TABLE V

ORGANOPHOSPHORUS-SUBSTITUTED DIARYLPHOSPHINIC ACIDS

Compd	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Phosphorus, % Calcd	Phosphorus, % Found	Equiv wt Calcd	Equiv wt Found
II[a]	53	192.5–193.5	$C_{24}H_{20}O_2P_2$	71.63	71.68	5.02	4.86	15.4	15.4	402	406
III	66	258–261	$C_{36}H_{29}P_3O_2$	73.72	73.50	4.98	4.97	15.8	15.5	586.5	575
IV	54	231–232[b]	$C_{24}H_{22}O_4P_2$[b]	66.20	65.57	5.07	4.97	14.2	14.6	436	438
V	82.5	192–196	$C_{36}H_{29}O_4P_3$	69.90	69.26	4.72	4.45	15.0	14.2	619	613
VI	86	268–270	$C_{24}H_{20}O_2P_2S$	66.40	67.15	4.64	4.91	14.3	14.6	434	436
VII[c]	93	>300	$C_{36}H_{29}O_2P_3S_2$	66.45	65.88	4.49	4.40	14.3	14.4	651	636

[a] Molecular weight by vapor pressure osmometry in chloroform, 848. [b] As the monohydrate, IV changed form at 144° and melted, resolidified at 155°, and then melted sharply at 231–232°. [c] *Anal.* Calcd: S, 9.86. Found: S, 9.63.

above, gave the corresponding 4-diphenylphosphinylbenzoic acid melting at 270–272° (lit.[18] mp 273–274°) and 4-diphenylthiophosphinylbenzoic acid melting at 180–182° (lit.[18] mp 181–182°), respectively.

Reaction of (4-Diphenylphosphinophenyl)phenylphosphinic Acid (II) and Thionyl Chloride.—A mixture of 25 ml of thionyl chloride and 2.0 g (0.0050 mole) of (4-diphenylphosphinophenyl)-phenylphosphinic acid (II) was stirred overnight at ambient temperature and then at reflux for 2 hr. The reaction mixture was cooled and the excess thionyl chloride was removed *in vacuo* by means of a water aspirator to yield a yellow oil which gradually formed a hard glass. The glass was hydrolyzed with excess water to give 1.8 g of a white solid which was recrystallized from isopropyl alcohol and water. The solid melted at 145°, resolidified at 155°, and remelted at 231–233° which is characteristic of the phosphine oxide–acid, (4-diphenylphosphinylphenyl)-phenylphosphinic acid (IV), not the tertiary phosphine–acid II starting material. The phosphine II melts sharply at 192.5–193.5°. The identity of the material as the oxide was confirmed by comparison of the infrared spectra of II and IV which showed it to be the oxide IV.

Reaction of (4-Diphenylthiophosphinylphenyl)phenylphosphinic Acid (XI) and Thionyl Chloride.—In a similar manner, 2 g (0.0046 mole) of (4-diphenylthiophosphinylphenyl)phenylphosphinic acid (VI) was allowed to react with 25 ml of thionyl chloride at reflux for 6 hr. After removal of the excess thionyl chloride, the yellow oil was hydrolyzed with water. The white solids were collected to give a nearly quantitative yield of the oxide IV and not the sulfide VI as evidenced by the melting-range characteristics of the solids. The product solids liquefied at about 145°, resolidified at 155°, and remelted at 230–232°, while sulfide VI melts at 268–270°. Comparison of the infrared spectrum of the product with those of both the corresponding sulfide VI and oxide IV further confirmed the identity of the product as the oxide IV.

Registry No.—II, 13119-04-5; III, 13135-36-9; IV, 13119-05-6; V, 13119-06-7; VI, 13119-07-8; VII, 13119-08-9.

