New Synthesis of 4-Aryl-2,3-dihydro- and 2,3,4,5-Tetrahydro-2(1*H*)-benzazepines and Corresponding 1,3-Diones

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Phthalaldehydic acid condenses with arylacetonitriles in the presence of sodium methoxide to give, after acidification, cyanostilbene acids, **1**. These and corresponding products **2** of hydrogenation (Pd) are cyclized respectively to seven-membered imides **3** and **4**. These two imide types, as well as their respective *N*-alkyl analogs **5** and **6**, were interrelated and their structures proven by hydrogenations **3** → **4** and **5** → **6**; hydride reductions of various alkylated imides were also carried out, giving a variety of new, 2- and 4-substituted 2,3,4,5-tetrahydro-2(1*H*)-benzazepines. Basic, solvolytic ring opening of the two novel imide systems, affording additional evidence of structure, is discussed briefly.

Owing to the frequently predominant formation of tetrahydro-1-benzazepin-2-ones in either Schmidt or Beckmann expansions of α-tetralones, 2,3,4,5-tetrahydro-2(1*H*)-benzazepin-1-ones are not often readily available by such routes.[1,2] Whereas various 1,4-naphthoquinone-derived azides have been expanded similarly in both possible directions, only the 1-benzazepine-2,4,5-triones survive the conditions of the reaction, the 2-benzazepine-1,3,5-triones collapsing to ylidenephthalimidines or -phthalides.[3,4] Although a few synthetic approaches, other than ring expansion, to tetrahydro-2-benzazepines and corresponding ones are now known,[5-7] they do not appear to be general, and thus a new route to 2-benzazepines would be potentially valuable. Such a route is described in this paper.

Phthalaldehydic acid is comparable to acid chlorides in its ease of reaction with nucleophiles,[8] including carbanions.[9] We explored, among other things, condensation of phthalaldehydic acid with phenylacetonitriles, a previously unreported reaction (see Scheme I). Sodium methoxide was used to generate the arylacetonitrile anion, no stronger bases appearing to be required or to serve our purpose as well. In its first stages, this facile reaction, like others of the type, apparently is reversible. Several experiments in which manipulations under various conditions were tried led, in one instance upon neutralization of the reaction mixture, to isolation of a phthalide corresponding to the intermediate aldol (see Scheme I), and in other instances wherein work-up involved basic, aqueous conditions, to regeneration of much phenylacetonitrile. However, if reaction solutions, after condensation, were acidified *before* water was introduced, good yields of cyano acids **1a–f** were obtained.

These compounds were reduced smoothly in the presence of palladium/charcoal to cyano acids **2a–f**. Preliminary experiments with acetic anhydride on **2a** yielded only the anhydride corresponding to **2a**, and there was neither internal acylation of the methine adjacent to CN nor imide formation The conversion of benzamide-2-thioacetic acid to 1,4-benzthiazepine-3,5-dione with acetic anhydride[10] or thionyl chloride,[11] as well as the formation of thianaphthenones from benzoic acid–2-thioacetamides with acetic anhydride and bases,[10] have been reported, but such reactions are not prone to occur in compounds **2**. However, polyphosphoric acid cyclization at 100° was found to convert cyano acids **2** readily to 2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-diones, **4**. Evidence, in addition to spectra, in agreement with the cyclic imide structure was soon forthcoming. Compounds **4** had, like phthalimide, an acidic imide proton, and in the presence of such bases as sodium hydride or potassium *tert*-butoxide were alkylated readily with iodomethane and other halides, giving *N*-alkylimides **6**, and these in turn were readily reduced with lithium aluminum hydride to the cyclic amines, 2,3,4,5-tetrahydro-2(1*H*)-benzazepines, **8**. A number of compounds, **2**, **4**, **6**, and **8**, Ar being various substituted phenyl groups and pyridyl as indicated in Scheme I, and R being H, CH_3, benzyl, other aralkyl, CH_2COOR, and β- or γ-dialkylaminoethyl or -propyl groups, were easily prepared.

Cyano acids **1** were also found to by cyclized with PPA at 100°. The results were gratifying, not only inasmuch as they constituted a direct route to 2-benzazepine-1,3-diones and another route to **4**, **6**, and **8**, but also because they afforded desired indication of the stereochemistry of **1**. Heating **1a** with PPA gave **3a** with properties very similar to those of **4a**. Hydrogenation (Pd) of **3a** gave **4a**, just as **1** had given **2**. Moreover, N-methylation of **3a** to **5a** and reduction of the latter gave **6a**, identical with that from methylation of **4a**. This sequence, together with the fact that **5a** was reduced with lithium aluminum hydride to **7a**, dispelled any remaining doubts concerning the seven-membered imide structures.

