cyanide (0.32 mol). The mixture was stirred at 60–70° for 1 hr, cooled, diluted with 30 ml of $H_2O$, acidified to pH 5 with HOAc, diluted with 150 ml of $H_2O$, and filtered. The crude product was crystallized from DMF–$H_2O$: yield 19.7 g; 34%; mp 284–285°; ir bands at 3230 (NH) and 2220 $cm^{-1}$ (CN) *Anal.* ($C_{18}H_{10}Cl_2N_2O_2$) C, H, N.

**Preparation of Symmetrically Substituted Pulvinic Lactones (VII, X = 3-Cl).** The above imino lactone (19.7 g, 55 mmol) was refluxed with 250 ml of AcOH, 125 ml of $H_2O$, and 105 ml of concentrated $H_2SO_4$ for 0.5 hr. The mixture was cooled; the precipitate of crude 3,3′-dichloropulvinic acid (16 g) was filtered off, washed with water, dried, and boiled with 160 ml of $Ac_2O$ for 0.5 hr. After cooling the product was filtered off, washed with a little AcOH, and dried: 13.7 g; 69%; mp 280–282°. *Anal.* ($C_{18}H_8Cl_2O_4$) C, H.

**Preparation of Symmetrically Substituted Vulpinic Acids (IX, X = 3-Cl).** The above dilactone (13.7 g, 38 mmol) was stirred with 130 ml of methanol and 5 ml of 18 *N* NaOH (90 mmol). After 5 min the resulting clear solution was diluted with water and acidified with concentrated HCl. The precipitate of crude product was filtered off and recrystallized from toluene: 12.9 g; 86%; mp 178–180°. *Anal.* ($C_{19}H_{12}Cl_2O_5$) C, H, Cl.

**Preparation of Vulpinic Acids by Direct Conversion from Imino Lactones (IX, X = 4-Cl).** 4,4′-Dichloroimino lactone (V, X = 4-Cl, 10 g, 28 mmol) was refluxed with 60 ml of MeOH and 20 ml of concentrated $H_2SO_4$ for 17 hr. After cooling, the crude product was filtered off, washed with MeOH, and recrystallized from BuOH: 3.7 g; 34%; mp 183–185°. *Anal.* ($C_{19}H_{12}Cl_2O_5$) C, H, Cl. Karrer[8] gives mp 214–216° but we have found 183–185° for material prepared by both this route and the dilactone route described above.

**4,4′-Dihydroxypulvinic Acid (VI, X = 4-OH).** Dimethoxypulvinic lactone (VII, X = 4-OMe, 9 g, 26 mmol) was refluxed with 110 ml of constant boiling HI and 450 ml of AcOH for 2 hr. The mixture was evaporated *in vacuo* and the residue was dissolved in 300 ml of $Et_2O$. The ethereal solution was extracted with 3 × 100 ml of saturated $Na_2S_2O_3$, washed with water, dried ($Na_2SO_4$), and evaporated *in vacuo* to a glass. The glass was crystallized from water to give the product: 3.0 g; 34%; mp 330–332° dec.

**4,4′-Diacetoxypulvinic lactone (VII, X = 4-OAc)** was prepared from 1.5 g of 4,4′-dihydroxypulvinic acid by the procedure described above for VII (X = 3-Cl): 1.55 g; 87%; mp 270–272° (see Table III).

**4,4′-Dihydroxyvulpinic Acid (IX, X = 4-OH).** 4,4′-Diacetoxypulvinic lactone (1.05 g, 2.59 mmol) was stirred with 15 ml of MeOH and 0.5 ml of 18 *N* NaOH (9 mmol) for 15 min. The resulting clear solution was diluted with 15 ml of water and acidified with concentrated HCl. The product was filtered off, washed with MeOH, and dried: 0.85 g; 90%; mp 360–362°. *Anal.* ($C_{19}H_{14}O_7 \cdot 0.5H_2O$) C, H.