2,5-Benzodiazocines and Intermediates[1]

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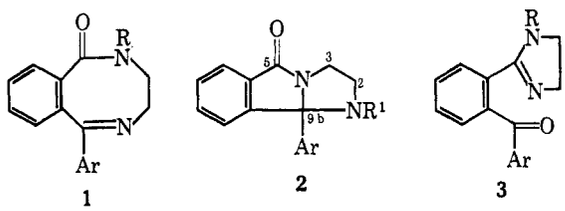
The condensation of ethylenediamines and *o*-aroylbenzoic acids has afforded a series of 9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-ones (**2**). An intermediate in the condensation has been isolated and identified as an α-(2-aminoethylimino)-α-aryl-*o*-toluic acid (**5**). An acid hydrolysis product of the imidazoisoindolones, 2-(2-aminoethyl)-3-aryl-3-hydroxyphthalimidine (**6**), could not be recyclized. The lithium aluminum hydride reduction of 1-unsubstituted 9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-ones in ether was shown to afford 1,2,3,4,5,6-hexahydro-2,5-benzodiazocines (**8**). One of the series, 1-(*p*-chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (**8a**), was resolved into optical isomers by means of *d*-camphorsulfonic acid.

Our interest in the pharmacological activity of medium-sized ring compounds[2] prompted us to examine the possibility of preparing some 2,5-benzodiazocines for biological evaluation. The recorded examples of this relatively unknown class of compounds are limited to several quaternary derivatives prepared from α,α′-dibromo-*o*-xylenes[3] and the tetrahydro-2,5-benzodiazocine-1,6-dione prepared from *o*-phthaloyl chloride and ethylenediamine.[4] A possible method of preparing 3,4-dihydro-2,5-benzodiazocin-1-ones (**1**) appeared to be through the condensation of an *o*-aroylbenzoic acid and ethylenediamine. This reaction of bifunctional molecules could, however, result in products other than the desired one or in a mixture of products. Other theoretically important possibilities would be the 1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]-isoindol-5-one (**2**) and the 2-(2-imidazolinyl)benzophenone (**3**).



Reaction of *o*-(*p*-chlorobenzoyl)benzoic acid with ethylenediamine in toluene afforded a single product with the empirical formula $C_{16}H_{13}N_2ClO$, mp 165–166°. The presence of carbonyl absorption at 5.90 μ in the infrared spectrum (KBr pellet) eliminated the benzophenone (**3**, Ar = *p*-chlorophenyl; R = H) from further consideration. The nmr spectrum of the condensation product was determined in deuteriochloroform. The spectrum consisted of a broadened, single-proton peak at δ 2.18 which disappeared on deu-

(1) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

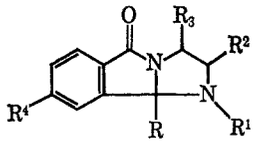
(2) (a) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962); (b) T. S. Sulkowski and S. J. Childress, *ibid.*, **28**, 2150 (1963).

(3) (a) M. Scholtz, *Ber.*, **35**, 3047 (1902); (b) W. E. Rosen, V. P. Toohey, and A. C. Shabica, *J. Am. Chem. Soc.*, **80**, 935 (1958).

(4) H. Stetter, L. Marx-Moll, and H. Rutzen, *Ber.*, **91**, 1775 (1958).