The cyclization **1** → **3** demonstrates rather conclusively that cyano acids **1** are *trans*-stilbenes (*cis*-cinnamonitriles), *i.e.*, have that geometry which permits the benzoic acid group to rotate into proximity with the nitrile. This was not unexpected, since *trans*-stilbenes are normally the products of base-catalyzed condensations in which aldols or aldolates are intermediates;[12]

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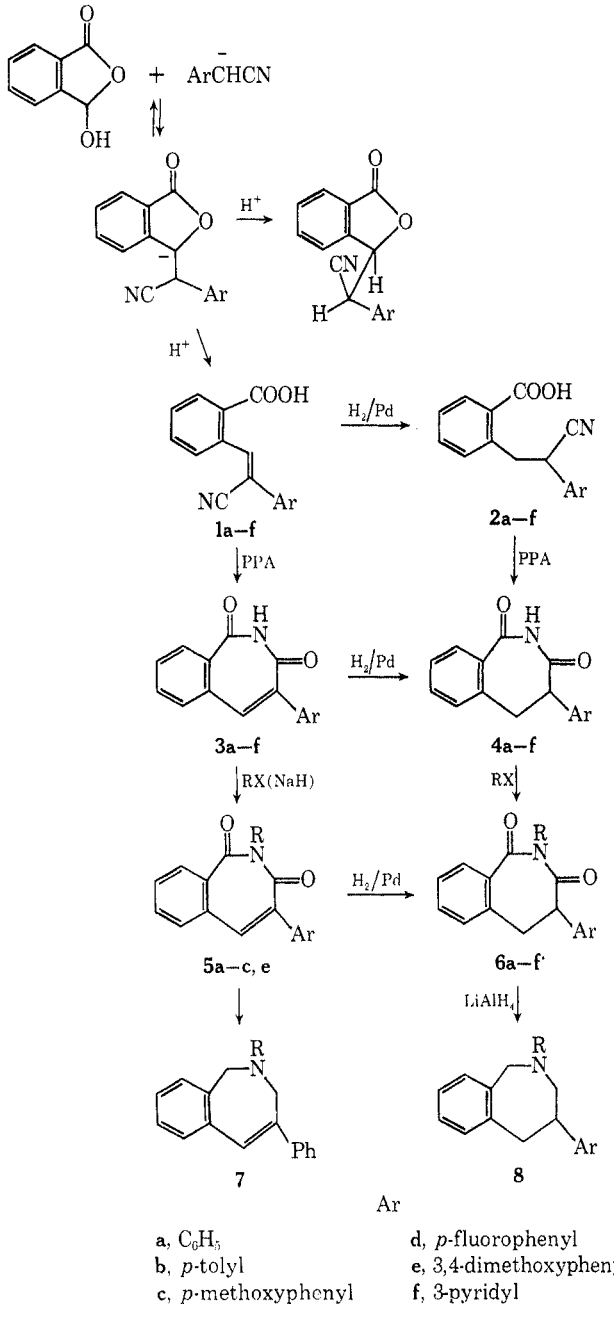
(3) H. W. Moore and H. R. Shelden, *J. Org. Chem.*, **32**, 3603 (1967).
(4) H. W. Moore and H. R. Shelden, *Tetrahedron Lett.*, 5431 (1968); 1243 (1969).
(5) M. H. Sherlock, U. S. Patents 3,225,031 (1965); 3,242,164 (1966).
(6) H. Fujimura and M. Hori, U. S. Patent 3,409,607 (1968).
(7) I. MacDonald and G. R. Proctor, *J. Chem. Soc.*, 1321 (1969); 2481 (1968).
(8) D. D. Wheeler, D. C. Young, and D. S. Erley, *J. Org. Chem.*, **22**, 547 (1957).
(9) R. C. Elderfield, *Heterocycl. Compounds*, **2**, 68 (1951).
(10) E. W. McClelland, M. J. Rose, and D. W. Stammers, *J. Chem. Soc.*, 81 (1948).
(11) R. Ponci, A. Baruffini, and F. Gialdi, *Farmaco, Ed. Sci.*, **19**, 515 (1964).
(12) See G. N. Walker, *J. Med. Chem.*, **8**, 583 (1965), and references therein.

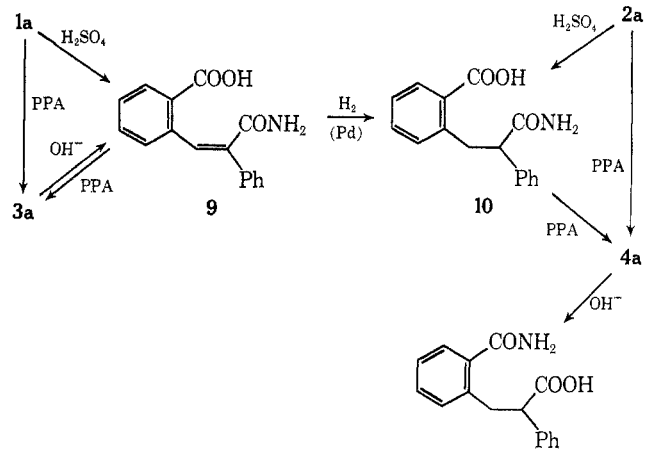
SCHEME I



furthermore, other investigators have prepared *cis*-cinnamonitrile having an *o*-carboxylic group by ring expansion of nitrosonaphthol,[13] and this acid nitrile subsequently was reported to be converted (PCl_5) to 3-chloro-2(1*H*)-benzazepin-1-one.[14]