**Preparation of Asymmetrically Substituted Imino Lactones (XI and XII, X = 3-Cl; Y = H) (Table IV).** Diethyl oxalate (465 g, 3.18 mol) was stirred with 172 g of NaOMe (3.185 mol) in 3 l. of dioxane (dried over molecular sieve type 4A) for 1 hr. *m*-Chlorobenzyl cyanide (475 g, 3.135 mol) was added and stirred for a further hour. The resulting solution of the sodium enolate of X (X = 3-Cl) was added to 376 g of benzyl cyanide (3.213 mol) which had been stirred with 690 g of NaOMe (12.8 mol) in 3 l. of dry dioxane for 2 hr. The resulting mixture was stirred for 20 hr, then poured into 100 l. of water, and acidified to pH 1 with concentrated HCl. The precipitate of crude product was filtered off, washed with EtOH, and dried: 510 g; 50.4%; mp 272–273°. This mixture of imino lactones was converted to 300 g (58.4%) of 3-chloropulvinic lactone (XIII, X = 3-Cl; Y = H) and then to 326 g (98.9%) of a mixture of vulpinic acids (XIV and XV, X = 3-Cl; Y = H) by exactly the same procedures as those described above for the symmetrical compounds.

**Separation of Isomeric Vulpinic Acids (XIV and XV, X = 3-Cl; Y = H).** The mixture of the two vulpinic acids (326 g) was dissolved in 3.3 l. of boiling MeOAc, cooled, and filtered. The residue (211 g) was recrystallized from 750 ml of MeOAc to give pure 3′-chlorovulpinic acid (XV, X = 3-Cl; Y = H): 160 g; 97%; mp 240–242°. *Anal.* ($C_{19}H_{13}ClO_5$) C, H, Cl. The filtrate from the original crystallization was evaporated *in vacuo* to 1 l. and cooled. The resulting precipitate (112 g) was recrystallized from 600 ml of MeOAc to give pure 3-chlorovulpinic acid (XIV, X = 3-Cl; Y = H): 63 g; mp 165–166°. *Anal.* ($C_{19}H_{13}ClO_5$) C, H, Cl. A further 28 g of 3-chlorovulpinic acid was recovered from the two mother liquors to give a total yield of 56%. The percentage yields calculated in this separation are based upon an equal distribution of isomers in the mixture. The differences in the nmr spectra of the two compounds are discussed in the text.

**Acknowledgments.** We are indebted to Drs. G. E. Davies, D. P. Evans, and B. B. Newbould for biological evaluations, Mr. C. Howarth for microanalyses, Mr. D. Greatbanks for nmr data, and Miss S. J. Alcock for the toxicological data.

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# *Notes*

## Hydroaromatic Analogs of 2-Nitro-1,3-indandiones

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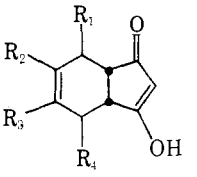
During a search for new antiallergic drugs we have previously reported potent activity, as measured by the rat passive cutaneous anaphylaxis or PCA test, in a series of 2-nitroindandiones **1**.[1] We now report our continuation of this work which has led to a study of analogous systems in which the aromatic or "support" ring has undergone varying degrees of saturation. Two series, the tetrahydroaromatic system **2** and the perhydroaromatic system **3**, both of which are novel, were synthesized and screened for biological activity. A dramatic reduction in activity in the rat PCA test relative to the aromatic indandione analogs was shown by compounds containing these systems.

In the indandiones **1** the aromatic ring necessarily confers planarity on the overall system with the effect of giving the molecule a plane of symmetry. This symmetry is more obvious when the preferred nitronic acid tautomer of

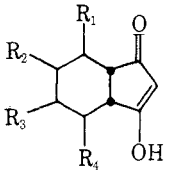
**Table I.** 3a,4,7,7a-Tetrahydroindan-1,3-diones



| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Mp (MeOH), °C | Lit. mp, °C | Formula | Analyses | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| 7 | Me | H | H | H | 139–140 | 145–146[a] | $C_{10}H_{12}O_2$ | C, H | 31 |
| 8 | H | Et | H | H | 92 | | $C_{11}H_{14}O_2$ | C, H | 61 |
| 9 | OAc | H | H | H | 168 | 162–163[b] | $C_{11}H_{12}O_4$ | C, H | 50 |
| 10 | $CO_2Me$ | H | H | H | 195–196 | 183–184[a] | $C_{11}H_{12}O_4$ | C, H | 14 |
| 11 | $CO_2H$ | H | H | H | 182 | 191[a] | $C_{10}H_{10}O_4$ | H; C[c] | 17 |
| 12 | Me | H | H | Me | 210 | | $C_{11}H_{14}O_2$ | C, H | 59 |
| 13 | H | Me | Me | H | 157–158 | 169.5–170.5[d] 178–178.5[e] | $C_{11}H_{14}O_2$ | C, H | 73 |
| 14 | 1-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 183 | | $C_{10}H_{10}O_2$ | C, H | 73 |
| 15 | 2-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 264 | | $C_{11}H_{12}O_2$ | C, H | 24 |