TABLE I

9b-ARYL-1,2,3,9B-TETRAHYDRO-5H-IMIDAZO[2,1-*a*]ISOINDOL-5-ONES



No.	R	R^1	R^2	R^3	R^4	Mp, °C	Yield, %	Recrystn solvent[a]	Formula	—Carbon, %— Calcd	Found	—Hydrogen, %— Calcd	Found	—Nitrogen, %— Calcd	Found
1	C_6H_5	H	H	H	H	155–157	61	A	$C_{16}H_{14}N_2O$	76.77	76.78	5.63	5.56	11.20	11.41
2	C_6H_5	C_2H_5	H	H	H	122–124	31	B–C	$C_{18}H_{18}N_2O$	77.66	77.43	6.52	6.34	10.07	9.86
3	C_6H_5	H	CH_3	CH_3	H	162–164	72	A	$C_{18}H_{18}N_2O$	77.66	77.71	6.52	6.58	10.07	10.34
4	C_6H_5	H	H	CH_3	H	149–151	93	A	$C_{17}H_{16}N_2O$	77.25	77.48	6.10	5.99	10.60	10.74
5[b]	C_6H_5	H	H	H	NO_2	203	43	A	$C_{16}H_{13}N_3O_3$	65.08	64.83	4.44	4.52	14.24	14.04
6	4-Cl-C_6H_4	C_2H_5	H	H	H	114	25	B–C	$C_{18}H_{17}ClN_2O$	69.11	69.17	5.47	5.60	8.96	8.86
7	4-ClC_6H_4	H	H	CH_3	H	130	59	B–C	$C_{17}H_{15}ClN_2O$	68.33	68.40	5.06	5.04	9.38	9.53
8	2-Thienyl	H	H	H	H	169	77	A	$C_{14}H_{12}N_2OS$	65.50	65.91	4.72	4.59	10.93	10.64
9[c]	2-Thienyl	H	CH_3	CH_3	H	152	41	B–C	$C_{16}H_{16}N_2OS$	67.57	67.68	5.67	5.70	9.85	9.81
10[d]	4-$CH_3OC_6H_4$	H	H	H	H	159	34	B	$C_{17}H_{16}N_2O_2$	72.84	72.79	5.75	5.72	10.00	10.04
11[e]	$C_6H_5CH_2$	H	H	H	H	115–117	45	B–C	$C_{17}H_{16}N_2O$	77.25	76.95	6.10	6.10	10.60	10.39
12[f]	4-FC_6H_4	H	H	H	H	193–195	67	A	$C_{16}H_{13}FN_2O$	71.62	71.52	4.88	4.72	10.44	10.19
13	4-HOC_6H_4	H	H	H	H	266–268	46	D	$C_{16}H_{14}N_2O_2$	72.16	72.10	5.30	5.38	10.51	10.23
14	3-ClC_6H_4	H	H	H	H	175–177	47	A	$C_{16}H_{13}ClN_2O$	67.47	67.24	4.60	4.29	9.85	9.78
15	4-BrC_6H_4	H	H	H	H	158–160	42	A	$C_{16}H_{13}BrN_2O$	58.37	58.47	3.98	4.05	8.51	8.52
16	4-ClC_6H_4	H	C_6H_5[g]	C_6H_5	H	227–229	75	D	$C_{28}H_{21}ClN_2O$	76.96	76.66	4.84	4.75	6.41	6.37
17[d]	4-$CF_3C_6H_4$	H	H	H	H	193–194	60	A	$C_{17}H_{13}F_3N_2O$	64.14	64.10	4.12	4.27	8.80	8.47
18	3-$CF_3C_6H_4$	H	H	H	H	140–142	46	A	$C_{17}H_{13}F_3N_2O$	64.14	64.34	4.12	4.35	8.80	8.79
19	4-$C_2H_5C_6H_4$	H	H	H	H	128–130	28	B–C	$C_{18}H_{18}N_2O$	77.65	77.64	6.52	6.80	10.06	10.35
20	3-Br-4-$CH_3C_6H_3$	H	H	H	H	191–193	42	D	$C_{17}H_{15}BrN_2O$	59.47	59.61	4.41	4.42	8.16	8.09
21[h]	3,4-$Cl_2C_6H_3$	H	H	H	H	219–221	80	A	$C_{16}H_{12}Cl_2N_2O$	60.20	59.89	3.79	3.96	8.78	8.53
22[i]	2,4-$Cl_2C_6H_3$	H	H	H	H	173–175	56	A	$C_{16}H_{12}Cl_2N_2O$	60.20	60.20	3.79	4.08	8.78	8.78
23	3-NH_2-4-ClC_6H_3	H	H	H	H	172–174	55	A	$C_{16}H_{14}ClN_3O$	64.10	64.18	4.70	4.89	14.02	14.00
24	3-NH_2-4-ClC_6H_3	CH_3	H	H	H	176–178	35	B–C	$C_{17}H_{16}ClN_3O$	65.06	65.25	5.14	5.04	13.39	13.28
25	5,6,7,8-Tetrahydro-2-naphthyl	H	H	H	H	165–167	59	A	$C_{20}H_{20}N_2O$	78.91	78.79	6.52	6.54	9.21	9.40