Further evidence for structures of imides **3** and **4** and a clearer idea on mechanism of their formation from **1** and **2**, respectively, were obtained through some work with related acid amides. Treatment of **1a** with concentrated sulfuric acid did not give **3a** but rather an acid amide **9** (Scheme II). The same **9** was obtained by ring opening of imide **3a** by the action of aqueous bases stronger than sodium bicarbonate. On hydrogenation, **9** gave **10**; identical acid amide **10** and not **4a** was obtained through the action of concentrated sulfuric acid on **2a**. Base-catalyzed, hydrolytic ring opening of **4a**, however, did not give **10** but a different acid amide **11**. The saturated imides **4** thus open in a different sense than do the unsaturated imides **3**, pointing up the fact that phenylacetic acid derivatives are more liable to nucleophilic attack than are stilbene-α-carboxylic acid derivatives. While **9** and **10** were reclosed with PPA to respective imides as shown, compound **11** was not. Clearly the success of the seven-membered imide syntheses encountered here is owing to generation of a benzoylium ion from a benzoic acid moiety and its further, direct attack on nitrogen of a nitrile or carboxamide group, in molecules so constituted as *not* to present any opportunity for collapse under acidic conditions of the compounds into five- or six-membered rings.

SCHEME II



Experimental Section[15]

α'-Cyano-*trans*-stilbene-2-carboxylic Acid (1a).—To a solution of 12.6 g of sodium in 450 ml of methanol was added 64.5 g of phenylacetonitrile and then, 10–20 min later at room temperature, 75 g of phthalaldehydic acid. The solution was boiled 0.5–1.0 hr on a steam cone, allowing 50–75% of the solvent to escape. The chilled solution was neutralized by adding glacial acetic acid, acidified strongly with concentrated HCl and poured into ice water (2 l.). Alternatively, the reaction solution was poured directly into 2 l. of ice and water containing 75 ml of concentrated HCl. The colorless, very voluminous crystals were collected, washed with water, pressed dry on the filter, and then dissolved in EtOAc. The organic solution upon drying ($MgSO_4$) and evaporating gave 101 g (81%) of **1a**: mp 175–176°, raised on recrystallization (EtOAc) to mp 178–180°; ir 4.47 and 5.91 μ; uv 302 nm (ϵ 14,450).

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.14; H, 4.62; N, 5.66.

Unless the cooled reaction solution was acidified, as described, before adding water, lower yields of **1a** were obtained and much phenylacetonitrile was recovered, owing to hydroxide-catalyzed, reverse aldol reaction. In one experiment the reaction mixture was neutralized soon after addition to water, and from an ether-washed, aqueous $NaHCO_3$ extract of crude product on careful treatment with dilute acid there was isolated crystalline **3-(α-cyano-α-phenylmethyl)phthalide**, mp 207–209°, after recrystallization from EtOAc: ir 4.45 and 5.69 μ; uv 280 and 302 nm (ϵ 4540 and 4410); nmr ($CDCl_3$) J (of the two benzhydryl protons) was 4 Hz, indicating threo form. On treatment with hydrochloric acid this compound gave **1a**.

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.37; H, 4.31; N, 5.62.

(13) J. A. Elvidge and D. E. H. Jones, *J. Chem. Soc.*, 2059 (1967).
(14) G. Simchen, *Angew. Chem.*, **80**, 484 (1968).

(15) Melting points were obtained using a calibrated, Thomas–Hoover stirred silicone oil bath. Infrared spectra (Nujol mulls, unless otherwise noted) were taken on a Perkin-Elmer double beam instrument, ultraviolet spectra (methanol solutions) with a Cary recording spectrophotometer, and nmr spectra using a Varian A-60 apparatus with TMS internal standard.

TABLE I
ACID NITRILES

Acid	Mp, °C	Ir, λ, μ	Uv, λ_{max}, nm (ε)	Recrystn solvent[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1b	191–193	4.49, 5.95	309 (17,070)	a	77.55	4.98	5.32	77.55	4.69	5.06
1c	193–195	4.49, 5.94	321 (16,850)	a	73.11	4.69	5.02	73.02	4.54	4.74
1d	210–212	4.49, 5.92	302 (14,300), 284	a	71.90	3.77	5.24	72.17	3.69	5.41
1e	232–234	4.48, 5.91	330 (14,290), 248 (13,260)	b	69.89	4.89	4.53	69.84	4.72	4.35
1f	255–257	4.50, 5.95	298 (14,820), 238 (11,630)	c[b]	71.99	4.03	11.20	72.10	3.99	11.19
2b	125–127	4.44, 5.96	272 (1530)	d	76.96	5.70	5.28	76.67	5.68	5.08
2c	115–118	4.44, 5.96	275 (3050), 282 (2780)	d	72.58	5.37	4.98	72.56	5.42	4.92
2d	157–158	4.46, 5.95	269 (2010)	d	71.36	4.49	5.19	71.63	4.33	5.23
2e	176–178	4.45, 5.92	279 (4940), 285 (4380)	a	69.44	5.50	4.50	69.70	5.57	4.41
2f	238–240	4.46, 5.95	261 (3870), 267 (3140)	b[b]	71.41	4.80	11.11	71.04	4.61	10.88

[a] Recrystallized from (a) EtOAc, (b) MeOH, (c) EtOH, (d) ether. [b] Mp dec.