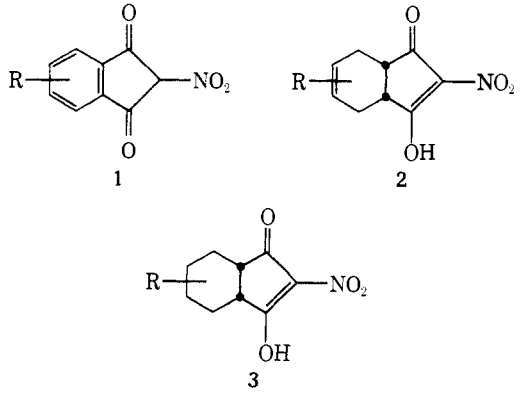
[a] H. O. House and G. H. Rasmusson, *J. Org. Chem.*, 28, 27 (1963). [b] V. P. Kucherov, T. A. Severina, L. N. Ivanova, G. A. Kogan, and B. A. Rudenko, *Izv. Akad. Nauk SSSR*, 1428 (1963). [c] C: calcd, 61.86; found, 61.05. [d] C. H. DePuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, 81, 4920 (1959). [e] V. F. Kucherov and L. I. Ivanova, *Dokl. Akad. Nauk SSSR*, 131, 1077 (1960).

**Table II.** Hexahydroindan-1,3-diones



| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Mp (MeOH), °C | Lit. mp, °C | Formula | Analyses | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| 16 | Me | H | H | H | 122 | | $C_{10}H_{14}O_2$ | C, H | 75 |
| 17 | H | Et | H | H | 89–90 | | $C_{11}H_{16}O_2$ | C, H | 56 |
| 18 | OAc | H | H | H | 135–138 | 132–133[a] | $C_{11}H_{14}O_4$ | C, H | 50 |
| 19 | Me | H | H | Me | 192–193 | | $C_{11}H_{16}O_2$ | C, H | 75 |
| 20 | H | Me | Me | H | 135–137 | | $C_{11}H_{16}O_2$ | C, H | 96 |
| 21 | 1-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 175–177 | 166–166.5[b] | $C_{10}H_{12}O_2$ | C, H | 74 |
| 22 | 2-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 254–255 | | $C_{11}H_{14}O_2$ | C, H | 84 |

[a] V. P. Kucherov, R. A. Severina, L. N. Ivanova, G. A. Kogan, and B. A. Rudenko, *Izv. Akad. Nauk SSSR*, 1428 (1963). [b] V. P. Kucherov and L. I. Ivanova, *Dokl. Akad. Nauk SSSR*, 131, 1077 (1960).

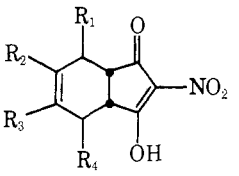


1 is considered. In the hydroaromatic derivatives 2 and 3, however, the method of synthesis necessarily produces a cis ring junction with overall bending from planarity and loss of symmetry. Moreover, the infrared spectra, which show the typical symmetric and asymmetric carbonyl bands of a non-enolic β-diketone, together with a hydroxyl group, suggest that these too exist preferentially as their nitronic acid tautomers. Possibly the difference in activity between the aromatic and reduced indandiones is reflected in the ring junction stereochemistry with the cis-fused systems being biologically less preferred. However, that the aromatic system itself is important has not yet been excluded.

The derivatives are conveniently synthesized from 4-cyclopentene-1,3-dione (4) which with 1,3-dienes has been shown[2,3] to afford good yields of the corresponding *cis*-tetrahydroindandiones (5, Scheme I). Catalytic reduction[2] of these intermediates over prereduced palladinized charcoal until 1 equiv of hydrogen is absorbed results in the hexa- or perhydroaromatic derivatives 6 in high yield.