[a] A = ethanol, B = ethyl acetate, C = hexane, D = dimethylformamide. [b] See F. C. Hahn and E. E. Reid, *J. Am. Chem. Soc.*, **46**, 1645 (1924), for starting acid. [c] See A. T. Peters and D. Walker, *J. Chem. Soc.*, 1525 (1957), for starting acid. [d] See J. G. Topliss, L. M. Konzelman, N. Sperber, and F. E. Roth, *J. Med. Chem.*, **7**, 453 (1964), for starting acid. [e] See C. L. Arcus and R. E. Marks, *J. Chem. Soc.*, 1627 (1956), for starting acid. [f] See Hahn and Reid in footnote *b* for starting acid. [g] Preparation of *meso*-stilbenediamine: H. Irving and R. M. Parkins, *J. Inorg. Nucl. Chem.*, **27**, 270 (1965). [h] See M. Philips, *J. Am. Chem. Soc.*, **49**, 473 (1927), for starting acid. [i] See A. A. Goldberg, *J. Chem. Soc.*, 2829 (1931), for starting acid.

teration, a four-proton multiplet at 3.1–4.0 (CH_2CH_2), and an eight-proton aromatic multiplet at 7.2–7.9. The exchangeable proton at δ 2.18 is typical of an alicyclic amine proton rather than an amide proton. The observed ultraviolet absorption of λ_{max} 227 mμ (ϵ 22,700) was not increased by adjusting the pH to 1 and was similar to that of known substituted phthalimidines (isoindolones).[5] On this basis, the condensation product was assigned the imidazoisoindolone structure **2**.[6]

The condensation of *o*-aroylbenzoic acids and ethylenediamines is preferably carried out by refluxing the acid with an excess (200%) of ethylenediamine in toluene while azeotropically removing water through a Dean–Stark trap.[7] The reaction is essentially completed in about 3 hr when N-unsubstituted ethylenediamines are used, and the yields are generally good. The use of N-monosubstituted ethylenediamines requires an extended refluxing period (6–18 hr) and gives moderate yields. Table I represents some 1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-ones obtained by this procedure. These compounds are characterized by carbonyl absorption in the infrared spectra (KBr pellet) at 5.90–5.95 and NH absorption (1-unsubstituted derivatives) at 3.0–3.1 μ. The nmr spectra of 1-unsubstituted derivatives in deuteriochloroform are characterized by a broad, single-proton peak in the δ 2.1–3.0 region (alicyclic >NH). The ultraviolet absorption of the imidazoisoindolones is characterized by a strong maximum in the 223–228-mμ region.

Refluxing molar equivalents of ethylenediamine and *o*-(*p*-chlorobenzoyl)benzoic acid in toluene permitted the isolation of an intermediate product, α-(2-aminoethylimino)-α-(*p*-chlorophenyl)-*o*-toluic acid (**5a**). Cyclization of **5a** to **4a** was effected by refluxing in pyridine for 3 hr (Scheme I). The possibility that **5a** proceeded to **4a** through the phthalimidine (**6a**) was examined. The phthalimidine (**6a**) was prepared by the reaction of the pseudo acid chloride of *o*-(*p*-chlorobenzoyl)benzoic acid and ethylenediamine in pyridine.[5] The same phthalimidine (**6a**) was also obtained as the hydrochloride by hydrolysis of **4a** in 50% hydrochloric acid in a steam bath for 15 min. Refluxing **6a** in pyridine for 17 hr led to nearly quantitative recovery of the starting material. Attempts to cyclize **6a** to **4a** by refluxing in ethylenediamine, toluene, or *o*-dichlorobenzene, or without solvents at 200° were also unsuccessful. In each case, **6a** was recovered and no isolable quantities of **4a** were obtained.