Following essentially the same procedure as for **1a**, other α′-cyanostilbene-2-carboxylic acids **1b–f**, listed in Table I, were prepared from phthalaldehydic acid and appropriate, commercially available phenylacetonitriles, in yields of about 80–90%. Compounds **1e** and **1f** formed exceptionally insoluble sodium salts which were readily isolated. Neutralization (HCl) of a hot water solution of the sodium salt of **1f** gave crystalline **1f**.

The nmr spectra of cyano acids **1a–f** had *inter alia* δ *ca.* 7 ppm (s, 1) signals, characteristic of the *trans*-stilbene proton.

The methyl ester corresponding to **1e** was prepared by 3-hr reflux of a solution of **1e** (26 g) in saturated, methanolic HCl (1.5 l.). The neutral product (13 g) on recrystallization from methanol gave pale yellow needles: mp 132–133.5°; ir 4.48 and 5.86 μ; uv 331 (ε 14,320) and inflection 248 nm (ε 14,130).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.68; H, 5.15; N, 4.22.

o-(2-Cyano-2-phenylethyl)benzoic Acid (2a).—Hydrogenation of a solution of 11.1 g of **1a** in 300 ml of EtOAc in the presence of 4 g of 10% Pd/C catalyst at 3 atm and 60° for 40 min until uptake ceased or slowed abruptly gave, after filtration and evaporation of solvent, a quantitative yield of **2a**: crystals from ether; mp 122–124°; ir 4.50 and 5.92 μ; uv 278 nm (ε 1370) with lesser maxima at 257, 263, and 286 nm (ε 930, 980, and 1020, respectively).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.50; H, 5.16; N, 5.55.

On a larger scale, the sodium salt of **1a** in water (ten parts) was hydrogenated similarly at room temperature, and **2a** was obtained from the filtered solution on acidification.

The anhydride of **2a** was obtained when 5 g of **2a** was refluxed 1.5 hr with 100 ml of acetic anhydride; evaporation and recrystallization of the residue from EtOAc gave crystals, mp 176–178°, ir 4.48 and 5.64 μ.

Anal. Calcd for $C_{32}H_{24}N_2O_3$: C, 79.32; H, 4.99; N, 5.79. Found: C, 79.45; H, 4.89; N, 5.78.

The corresponding diacid, **o-carboxy-2-phenylhydrocinnamic acid**, was obtained by concentrated HCl–glacial HOAc hydrolysis (3.5-hr reflux) of **2a** and was recrystallized from ether (Norit), mp 193–195°, ir 5.86–5.92 μ.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.10; H, 5.07.

Cyano acids **2b–f** (Table I) were prepared by hydrogenation of **1b–f**, as for **2a**. Compound **2e** was difficult to obtain in large amounts owing to low solubility of **1e** in both organic solvents and aqueous bases.

The methyl ester corresponding to **2e** was obtained by similar hydrogenation of the methyl ester of **1e**: colorless crystals from ether; mp 100–102°; ir 4.47 and 5.82 μ; uv 280 nm (ε 4800) and infl 284 (4360).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.40; H, 6.02; N, 4.20.

4-Phenyl-2,3-dihydro-2(1*H*)-benzazepine-1,3-dione (3a).—A mixture of 30 g of **1a** and 500 g of polyphosphoric acid was heated at 100° with stirring for 2.5 hr. The cooled, brown solution was hydrolyzed with ice and water (2 l.), and the suspension of crystals was stirred at room temperature 1–2 hr. The product was collected, washed with several portions of water, and then triturated thoroughly with 5% sodium bicarbonate solution, again collected, washed with water, and dried, yield 23 g (76.5%), mp 207–209°. Recrystallization (ethyl acetate) gave colorless crystals: mp 211–213°; ir 3.16, 3.27 (bonded NH) and 6.06 with lesser peaks 5.92, 6.18, and 6.28 μ; uv 227 and 316 nm (ε 37,600 and 11,410) with inflections at 256 and 324 (12,080 and 11,310); nmr (DMSO) δ 11.4 (s, 1, D_2O exchanged, NH), 8.4 (m, 1, peri aromatic proton), 7.9–7.2 (m, 9, aromatic and vinyl H).

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 77.20; H, 4.29; N, 5.45.

The imide was soluble in 5–10% sodium hydroxide solution and dissolved more slowly in potassium carbonate solution. On acidification of resulting solutions, there was obtained ***trans*-stilbene-2-carboxylic acid α′-carboxamide (9)**: mp 195–196° (solvated) after recrystallization from methanol–ether, and mp 184–186° after drying *in vacuo* (65°); ir 2.87 and 2.97 (intense, NH peaks), 5.85–5.91, 6.02, 6.17, and 6.32 μ; uv 254 nm (ε 10,490); nmr (DMSO) three D_2O-exchangeable protons. Treatment with PPA at 100° regenerated **3a**.

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.90; H, 4.94; N, 5.11.

This same acid amide was obtained when 4 g of **1a** was dissolved in 100 ml of concentrated H_2SO_4; the solution was let stand 7 hr and hydrolyzed (ice), and the crystalline product recrystallized from EtOAc: mp 184–185°; mmp (with sample from imide) 184–185° (undepressed); and ir spectra the same.

By the same general procedure of action of PPA on cyano acids **1**, there were also obtained the following imides **3**.

