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°; ν max (Nujol) 2500 (br, OH), 1670, 1575 cm^{-1} (C=O); nmr (DMSO-d_6) δ 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°; ν max (Nujol) 2500 (br, OH), 1675, 1560 cm^{-1} (C=O); nmr (DMSO-d_6) δ 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.

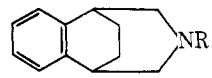
The compounds described in Table I were prepared and tested as analgetics because the relatively planar 2,3,4,5-tetrahydro-1*H*-3-benzazepines, without the angular 1,5 bridge, have been found to possess analgetic action.[1] The substituents chosen for the amino group were those which often enhance this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

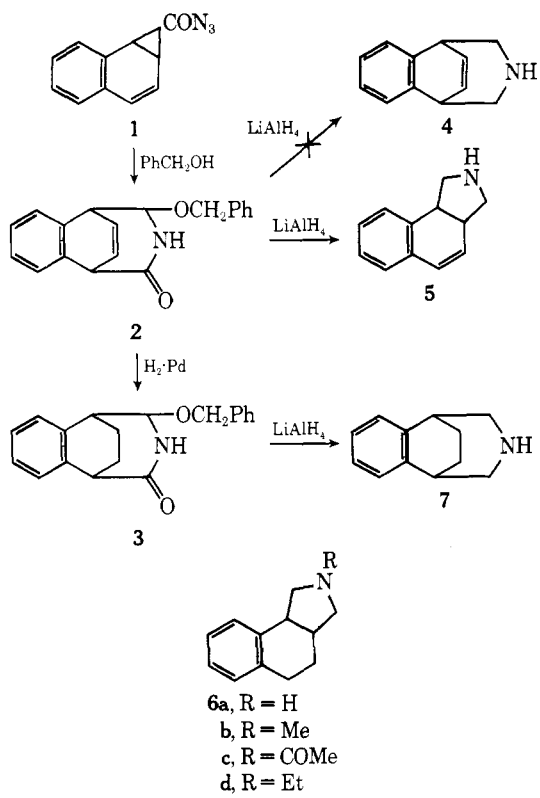
Table I. 1,5-Ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepines



No.	R	Mp, °C	Crystn solvent	Yield, %	Formula	Analyses	Doses tested, mg/kg
7	H	113–114	MeOH	86	$C_{12}H_{15}N$	C, H	
7a	H·HCl	305–308	EtOH		$C_{12}H_{16}ClN$	C, H	30 po; 10, 30[a] ip
8	Me[b]	83–84	Hexane	95	$C_{13}H_{17}N$	C, H	
8a	Me·HCl	281–283	*i*-PrOH		$C_{13}H_{18}ClN$	C, H	30 po; 30, 100[a] ip
9	$(CH_2)_2OH$·HCl[c]	220–222	*i*-PrOH	84	$C_{14}H_{20}ClNO$	C, H, N	30 po; 30, 100[a] ip
10	$CH_2CH{=}CH_2$·HCl[d]	246–247	EtOH		$C_{15}H_{20}ClN$	C, H, N	30 po; 30, 100[a] ip
11	CH_2–	49–51.5	Hexane	65	$C_{16}H_{21}N$	C, H, N	
11a	CH_2–	261–263	MeCN		$C_{16}H_{22}ClN$	C, H, N	100, 300[a] po
12	$(CH_2)_2Ph$[e]	77–79	Hexane	78	$C_{20}H_{23}N$	C, H, N	
12a	$(CH_2)_2Ph$·HCl	280–283	EtOH		$C_{20}H_{24}ClN$	C, H, N	100 po; 100, 300[a] ip
13	$COCH_2Ph$	119–121	MeOH	91	$C_{20}H_{21}NO$	C, H, N	
14	Me_2·I	251–253			$C_{14}H_{20}IN$	C, H, N	

[a] Lethal dose. [b] Prepared from 7 as described for **6b**. [c] From 7 and 1.1 mol of $(CH_2CH_2)O$ in MeCN for 12 hr at 25°. [d] From 7, 1.1 mol of C_3H_5Br, and 2 mol of anhydrous K_2CO_3; 8 hr of reflux in $(CH_3)_2CO$ with stirring. [e] From the $LiAlH_4$ reductions of 13 as described for 11.

Scheme I



peritoneally or 30 mg/kg orally was the minimal dose producing 50% of the maximum analgetic response. None of the compounds gave morphine-type analgesia at the doses tested (Table I). Also tested as their hydrochlorides (test dose, td; lethal dose, ld; in mg/kg) were **6a**, td 30 ip, 100 po, ld 100 po; **6b**, td 100 po, ld 300 po; and **6d**, td 100 po, ld 300 po. These compounds were inactive also.