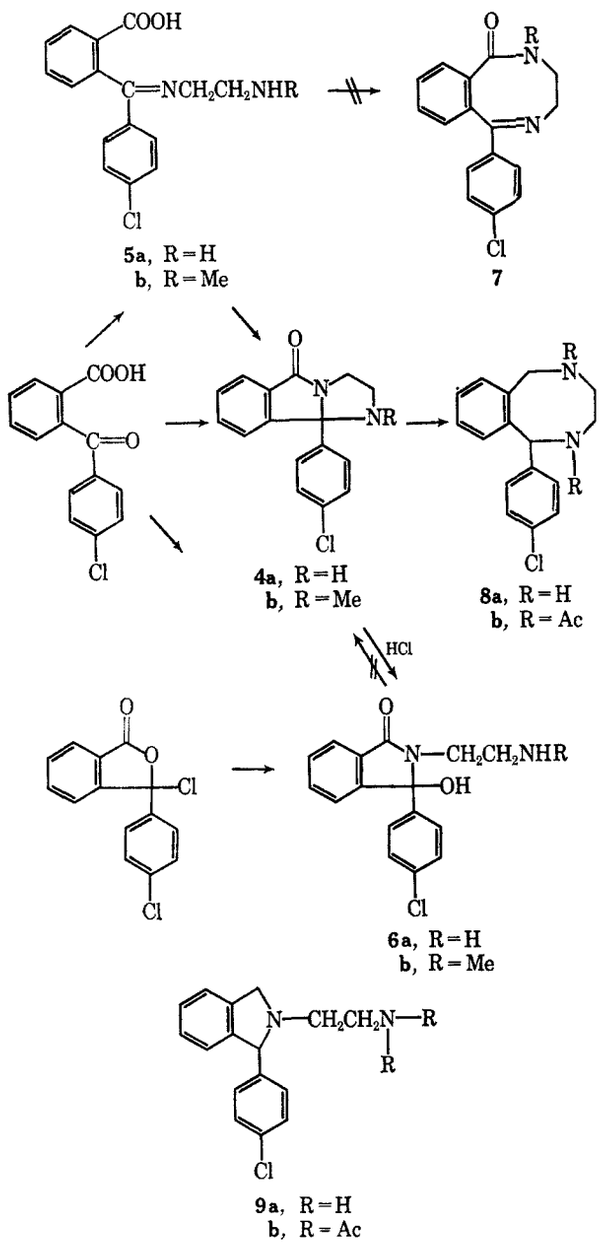
Identical results were obtained with **5b**. Refluxing **5b** in pyridine afforded **4b** (nmr in $CDCl_3$, three-proton singlet at δ 2.0, $>NCH_3$). All attempts to cyclize **6b** to **4b** afforded unchanged starting material. From the

(5) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

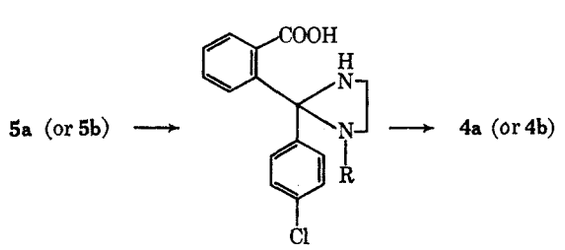
(6) These products were initially thought to be the dihydro-2,5-benzodiazocin-1-one structure: T. S. Sulkowski and M. A. Wille, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 16P. The imidazoisoindolone structure has also been assigned to these condensation products in Belgian Patent 659,530 (issued to J. R. Geigy A.-G., Aug 10, 1965); *Chem. Abstr.*, **64**, 6664 (1966).

(7) The azeotrope which separates contains about 57% (by volume) water determined by Karl Fisher titration.

SCHEME I



failures of **6a** and **6b** to cyclize to **4a** and **4b** under conditions which effect the cyclization of **5a** and **5b**, it is unlikely that the phthalimidine (**6a** or **6b**) is an intermediate in this preparation. The cyclization of **5b** to **4b** would also obviate the benzodiazocinone **7** as an intermediate in this reaction. The imidazolidine **10** could be an intermediate to **4a** (or **4b**). Addition of the amine of **5a** (or **5b**) to the imine would afford **10**. Further cyclization would lead to **4a** (or **4b**).