Compound 3b was obtained from 15 g of **1b** with 500 g of PPA in 10.5 g yield and crystallized from ethyl acetate as colorless crystals: mp 198–200°; ir bonded NH and 6.09 μ (sharp, intense, with shoulder 6.05 μ and lesser peaks 6.22 and 6.28 μ); uv 225 and 327 nm (ε 58,080 and 12,660).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.29; H, 4.86; N, 5.36.

Compound 3c was similarly recrystallized from EtOAc as yellow crystals: mp 208–210°; ir 3.00, 5.96 and 6.03 μ; uv 228, infl 268, and 338 nm (ε 45,080, 10,340, and 12,120).

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.4; H, 4.4; N, 4.90.

Compound 3d was obtained as colorless crystals from EtOAc: mp 196–197°; ir 3.14 (bonded), 5.94 and 6.05 μ; uv 226 nm (ε 38,080), infl 256 (12,710), and 316–324 (11,900).

Anal. Calcd for $C_{16}H_{10}FNO_2$: C, 71.90; H, 3.77; N, 5.23. Found: C, 72.2; H, 3.59; N, 5.08.

Compound 3e was obtained as light greenish yellow, dense crystals, from EtOAc: mp 223.5–226°; ir 3.19, 3.31, 5.96, 6.06, 6.15, and 6.26 μ; uv 224 nm (ε 37,810), 262–272 (12,850), 330 (9280), and infl 344 (8990); nmr (DMSO) δ 11.3 (broad s, 1, D_2O exchanged, NH), 8.3 (m, 1, peri aromatic H), 7.8–6.8 (m, 7, aromatic and vinyl H), and 3.8 (s, 6, methoxyl CH_3).

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.66; H, 4.86; N, 4.43.

Compound 3f.—After heating 10.3 g of **1f** and 74 g of PPA at 100° for 3 hr, addition of water to the cooled solution gave a very voluminous, colorless solid (9 g), mp >320°, which appeared to be a phosphate salt of **3f**. Treatment of this solid with saturated $NaHCO_3$ solution, followed by warm methanol trituration of the collected washed and dried crystals, and finally recrystallization from ethanol or methanol, gave colorless crystals: mp 249–251°; ir 5.93 and 6.08 μ; uv 228 nm (ε 30,460) and 306 (12,840) with infl 256 (14,590).

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.62; H, 4.20; N, 11.20.

2-(β-Phenylethylbenzoic acid)-β-carboxamide (10). A.—Sulfuric acid (100 ml, concentrated) solution of **2a** (10 g) after standing overnight was poured over ice, and the crystalline, bicarbonate-soluble product was collected, washed with water, dried, and recrystallized from ethyl acetate: colorless crystals; mp 203–205°; ir 2.93, 3.14, and 5.94–6.03 μ (doublet); uv 278 nm (ε 1440).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.13; H, 5.72; N, 5.09.

B.—Hydrogenation of 3 g of *trans*-stilbene-2-carboxylic acid α′-carboxamide in the presence of 2 g of 10% Pd/C catalyst in 275 ml of EtOAc and 10 ml of MeOH for 2 hr at 3 atm and 70° gave, on evaporation of the filtered solution, 2.6 g of crystals, mp 204–207°, mixture melting point with A product undepressed, and ir spectra identical.

A hemimethanolate of the acid amide, mp 208–210°, was obtained when the compound was recrystallized from methanol–ethyl acetate and dried *in vacuo* at 80°.

Anal. Calcd for $C_{16.5}H_{17}O_{3.5}N$: C, 69.46; H, 6.01; N, 4.91. Found: C, 69.29; H, 6.41; N, 4.99.

Cyclization of the acid amide with PPA at 100° gave **4a**.

4-Phenyl-2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3 dione (4a). A. By Cyclization.—A suspension of 50 g of **2a** in 650 g of PPA was heated to 95–100° and stirred for 2.5 hr. Hydrolysis of the cooled solution with ice water (2 l.) gave the crude solid which was collected, washed with water, stirred 0.5 hr with 300 ml of *ca.* 2% sodium bicarbonate solution, and again filtered, washed with water, and dried; yield of the crude imide was 35 g. Recrystallization from ethyl acetate afforded 30 g of colorless crystals: mp 175–177°, raised on further recrystallization to mp 180–182°; ir 3.15 (bonded NH) and intense, sharp peak 6.01 μ with satellite peaks 5.90, 5.95, and 6.07 μ; uv 238 nm (ε 10,980) and 284 (1750); nmr (DMSO) δ 10.9 (s, broad, 1, D_2O exchanged, NH), 7.9 [m, 1, peri (9) proton], 7.5–7.0 (m, 8, aromatic protons), 4.2 (1, doubled doublet, X of ABX, 4 proton), and *ca.* 3.3 (m, 2, poorly resolved quartet of doublets, AB of ABX, 5-methylene protons).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.74; H, 5.10; N, 5.46.

By acidification of bicarbonate wash solution from this experiment, as well as from separate, base-promoted hydrolyses of **4a**, there was obtained **2-(β-phenylethylbenzamide)-β-carboxylic acid (11)**, crystallizing from methanol as colorless crystals: mp 231–232°; ir 2.90, 3.02, 3.14, 5.80, 6.09, and 6.18–6.26 μ (doublet); uv 258 nm (ε 730) with infl 220 (15,220).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.49; H, 5.35; N, 4.97.