Thus, the addition of a 1,5-ethano bridge to this tetrahydrobenzazepine structure inhibits analgetic activity.

Experimental Section

Melting points were taken in open capillary tubes with a Herschberg apparatus and uncorrected. Ir spectra were taken with a Perkin-Elmer Model 221 spectrometer and nmr spectra with a Varian A-60 (Me_4Si). Where analyses are indicated by symbols of the elements the results were within 0.4% of the theoretical values.

2-Benzyloxy-1,5-etheno-4-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2). This compound, prepared from 1 in 70–75% yield by Doering's method,[2] always melted at 145–150° and material with published mp 180–184° was never obtained. Its melting point sometimes was raised to 170–175° by several crystallizations from Me_2CO only to have it fall to 145–150° with another crystallization. Perhaps a trace of H_2O induced ring opening and the material was a mixture of exo and endo forms. It gave acceptable analyses, an nmr spectrum with the correct ratio of aromatic to aliphatic protons, and absorbed the theoretical amount of H_2 when hydrogenated.

2-Benzyloxy-1,5-ethano-4-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3). The above material, 10 g in 150 ml of EtOAc, was hydrogenated with 0.5 g of 5% Pd/C as described[2] and gave 9.6 g of crystals, mp 120–125°. This presumed mixture of exo and endo forms was used directly. Its crystallization from cyclohexane gave material of published mp 146–148° whose melting point fell to 125–130° in a few weeks.

1,5-Ethano-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7). A solution of 53.8 g (0.2 mol) of crude 3 in 900 ml of THF was added over 2 hr to a stirred refluxing mixture of 20 g (0.53 mol) of $LiAlH_4$ in 1800 ml of THF and refluxed for 2 hr. The cooled mixture was treated sequentially with 18 ml of H_2O, 18 ml of 15% NaOH, and 54 ml of H_2O and stirred until the excess reagent had reacted. The solids were filtered, washed with ether, stirred with 500 ml of ether until well dispersed, and again filtered and washed. The solvents were distilled and the residue was dissolved in ether and extracted with 5% HCl. Basification of the extract gave 27.5 g of crystalline product.

Attempted Preparation of 1,5-Etheno-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4). With all operations done under N_2, 15 g (0.055 mol) of 2 in 200 ml of THF was added with stirring to 6 g (0.158 mol) of $LiAlH_4$ in 400 ml of THF. The mixture gradually turned greenish-yellow and the temperature rose slowly to 35°. It was refluxed for 2 hr and worked up as described for 7. The crude product after removal of the solvent was a light yellow oil which darkened rapidly in air. An ether solution of this oil was shaken with ice-cold 5% HCl and some viscous black oil separated which was insoluble in H_2O. The dried (K_2CO_3) ether solution of the base recovered from this acid extract gave with dry HCl 6–7 g of white to blue-gray crystals, mp 180–200°. This salt could be recrystallized from MeCN or Me_2CO but with marked loss and further darkening even with N_2 passing through the solution, and the melting point was not raised. The highest melting material obtained from a reaction, mp 188–195°, gave a uv (MeOH) 265 mμ (sl sh, ε 16, 650); nmr ($CDCl_3$) δ 7.08 (s, 4 arom H), 6.32 (d, 0.4 H, J = 10 Hz), 5.62 (d, 0.4 H, J = 10 Hz), 1.32–1.90 (m, 3 H, including NH). *Anal.* ($C_{12}H_{13}N$·HCl) C, H, N.

***cis*-3a,4,5,9b-Tetrahydrobenzo[*e*]isoindoline Hydrochloride (6a).** The above salt, 5 g in 100 ml of EtOH, was hydrogenated with 0.2 g of PtO_2 and H_2 at 4.2 kg/cm^2 until uptake ceased. The catalyst and solvent were removed and the product was crystallized several times from EtOH: yield 4.2 g; mp 228–230°. *Anal.* ($C_{12}H_{15}N$·HCl) C, H.

***cis*-2-Methyl-3a,4,5,9b-tetrahydrobenzo[*e*]isoindoline (6b). Method A.** The base from 3 g of the **6a** salt above, 14.5 ml of 90% HCOOH, and 9.5 ml of 37% HCHO were heated under reflux in an oil bath for 4 hr. The mixture was cooled, 10 ml of 10% HCl was added, and it was distilled to dryness. Excess dilute NaOH was added to the residue and the product was extracted with ether, dried over K_2CO_3, and distilled: bp 130–132° (4 mm). *Anal.* ($C_{13}H_{17}N$) C, H, N.