10

The reduction of **4a** with excess lithium aluminum hydride in ether afforded the hexahydro-2,5-benzodiazocine **8a**. The structural assignment was made on the basis of the empirical formulas and infrared spectra of the base, dihydrochloride, and the diacetyl derivative. The infrared spectrum of the base is characterized by NH absorption at 3.15 μ and the absence of absorption in the carbonyl region. The dihydrochloride is characterized by secondary amine salt bands at 3.8 μ. The absence of primary amine salt bands in the 3.0–3.5-μ region[8] favors **8a** over the alternative isoindoline structure **9a**. The presence of a single carbonyl absorption at 6.1 μ in the infrared spectrum of the diacetyl derivative supports structure **8b** since the alternative isoindoline **9b** would be expected to have two widely separated carbonyl bands in the regions 5.58–5.81 and 5.85–6.0 μ.[9] Nmr studies in deuteriochloroform further substantiated the 2,5-benzodiazocine structure assignment. The signal assignments are made as follows: aromatic multiplet (8 H) at δ 6.6–7.4, singlet (1 H) at 5.45 (benzylic proton, C-1), AB quartet (2 H) centered at 4.18 (benzylic protons at 3-6), multiplet (4 H) centered at 2.9, methylene groups at C-3 and C-4, and a singlet (2 H) at δ 1.6 (alicyclic >NH). The singlet at δ 1.6 readily disappears on deuteration.

The reduction of the imidazoisoindolones is preferably carried out by addition to lithium aluminum hydride in ether and refluxing for 16–20 hr. The use of tetrahydrofuran or dioxane results in considerably lower yields and isolation difficulties. The bases not readily isolated in crystalline form can be isolated from alcohol as stable dihydrochlorides by saturation with hydrogen chloride. Table II presents some 1-substituted hexahydro-2,5-benzodiazocines prepared by this procedure.

The reduction to 2,5-benzodiazocines is generally applicable only to the N-unsubstituted imidazoisoindolones. With N-substituted derivatives, reduction with lithium aluminum hydride appears to cause opening of the imidazo ring through the N-1–C-9b bond of **2** (R = alkyl) with no isolable amounts of the corresponding N-substituted 2,5-benzodiazocine.[10] Possibly the imidazoisoindolone is in equilibrium with the dihydrobenzodiazocinone (**2** $\rightleftharpoons$ **1**) and is reduced in this form. The fact that the N-substituted imidazoisoindolones can exist only in the tricyclic form may account for the different reduction product obtained instead of the hexahydro-2,5-benzodiazocine. There are, however, no experimental data in support of this equilibrium.

The 1-substituted hexahydro-2,5-benzodiazocines possess an asymmetric carbon at C-1. Pharmacological study requirements necessitated the resolution of one of these into the optical isomers. The resolution of **8a** was accomplished by means of *d*-10-camphorsulfonic acid into a single, crystalline salt (*l* isomer) and a viscous residue (*d* isomer). Work-up of each fraction afforded the separate pure isomer bases.

Pharmacological evaluation disclosed that the hexahydro-2,5-benzodiazocines possess strong anorectic

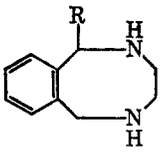
(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, pp 259, 260.

(9) Reference 8, p 221.

(10) The reduction of the 1-substituted tetrahydro-5H-imidazo[2,1-*a*]-isoindol-5-ones will be discussed in a forthcoming communication.