B. By Hydrogenation of Unsaturated Imide 3a.—A solution of **3a** (1–5 g) in EtOAc with 10% Pd/C (0.5–3 g) was shaken under 3 atm of H_2 at 70° for 3–4 hr and filtered. The solution evaporated and the residue recrystallized from EtOAc to give colorless crystals: mp 179–181°; mixture melting point with product A undepressed; ir and uv spectra identical.

By methods A or B, there were prepared in addition the following imides **4**.

Compound 4b, preferably prepared from **3b** by method B and also obtained in low yield by cyclization of **2b,** was crystallized from EtOAc: mp 206–208°; ir 3.18–3.30, 5.89–6.00–6.09 (triplet); uv 272 and 282 nm (ε 1720 and 1770) and infl 235 (11,480),

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.96; H, 6.0; N, 5.15.

Compound 4c, obtained from **3c** by method B, was recrystallized from EtOAc: mp 158–160°; ir 3.15–3.27 (bonded NH), 5.88 and 6.06 μ; uv 225 nm (ε 23,442), 276 (3054), 282 (2995), and infl 244 (11,597).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.66; H, 5.58; N, 4.90.

Compound 4d, obtained from **2d** by method A in 70% yield, was recrystallized from EtOAc: mp 180–181°; ir 3.15–3.26, 5.88, and 5.99–6.06 μ; uv 238 nm (ε 11,140), 270 (2060), and 282 (1770).

Anal. Calcd for $C_{16}H_{12}FNO_2$: C, 71.36; H, 4.50; N, 5.19. Found: C, 71.22; H, 4.62; N, 4.83.

Compound 4e was obtainable only by reduction of **3e** (method B) and, owing to sparing solubility of **3e** in EtOAc and other solvents, it was practical to reduce only *ca.* 3–4 g per run (in *ca.* 300 ml of EtOAc) using the standard Parr shaker, at 70°; on occasion the Pd/C catalyst had to be renewed and the reaction time prolonged (4–5 hr). Recrystallization from ethyl acetate gave colorless needles: mp 130.5–132.5°, still slightly solvated (nmr, EtOAc) after prolonged drying at 80°; ir 3.15–3.26 (bonded NH), 5.78–5.85 (doublet) and 6.05 μ; uv 230 nm (ε 17,200) and 279 (4230); nmr ($CDCl_3$) δ 8.6 (s, 1, slowly D_2O exchanged, NH), 8.1 (m, 1, peri 9 proton), 6.5–7.5 (m, 6, aromatic protons), 4.0 (m, 1, methine 4 proton), 5.19 and 5.22 (singlets, 3 each, methoxyl CH_3), 2.9–3.4 (m, 2, methylene protons), and EtOAc fingerprint.

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.27; H, 5.94; N, 4.20.

Compound 4f was prepared by PPA (150 g) cyclization of **2f** (5 g) following method A. The phosphoric acid solution obtained on treatment of the reaction mixture with water was treated with $NaHCO_3$ to precipitate the product which was collected, washed with water, dried (yield, 4.4 g), and recrystallized from EtOAc: colorless crystals; mp 220–222°; ir 5.92 and 6.00 μ and bands indicating zwitterionic transfer of imide proton to pyridyl N; uv 242 nm (ε 12,370), 282 (1750), and infl 267 (3790).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.71; H, 4.68; N, 11.14.

2-Methyl-2,3-dihydro-4-phenyl-2(1*H*)-benzazepine-1,3-dione (5a) (R = CH_3).—A solution of 10 g of **3a** in 80 ml of DMF was treated with 1.9 g of 56% sodium hydride (oil); after stirring a few minutes at ambient temperature, there was added 45 ml of iodomethane. The mixture was stirred 5 hr. About half of the DMF was removed *in vacuo*, and the residue was treated with cold water. Ether extract of the organic material was washed thrice (water), dried ($MgSO_4$), and evaporated. The residue on trituration with ether gave 8.9 g of colorless crystals, mp 125–127°. A sample, recrystallized from ether, had mp 126.5–127.5°; ir 5.95, 6.07, and 6.15 μ; uv 233 nm (ε 32,630) and 306 (11,720); nmr ($CDCl_3$) δ 8.26 (m, 1, peri 9 proton), 7.3–7.75 (m, 8, remaining aromatic protons), 7.23 (sharp s, 1, vinyl proton), and 5.27 (s, 3, methoxy CH_3).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.29; H, 4.67; N, 5.31.

Potassium *tert*-butoxide instead of NaH, with *tert*-butyl alcohol in place of DMF, were used with equal success in the above procedure.

2-Methyl-4-phenyl-2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-dione (6a) (R = CH_3). A.—Alkylation of **4a** (5 g) with iodomethane (20 ml) in the presence of NaH (0.95 g, 56% in oil) in DMF (30 ml), following the procedure of the preceding experiment, gave 2.6 g of colorless crystals: mp 132–134°, raised on recrystallization (ether) to mp 135–136°; ir 5.88 and 6.05 μ; uv benzenoid.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.95; H, 5.45; N, 5.18.