Nitration of both 5 and 6 can be accomplished with ease at −20° with fuming nitric acid in ether, the nitro products forming in moderate to good yield. Attempts to ni-

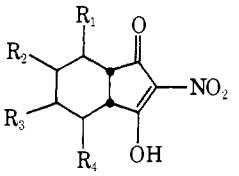
**Table III.** 2-Nitro-3a,4,7,7a-tetrahydroindan-1,3-diones



| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Mp (MeOH), °C | Formula | Analyses | Yield, % |
|---|---|---|---|---|---|---|---|---|
| 23 | Me | H | H | H | 101 | $C_{10}H_{11}NO_4$ | C, H, N | 44 |
| 24 | H | Et | H | H | 98 | $C_{11}H_{13}NO_4$ | H, N; C[a] | <5 |
| 25 | $CO_2Me$ | H | H | H | 139 | $C_{11}H_{11}NO_6$ | C, H, N | 41 |
| 26 | $CO_2H$ | H | H | H | 175 dec | $C_{10}H_9NO_6$ | C, H, N | 77 |
| 27 | Me | H | H | Me | 128–129 | $C_{11}H_{13}NO_4$ | C, H, N | 59 |
| 28 | H | Me | Me | H | 156–157.5 | $C_{11}H_{13}NO_4$ | C, H, N | 61 |
| 29 | 1-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 195 dec | $C_{10}H_9NO_4$ | C, H, N | 65 |
| 30 | 2-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 206 | $C_{11}H_{11}NO_4$ | C, H, N | 67 |

[a] C: calcd, 59.19; found, 58.36.

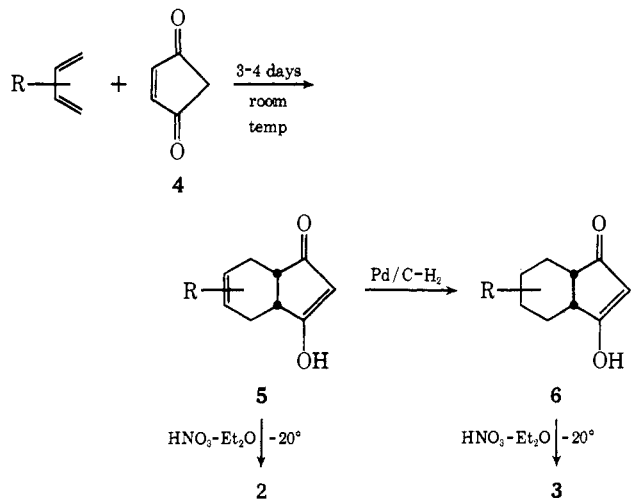
**Table IV.** 2-Nitrohexahydroindan-1,3-diones



| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Mp (MeOH), °C | Formula | Analyses | Yield, % |
|---|---|---|---|---|---|---|---|---|
| 31 | Me | H | H | H | 118–120 | $C_{10}H_{13}NO_4$ | H, N; C[a] | 58 |
| 32 | OAc | H | H | H | 147 | $C_{11}H_{13}NO_6$ | C, H, N | 59 |
| 33 | Me | H | H | Me | 111 | $C_{11}H_{15}NO_4$ | C, H, N | 60 |
| 34 | H | Me | Me | H | 169–170 | $C_{11}H_{15}NO_4$ | C, H, N | 61 |
| 35 | 1-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 167 | $C_{10}H_{11}NO_4$ | C, H, N | 63 |
| 36 | 2-C bridge $R_1R_4$; $R_2 = R_3 = H$ | | | | 199 | $C_{11}H_{13}NO_4$ | C, H, N | 67 |

[a] C: calcd, 56.86; found, 56.41.

**Scheme I**




trate the allylic acetate **9** under both the above and milder conditions were unsuccessful due to the lability of the acetate moiety. After reduction of the olefinic bond, however, facile nitration to the perhydroaromatic derivative **32** occurred.

The hydroaromatic derivatives **2** and **3** all show marked acidity, although to a lesser degree than the aromatic analogs **1** but, unlike the latter, are devoid of noticeable color.