TABLE II

HEXAHYDRO-2,5-BENZODIAZOCINES



No.	R	Mp, °C Base	Mp, °C 2 HCl	Yield, %[a]	Formula[b]	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found
1	C_6H_5	125–127	303 dec	54	$C_{16}H_{20}Cl_2N_2$	61.74	61.49	6.48	6.50	9.00	8.79	22.78	22.61
2	4-FC_6H_4	127–129	303 dec	45	$C_{16}H_{17}Cl_2FN_2$	58.37	58.30	5.82	6.07	8.51	8.73	21.54	21.5
3	$C_6H_5CH_2$		238–239	37	$C_{17}H_{22}Cl_2N_2$	62.77	62.63	6.81	6.83	8.61	8.53	21.8	21.7
4	4-$MeOC_6H_4$	130	260	46	$C_{17}H_{22}Cl_2N_2O$	59.82	59.56	6.49	6.47	8.21	8.49	20.78	20.5
5	3,4-$Cl_2C_6H_3$		>320 dec	46	$C_{16}H_{18}Cl_4N_2$	50.55	50.88	4.77	5.06	7.37	7.41	37.31	37.1
6	2,4-$Cl_2C_6H_3$		>320 dec	24	$C_{16}H_{18}Cl_4N_2$	50.55	50.23	4.77	4.87	7.37	7.18	37.31	37.3
7	3-ClC_6H_4		315 dec	60	$C_{16}H_{19}Cl_3N_2$	55.59	55.46	5.54	5.80	8.09	8.20	30.59	30.80
8	4-BrC_6H_4	96–98	320 dec	67	$C_{16}H_{19}BrCl_2N_2$	49.25	49.41	4.91	5.10	7.18	6.94	18.17	18.3
9	4-$CF_3C_6H_4$		322 dec	56	$C_{17}H_{19}Cl_2F_3N_2$	53.83	53.62	5.05	4.77	7.38	7.04	18.69	18.6
10	3-Br-*p*-tolyl		310 dec	65	$C_{17}H_{21}BrCl_2N_2$	50.51	50.38	5.24	5.52	6.93	7.11	17.54	17.3
11	2-Thienyl	148	241 dec	42	$C_{14}H_{18}Cl_2N_2S$	52.99	52.76	5.72	6.04	8.83	8.54	22.35	22.1
12[c]	5,6,7,8-Tetrahydro-2-naphthyl	112–114		25	$C_{20}H_{24}N_2$	82.14	81.88	8.27	7.98	9.58	9.73		

[a] Yields, except for no. 12, are based on the dihydrochloride. The hydrochlorides were recrystallized from 90% ethanol. [b] Dihydrochlorides, except no. 12. [c] Base was recrystallized from cyclohexane.

properties. The pharmacology of one of these (**8a**) has been presented elsewhere.[11]

Experimental Section[12]

α-(2-Aminoethylimino)-α-(*p*-chlorophenyl)-*o*-toluic Acid (5a).—A mixture of 26 g (0.1 mole) of *o*-(*p*-chlorobenzoyl)benzoic acid, 6.6 g (0.11 mole) of ethylenediamine, and 125 ml of toluene was refluxed in a flask equipped with a Dean–Stark distillation receiver. After 0.5 hr, solid began to precipitate and bump vigorously. The mixture was cooled and the solid was separated by filtration. The solid was slurried with cold ethanol and then dried to obtain 23 g (75.9%) of white solid, mp 228–230° dec. An analytical sample was prepared from 95% ethanol: mp 230° dec; infrared spectrum, 3.4 (NH_3^+ stretching), 6.14 μ (ionized carboxyl); nmr peaks (*d*-DMSO) at δ 2.9 (2 H, broad band, CH_2), 3.4 (2 H, broad band, CH_2), 6.9 (3 H, broad band, NH_3^+, disappears on deuteration), and 7.2–8.1 (8 H, multiplet, aromatic protons).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; Cl, 11.71; N, 9.26. Found: C, 63.40; H, 4.76; Cl, 11.6; N, 9.21.

α-(2-Methylaminoethylimino)-α-(*p*-chlorophenyl)-*o*-toluic Acid (5b).—A mixture of 15 g (0.058 mole) of *o*-(*p*-chlorobenzoyl)-benzoic acid, 4.5 g (0.061 mole) of N-methylethylenediamine, and 45 ml of toluene was heated at reflux until a precipitate began to form (0.5 hr). The mixtue was cooled and the solid was separated by filtration. The solid was washed thoroughly with alcohol and then dried to obtain 8.5 g (46.5%) of granular, white solid, mp 237° dec.

Anal. Calcd for $C_{17}H_{16}ClN_2O_2$: C, 64.66; H, 5.10; Cl, 11.23; N, 8.87. Found: C, 64.41; H, 5.02; Cl, 11.0; N, 8.59.

9b-Aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-ones. General Procedure.—A mixture of 0.1 mole of *o*-aroylbenzoic acid (or ester), 0.3 mole of ethylenediamine, and 125 ml of toluene was refluxed in a flask equipped with a Dean–Stark distillation receiver until the separation of water ceases (2–18 hr).[7] The solution was filtered to remove trace impurities and then cooled. If the product would not separate on cooling, the toluene portion was extracted with water and then dried over magnesium sulfate. The solution was evaporated to dryness and the residue was recrystallized from an appropriate solvent.