6b hydrochloride was crystallized from MeCN: mp 175–177°. *Anal.* ($C_{13}H_{18}NCl$) C, H, N.

Method B. *cis*-1,2-Dihydronaphthalene-1,2-dicarboxylic anhydride,[4] 15 g in 200 ml of EtOAc, was hydrogenated with 2 g of 5% Pd/C and H_2 at 4.2 kg/cm^2. This gave 11 g of the *cis*-1,2,3,4-tetrahydro anhydride,[5] mp 61–63°. Anhydrous $MeNH_2$ was passed through a solution of 10 g of this anhydride in 200 ml of xylene while the temperature was raised slowly to 100°. The mixture was refluxed with removal of H_2O for 2 hr and evaporated *in vacuo* and the residue was crystallized from ether, yielding 7 g of *cis*-*N*-methyl-1,2,3,4-tetrahydronaphthalene-1,2-dicarboximide, mp 79–80°. *Anal.* ($C_{13}H_{13}NO_2$) C, H, N. This material, refluxed for 12 hr with 4 g of $LiAlH_4$ in 500 ml of ether and worked up as described for **7**, gave 4.2 g of amine identical with that obtained by method A (ir and nmr spectra, melting point, and mixture melting pont of the hydrochlorides).

***cis*-2-Acetyl-3a,4,5,9b-tetrahydrobenzo[*e*]isoindoline (6c).** The base **6a** with $(CH_3CO)_2O$ in the usual manner gave crystals, mp 76–78°, from ether. *Anal.* ($C_{14}H_{17}NO$) C, H, N.

***cis*-2-Ethyl-3a,4,5,9b-tetrahydrobenzo[*e*]isoindoline Hydrochloride (6d).** The reduction of 5 g of **6c** with 2 g of $LiAlH_4$ in 200 ml of refluxing ether for 7 hr gave the amine which with dry HCl in ether yielded 3.8 g of this salt, mp 179–180° from MeCN. *Anal.* ($C_{14}H_{19}N$·HCl) C, H, N.

3-Cyclopropylmethyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (11). A solution of 17.3 g (0.1 mol) of **7** in 500 ml of benzene was stirred and 5.3 g (0.05 mol) of cyclopropylcarbonyl chloride in 50 ml of benzene was added. After 0.5 hr the salt was filtered and the benzene was washed with dilute HCl, dilute NaOH, and H_2O. Distillation of the solvent left a viscous residue of the amide which was reduced to **11** as described for **6d**.

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Correlation of Psychotomimetic Activity of Phenethylamines and Amphetamines with 1-Octanol–Water Partition Coefficients

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In an attempt to relate the hallucinogenic potencies in man of some biologically important amphetamines and phenethylamines, the 1-octanol–water partition coefficients for 11 amphetamines were determined. Using these values and published Hansch π constants, the log P for 17 additional amines was estimated. It was found that lipophilicity, as measured by the log of the partition coefficient, may be a significant determinant of the level of hallucinogenic potency. The study also suggests that an ideal log P value for psychotomimetic activity in man may be from 2.89 to 3.72.

The persisting major problem of research with psychotomimetic agents is the relationship of activity to physicochemical and structural properties of the active drugs. For the psychotomimetic amines, correlations have been attempted between activity and (1) the energy of the highest occupied molecular orbital;[1,2] (2) ultraviolet absorption maxima and molar absorptivity;[3] (3) degree of fluorescence;[4] and (4) stability of molecular complexes with dinitrobenzene.[5] Several correlations have been suggested between activity and conformation[6-8] and between activity and ability to stimulate various physiological receptors.[9,10] Numerous other studies have focused on relating metabolism, substitution patterns, and other chemical or metabolic factors to psychotomimetic activity.

The relationship between lipophilicity and activity has not been established. While drug action ultimately may be related to chemical or electronic factors, distribution and transport to the receptor may also be important in assigning relative contributions to the various components of drug action *in vivo*. We decided to study 1-octanol–water partition coefficients of psychotomimetic amines and examine whether a relationship exists between this parameter and activity.

Method. Partition coefficients were determined in the 1-octanol–water system according to published procedures.[11] The aqueous phase was buffered to pH 7.4 using phosphate buffer and the partitioning was done at room temperature. Under these conditions the amines are partially ionized. The partition coefficients are reported as that of the neutral species with correction for ionization being made according to Albert.[12] The pK_a of 2,5-dimethoxyamphetamine, which is reported to be 9.60,[13] was used in the correction. This is identical with the pK_a reported for mescaline.[14] The additive nature of log P[15] was used to estimate this parameter for those agents for which it was not available experimentally.