**Biology.** Using previously described conditions[1] compounds **23–36** showed only marginal antiallergic activity in that the doses required for 50% inhibition in the rat PCA test following subcutaneous administration were all greater than 100 mg/kg. Disodium cromoglycate and 2-nitroindandione when given subcutaneously 10 min prior to challenge gave respectively $ED_{50}$ 6.7 (4.9–9.3, 147, 56) and 7.4 mg/kg (5.1–10.6, 49, 84), where the figures in parentheses are 95% confidence limits, slope of inhibition/log dose line; number of animals used.

Compounds soluble in isotonic saline buffered to pH 7 were given subcutaneously, in this solution, to different groups of six rats just before and 30 min before intravenous antigen challenge while compounds incompletely soluble at the concentrations used were given in a similar way, but as a suspension in isotonic saline buffered to pH 7 and containing 0.5% methylcellulose, just before and 60 min before challenge.

## Experimental Section

Melting points were determined using Kofler hot-stage apparatus and are recorded uncorrected. All compounds were consistent

with their ir and nmr spectra, the latter of which were determined in $CDCl_3$ for the intermediate diones and DMSO-$d_6$ for the nitro derivatives. Where analogs are represented by elemental symbols (Tables I–IV), the results for the elements fall within ±0.3% of the calculated values.

Compounds 7–15 were prepared by reaction of the appropriate diene with 4-cyclopentene-1,3-dione[4] using a modification of the procedure of House and Rasmusson.[2] In general, the dione 4 was treated with 1–2 mol of diene in benzene containing a trace of 2,5-di-*tert*-butylhydroquinone and the mixture left to stand at ambient temperature over 3–4 days. During this period the adduct usually separated as a crystalline solid. Perhydro aromatic derivatives 16–22 were readily formed by reduction of methanolic solutions of the tetrahydro adducts over prereduced palladinized charcoal until 1 equiv of hydrogen was absorbed.

Nitrations were generally carried out at −20° in anhydrous ether using fuming nitric acid. The 4-carboxy derivative 11, however, was unaffected by this treatment and required nitration at room temperature. Representative examples of the three techniques are given below by reference to the 5,6-dimethyl analogs.

**5,6-Dimethyl-*cis*-3a,4,7,7a-tetrahydroindan-1,3-dione (13).** A solution of 4-cyclopentene-1,3-dione (5.84 g, 0.06 mol) and 2,3-dimethylbutadiene (10.4 g, 0.127 mol) in dry PhH (20 ml) was treated with a trace of 2,5-di-*tert*-butylhydroquinone and left to stand at ambient temperature for 4 days. At the end of this period excess diene was expelled by refluxing for 4 hr and the adduct separated by filtration after cooling. Recrystallization from PhH–MeOH gave 7.85 g (73%) of material, mp 157–158°. *Anal.* ($C_{11}H_{14}O_2$) C, H.

**5,6-Dimethyl-*cis*-hexahydroindan-1,3-dione (20).** To prereduced 10% palladinized charcoal (0.15 g) in MeOH (15 ml) was added a solution of 5,6-dimethyl-*cis*-3a,4,7,7a-tetrahydroindan-1,3-dione (1.78 g, 0.01 mol) in MeOH (15 ml) and the mixture hydrogenated until 245 ml of hydrogen was absorbed (224 ml at NTP). After removal of the catalyst evaporation gave 1.735 g (96%) of material, mp 128–133°. Recrystallization from EtOAc–$Et_2O$ or MeOH gave material of mp 135–137°. *Anal.* ($C_{11}H_{16}O_2$) C, H.

**5,6-Dimethyl-2-nitro-*cis*-3a,4,7,7a-tetrahydroindan-1,3-dione (28).** Fuming $HNO_3$ (1.0 ml, *d* 1.52) was added dropwise to a stirred suspension of 5,6-dimethyl-*cis*-3a,4,7,7a-tetrahydroindan-1,3-dione (0.89 g, 0.05 mol) in dry $Et_2O$ (8.0 ml) at −18°. After a further 45 min at −20° the mixture was filtered, washed well with dry $Et_2O$, and recrystallized from MeOH to give 0.68 g (61%) of material: mp 156–157.5°; $\nu$ max (Nujol) 2500 (br, OH), 1670, 1575 $cm^{-1}$ (C=O); nmr (DMSO-$d_6$) $\delta$ 1.59 (6 H, s, Me), 2.18 (4 H, br s, allylic $CH_2$), 2.75 (2 H, m, bridgehead methine), 10.40 (1 H, exchangeable s, OH). *Anal.* ($C_{11}H_{13}NO_4$) C, H, N.