B.—Hydrogenation of **5a** (R = CH_3) (4.4 g) in glacial acetic acid in the presence of 2 g of 10% Pd/C at 3 atm and 70° for 2 hr, evaporation of the filtered solution, and recrystallization of the product (3.8 g) from ether gave colorless crystals: mp 135–136°; mmp (with A imide) 135–136°; ir and uv spectra identical.

Other *N*-alkylimides **5** and **6**, listed in Table II, were prepared following procedures exemplified by the preceding experiments. The NaH in DMF method served well in alkylating **4** in general and **5** with basic halides (β- and γ-dimethylaminoethyl- and -propyl chlorides). In the latter *ca.* 2–3 molar equiv of chloroamine per mol of imide, and the ether-extracted products (after washing) were dried over K_2CO_3. None of the resulting imides **6** having R = $(CH_2)_{2-3}NMe_2$ were crystalline, nor could well-characterized hydrochlorides, picrates, or methiodides be obtained from many of them, and therefore in each case crude, basic side-chain substituted compounds **6** were reduced with $LiAlH_4$ according to standard methods, and the resulting dibasic amines **8** [R = $(CH_2)_{2-3}NMe_2$] characterized as corresponding dipicrates or bismethiodides, purified by recrystallization from methanol or ethanol and also listed in Table II.

Alkylation of **3** with the higher molecular weight halides was best carried out using a slight excess of the appropriate bromide or iodide, and potassium *tert*-butoxide in *tert*-butyl alcohol as basic agent and solvent, respectively, at ambient temperatures or with a brief period of gentle warming (*ca.* 40–50°) following addition of the halide. Products **5** are also listed in Table II.

Compound **6e**, R = CH_3, was obtained by hydrogenation of **5e**, R = CH_3. Compound **8a** (R = CH_2CH_2OH) was obtained from $LiAlH_4$ reduction of crude, noncrystalline **6a** (R = CH_2-COOEt).

Lithium Aluminum Hydride Reduction of Imides. General Procedure.—In 600 ml of dry ether (for neutral compound) or tetrahydrofuran (for basic imides), 20 g of $LiAlH_4$ was stirred and

TABLE II

N-ALKYLIMIDES 5 AND 6 AND REDUCTION PRODUCTS 7 AND 8[a]

Compd	R	Mp, °C	Formula
5a	$CH_2C_6H_5$	111–112	$C_{23}H_{17}NO_2$
	CH_2COOEt	104–106	$C_{20}H_{17}NO_4$
5b	CH_3	74–76	$C_{18}H_{15}NO_2$
5c	CH_3	122–124	$C_{18}H_{15}NO_3$
5e	CH_3	149–151	$C_{19}H_{17}NO_4$
6a	$CH_2C_6H_5$	99–100	$C_{23}H_{19}NO_2$
	$(CH_2)_2C_6H_5$	96–97	$C_{24}H_{21}NO_2$
	CH_2CN	123–124	$C_{18}H_{14}N_2O_2$
	$(CH_2)_2NMe_2 \cdot MeI$	191–195 dec	$C_{21}H_{27}IN_2O_3$
6b	CH_3	140–141	$C_{18}H_{17}NO_2$
6d	CH_3	122–123	$C_{17}H_{14}FNO_2$
6e	CH_3	116–118	$C_{19}H_{19}NO_4$
6f	CH_3	171–172	$C_{16}H_{14}N_2O_2$
	$CH_3 \cdot MeI \cdot {}^1/_2H_2O$	176–178	$C_{17}H_{18}IN_2O_{2.5}$
7a	$CH_3 \cdot HCl$	242–244 dec	$C_{17}H_{18}ClN$
8a	$CH_3 \cdot HCl$	218–219 dec	$C_{17}H_{20}ClN$
	$CH_2C_6H_5$	130–131	$C_{23}H_{23}N$
	$(CH_2)_2C_6H_5$	98–99	$C_{24}H_{25}N$
	$(CH_2)_2C_6H_5 \cdot HCl$	271–275 dec	$C_{24}H_{26}ClN$
	$(CH_2)_2OH \cdot$ picrate	150–151	$C_{24}H_{24}N_4O_8$
	$(CH_2)_2OH \cdot HCl$	186–188	$C_{18}H_{22}ClNO$
	$(CH_2)_3OC_6H_5$	79–80.5	$C_{25}H_{27}NO$
	$(CH_2)_3OC_6H_5 \cdot HCl$	153–155	$C_{25}H_{28}ClNO$
	$(CH_2)_2NMe_2 \cdot$ picrate	220–221 dec	$C_{32}H_{32}N_8O_{14}$
	$(CH_2)_3NMe_2 \cdot$ picrate	203–205 dec	$C_{33}H_{34}N_8O_{14}$
	$(CH_2)_3NMe_2 \cdot MeI$	261–263 dec	$C_{23}H_{34}I_2N_2$
8b	$CH_3 \cdot HCl \cdot H_2O$	173–174	$C_{18}H_{22}ClN \cdot H_2O$
	$(CH_2)_3NMe_2 \cdot$ picrate	198–200 dec	$C_{34}H_{36}N_8O_{14}$
8c	$(CH_2)_3NMe_2 \cdot$ picrate	198–200 dec	$C_{34}H_{36}N_8O_{15}$
8d	$(CH_2)_3NMe_2 \cdot$ picrate	189–191 dec	$C_{33}H_{33}FN_8O_{14}$
8e	CH_3	104–105	$C_{19}H_{23}NO_2$

