-2 *in benzene or toluene.* Ketone X‡ (9·40 g; 0·063 mole), MeONa

* Prepared from 6-methoxy-5,8-dihydrotetraline.

† UV spectrum of IX (EtOH): 238 (ε = 16,100) nm.

‡ Prepared from 6-methoxy-5,8-dihydrotetraline[19] by treatment with a solution of oxalic acid dihydrate in EtOH–water, analogous to the procedure described for the preparation of IV.

(3·78 g; 0·070 mole) and ethyl formate (7·60 g; 0·103 mole) in 50 ml anhyd toluene afforded, after following the procedure described for the formylation of IX in toluene, 8·66 (78%) of XI, m.p. after recrystallization from EtOH–water 90–92°. (Found: C, 74·09; H, 8·04; $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92%); UV (EtOH): 275 (ε = 7500) nm. The IR and NMR absorptions were identical with those indicated immediately above. From the toluene layer of the reaction mixture was obtained 1·8 g of a colourless liquid that presumably consisted of ca. 70% IX and 30% X as indicated by its IR and UV (EtOH): 236 (ε = 10,800) nm[21] spectra.

Using benzene instead of toluene in the described procedure afforded XI in 70% yield.

Reaction medium t-*butanol.* To a stirred soln of 0·80 g (0·020 at) K and 2·50 g (0·034 mole) ethyl formate in 15 ml dry t-butanol, 3·0 g (0·02 mole) of X* dissolved in 15 ml t-butanol, was added under the conditions described above. After the mixture was stirred under N_2 for 15 hr, most of the solvent was evaporated and the residue diluted with water. The aqueous soln was washed with ether, cooled to 0° and acidified to give 2·3 g (64%) of a crystalline hydroxymethylene ketone, identical with XI prepared as described above.

Reaction medium ethanol. Ketone X[22] (3·00 g; 0·020 mole), 0·46 g (0·02 at) Na and 2·50 g (0·034 mole) ethyl formate in 25 ml anhyd EtOH yielded 0·7 g (20%) of XI by following the procedure, described for the formylation of X in t-butanol. In addition to XI, 2·0 g of a mixture of IX and X was isolated, of which the UV (EtOH): 235 (ε = 10,100) nm[21] indicated the presence of ca 65% IX and 35% X.

2H-1,4,5,6,7,8-*Hexahydronaphto*[2.3-c]*pyrazole* (XIIa). After refluxing a mixture of 2·0 g XI, 30 ml hydrazine hydrate and 25 ml EtOH for 10 hr, most of the solvent was evaporated and the residue diluted with water. The crystalline ppt was collected and dried (1·62 g; 83%; m.p. 134–138°) and recrystallized from EtOH–water, m.p. 141–142°. (Found C, 76·00; H, 8·03; N, 16·09; $C_{11}H_{14}N_2$ requires: C, 75·82; H, 8·10; N, 16·08%); UV (EtOH): 221 (ε = 4000) nm; IR (KBr): 3160, 3110, 1605, 1435, 1175 and 965 cm^{-1}. The NMR spectrum showed absorptions at δ 3·10 (s 4p, 1-H_2 and 4-H_2) and δ 7·30 (s 1p, H at C-atom pyrazole ring).

2-*Phenyl*-1,4,5,6,7,8-*hexahydronaphto*[2.3-c]*pyrazole* (XIIb). Following the procedure described for the preparation of VII, reaction of 2·0 g XI and 4 ml freshly distilled phenylhydrazine in 40 ml EtOH yielded 1·95 g (70%) of XIIb, m.p. 113–115°, after recrystallization from EtOH 114·5–115°. (Found: C, 81·45; H, 7·31; N, 11·15; $C_{17}H_{18}N_2$ requires: C, 81·56; H, 7·25; N, 11·19%); UV (EtOH): 211 (ε = 15,500), 270 (ε = 21,000) nm; IR (KBr); 1600, 1575, 1510, 1380, 1040, 950 and 740 cm^{-1}. In the NMR spectrum the absorption of the methylene protons at C_1 and C_4 were observed as a multiplet at δ 3·07.

Treatment of XI *with hydrogen and* Pd-C (10%). After hydrogenation of 3·5 g XI via the procedure outlined for VI, 1·0 g (31%) of 6-hydroxy-7-methyltetraline was isolated, m.p. 88°, after sublimation 89·5–90·5° (lit:[18] 88–89°) (Found: C, 81·26; H, 8·67; $C_{11}H_{14}O$ requires: C, 81·44; H, 8·70%); UV (EtOH): 212 (ε = 9000) and 283 (ε = 2750) nm; IR (KBr): 3400, 1620, 1590, 1520, 1260, 1200 and 865 cm^{-1}. In the NMR spectrum the Me group was observed as a singlet at δ 2·25 and the aromatic protons as two singlets at δ 6·42 and δ 6·79. The alcali-insoluble material of the reaction mixture showed no significant UV absorption and consisted presumably of a mixture of saturated 3-methyl-2-decalones, as indicated by its NMR and IR (liq): 1605, 1450, 1190 and 1090 cm^{-1} spectra.

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* Prepared from 6-methoxy-5,8-dihydrotetraline[19] by treatment with a solution of oxalic acid dihydrate in EtOH–water, analogous to the procedure described for the preparation of IV.

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