**5,6-Dimethyl-2-nitro-*cis*-hexahydroindan-1,3-dione (34).** Similar nitration of 5,6-dimethyl-*cis*-hexahydroindan-1,3-dione (0.89 g, 0.05 mol) with fuming $HNO_3$ afforded 0.68 g (61%) of the 2-nitro derivative as a colorless crystalline solid: mp (MeOH) 169–170°; $\nu$ max (Nujol) 2500 (br, OH), 1675, 1560 $cm^{-1}$ (C=O); nmr (DMSO-$d_6$) $\delta$ 0.72 (6 H, d, $J$ = 6.0 Hz, Me), 1.62 (6 H, br s, $CH_2$ + $C_5$ and $C_6$ methine), 2.68 (2 H, m, bridgehead methine), 11.58 (1 H, exchangeable s, OH). *Anal.* ($C_{11}H_{15}NO_4$) C, H, N.

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# 1,5-Ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepines

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1,5-Ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepine, from the $LiAlH_4$ reduction of 2-benzyloxy-1,5-ethano-4-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine, was converted to *N*-alkyl, aralkyl, cycloalkyl, and alkenyl derivatives which were inactive as morphine type analgetics in mice. The $LiAlH_4$ reduction of 2-benzyloxy-1,5-etheno-4-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine gave unstable products from which only the skeletally rearranged dihydro- and tetrahydrobenzo[*e*]isoindolines, were isolated.

The compounds described in Table I were prepared and tested as analgetics because the relatively planar 2,3,4,5-tetrahydro-1*H*-3-benzazepines, without the angular 1,5 bridge, have been found to possess analgetic action.[1] The substituents chosen for the amino group were those which often enhance this action.

The key to the synthesis of these compounds was the reported[2] conversion of 1 to 2 in good yield by the unusual rearrangement shown in Scheme I. The acyl azide 1 was prepared as described[2] by heating ethyl diazoacetate with excess naphthalene and the elimination of nitrogen gave ethyl benznorcaradienecarboxylate. The nitrosation of the hydrazide obtained from this ester with hydrazine gave 1. Comments on its conversion to 2 are given in the Experimental Section. Compound 2 was hydrogenated to 3 and the latter was reduced with $LiAlH_4$ to 7. This compound was converted to the other compounds in Table I by the usual procedures indicated in the footnotes.

Attempts to obtain 4, an original goal, by the $LiAlH_4$ reduction of 2 failed. Doering and Hoffmann[2] obtained an amine from this reduction which they converted to a quaternary methiodide but its structure was not determined. In our hands this reduction of 2 in tetrahydrofuran gave products which decomposed in light and air. The hydrochloride of the basic material so obtained gave analyses acceptable for the desired 4 but its broad melting point indicated it was a mixture. A strong uv absorption at 265 nm, not shown by 2, suggested a double bond was conjugated with the aromatic ring. Its nmr spectrum indicated the presence of dissimilar vinyl protons though the lowered proportion of vinyl to aromatic protons and the presence of signals above $\delta$ 2 showed that some reduction of the double bond had occurred. This salt was unstable to light and heat and could not be purified. Its catalytic hydrogenation gave 6a as the only isolable pure product. Since acid treatment might have caused a rearrangement the hydrogenation of the mixture of free bases from the reduction was attempted with platinum and with palladium but this failed. When the $LiAlH_4$ reduction was continued for 2 days 6a was isolated as its hydrochloride directly. The structure of 6a was established by its methylation to 6b which was identical (ir and nmr spectra, melting point, and mixture melting point of its hydrochloride) with that of 6b obtained from the $LiAlH_4$ reduction of *cis*-*N*-methyl-1,2,3,4-tetrahydronaphthalene-1,2-dicarboximide. These facts suggest that 5 is a major product of this reaction. Perhaps carbanion formation at C-5 is involved in this arrangement but we can offer no mechanism.

**Pharmacology.** The compounds were tested by a modification of a published method.[3] The test, in mice, was the hind limb withdrawal response to the pinching of the limb with a forceps. Morphine sulfate at 10 mg/kg intra-