[a] Satisfactory analytical values (±0.35% for C, H, and N) were reported for all compounds: Ed.

to the suspension was added 10 g of imide as a concentrated THF solution. Refluxing and stirring were continued 6–7 hr, and the cooled, stirred suspension was treated gradually with 100 ml of water, stirred 1 hr, and filtered. The solvent was evaporated, the residue dissolved in ether, and the ether solution dried (K_2CO_3) and evaporated to give crude 2,3,4,5-tetrahydro-2(1*H*)-benzazepines which were either recrystallized from ether or ethanol or converted to suitable derivatives (Table II) by standard methods.

Compound 8a, R = H, from $LiAlH_4$ (13.5 g) reduction of **4a** (6.8 g) in THF (300 ml) was obtained as a crude oil (6 g) and was converted to the corresponding hydrochloride (2.8 g): hygroscopic, colorless crystals from ethanol–ether; mp 242–243° dec; ir devoid of peaks indicating carbonyl or conjugated groups; uv 257 nm (ε 540).

Anal. Calcd for $C_{16}H_{17}N \cdot HCl$: C, 73.97; H, 6.98; N, 5.39. Found: C, 73.88, 73.63; H, 6.89, 7.07; N, 5.32.

An attempt was made to reduce **3a** to **7a** (R = H), but the resulting base was unstable to air and to acids and was not characterized.

Registry No.—**1a**, 26926-14-7; **1b**, 26926-15-8; **1c**, 26926-16-9; **1d**, 26926-17-0; **1e**, 26926-18-1; methyl ester of **1e**, 26932-25-2; **1f**, 26926-19-2; **2a**, 26926-20-5; anhydride of **2a**, 26926-21-6; **2b**, 26925-62-2; **2c**, 26925-63-3; **2d**, 26925-64-4; methyl ester of **2e**, 26925-65-5; **2f**, 26925-66-6; **3a**, 26925-67-7; **3b**, 26925-68-8; **3c**, 26925-69-9; **3d**, 26925-70-2; **3e**, 26925-71-3; **3f**, 26963-62-2; **4a**, 26925-72-4; **4b**, 26925-73-5; **4c**, 26925-74-6; **4d**, 26925-75-7; **4e**, 26925-76-8; **4f**, 26925-77-9; **5a** (R = CH_3), 26925-78-0; **5a** (R = $CH_2C_6H_5$), 26925-79-1; **5a** (R = CH_2COOEt), 26925-80-4; **5b** (R = CH_3), 26925-81-5; **5c** (R = CH_3), 26925-82-6; **5e** (R = CH_3), 26925-83-7; **6a** (R = CH_3), 26925-84-8; **6a** (R = $CH_2C_6H_5$), 26925-85-9; **6a** [R = $(CH_2)_2C_6H_5$], 26925-86-0; **6a** (R = CH_2CN), 26925-87-1; **6a** [R = $(CH_2)_2NMe \cdot MeI$], 26925-88-2; **6b** (R = CH_3), 26925-89-3; **6d** (R = CH_3), 26925-90-6; **6e** (R = CH_3), 26925-91-7; **6f** (R = CH_3), 26925-92-8; **6f** (R = $CH_3 \cdot MeI$), 26925-93-9; **7a** (R = $CH_3 \cdot HCl$), 26925-94-0; **8a** (R = H) hydrochloride, 26932-26-3; **8a** (R = $CH_3 \cdot HCl$), 26925-95-1; **8a** (R = $CH_2C_6H_5$), 26925-96-2; **8a** [R = $(CH_2)_2C_6H_5$], 26925-97-3; **8a** [R = $(CH_2)_2C_6H_5 \cdot HCl$], 26925-98-4; **8a** [R = $(CH_2)_2OH \cdot$ picrate], 26925-99-5; **8a** [R = $(CH_2)_2OH \cdot HCl$], 26926-00-1; **8a** [R = $(CH_2)_3OC_6H_5$], 26926-01-2; **8a** [R = $(CH_2)_3OC_6H_5 \cdot HCl$], 26926-02-3; **8a** [R = $(CH_2)_2NMe \cdot$ picrate], 26926-03-4; **8a** [R = $(CH_2)_3NMe \cdot$ picrate], 26926-04-5; **8a** [R = $(CH_2)_3NMe \cdot MeI$], 26926-05-6; **8b** (R = $CH_3 \cdot HCl$), 26963-63-3; **8b** [R = $(CH_2)_3NMe \cdot$ picrate], 26926-06-7; **8c** [R = $(CH_2)_3NMe \cdot$ picrate], 26963-64-4; **8d** [R = $(CH_2)_3NMe \cdot$ picrate], 26926-07-8; **8e** (R = CH_3), 26932-17-2; **9**, 26932-18-3; **10**, 26932-19-4; **11**, 26932-20-7; *threo*-3-(α-cyano-α-phenylmethyl)phthalide, 26932-27-4; *o*-carboxy-2-phenylhydrocinnamic acid, 26925-61-1.

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