9-(*p*-Chlorophenyl)-1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]-isoindol-5-one (4a). A. General Method.—A mixture of 65.3 g (0.25 mole) of *o*-(*p*-chlorobenzoyl)benzoic acid, 45 g (0.75 mole) of ethylenediamine, and 250 ml of toluene was heated at reflux in a flask equipped with a Dean–Stark distillation receiver. Water ceased separating after refluxing 2.5 hr. The hot solution was filtered and then cooled in an ice bath. The precipitated solid was separated by filtration and recrystallized from ethanol. On drying, 53 g (74%) of white crystals were obtained: mp 165–166°; infrared spectrum, 3.1 (NH), 3.5 (CH_2), 5.90 μ (carbonyl); λ_{max}^{EtOH} 227 mμ (ε 22,700), $\lambda_{max}^{0.1NHCl}$ 228 mμ (ε 21,000); nmr peaks ($CDCl_3$) at δ 2.18 (1 H, broad peak NH, disappears on deuteration), 3.1–3.9 (4 H, multiplet, CH_2CH_2), and 7.2–7.8 (8 H, multiplet, aromatic protons).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.48; H, 4.60; Cl, 12.45; N, 9.84. Found: C, 67.46; H, 4.47; Cl, 12.3; N, 9.88.

B. From 5a.—A suspension of 6.0 g (0.02 mole) of **5a** and 20 ml of pyridine was heated at reflux for 3 hr, the solution was evaporated to dryness, and the residue was extracted with ethyl acetate and water. The ethyl acetate portion was evaporated to dryness and the residue was recrystallized from ethanol. On drying, 3.5 g (61.4%) of **4a** was obtained, mp 164–166°, identical with that obtained above when compared by the usual criteria.

9b-(*p*-Chlorophenyl)-1-methyl-1,2,3,9b-tetrahydro-5H-imidazo-[2,1-*a*]isoindol-5-one (4b). A. General Method.—A mixture of 39 g (0.15 mole) of *o*-(*p*-chlorobenzoyl)benzoic acid, 33.5 g (0.45 mole) of N-methylethylenediamine, and 100 ml of toluene was heated at reflux in a flask equipped with a Dean–Stark distillation receiver. Water ceased separating after refluxing 6 hr. The solution was cooled and extracted twice with water and the toluene layer was evaporated to dryness *in vacuo*. The residue solidified on cooling. Two recrystallizations in 80% ethanol afforded 24 g (53.6%) of white crystals: mp 134–136°; infrared spectrum, 3.5 (CH_2), 5.90 μ (carbonyl); nmr peaks ($CDCl_3$) at δ 2.0 (3 H, singlet, NCH_3), 2.9–3.5 (3 H, multiplet), 3.8–4.2 (1 H, multiplet), and 7.2–7.9 (8 H, multiplet, aromatic protons); λ_{max}^{EtOH} 227 mμ (ε 22,700).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.33; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 68.18; H, 4.99; Cl, 11.8; N, 9.14.

B. From 5b.—A mixture of 2.9 g (9.0 mmoles) of **5b** and 15 ml of pyridine was refluxed for 3 hr and the solution was evaporated to dryness. Two recrystallizations of the residue from 80% ethanol afforded 1.1 g (40.8%) of **4b**, mp 134–136°, identical with that obtained above when compared by the usual criteria.

2-(2-Aminoethyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine (6a). A. Acid Chloride Method.—A solution of 28 g (0.1 mole) of pseudo acid chloride of *o*-(*p*-chlorobenzoyl)benzoic acid[7] in 50 ml of benzene was added dropwise, with stirring, to a mixture of 100 ml of ethylenediamine and 150 ml of benzene. The mixture was stirred at room temperature for 1 hr, heated for 15 min, and evaporated to dryness *in vacuo*. The residue was extracted with ethyl acetate and water. The ethyl acetate portion was evaporated to dryness to obtain 18 g of **6a**, mp 166–169°. Recrystallization in ethanol afforded 13 g of white solid: mp 169–

(11) (a) M. I. Gluckman, *Pharmacologist*, **7**, 146 (1965); (b) T. Baum, *ibid.*, **7**, 147 (1965); (c) R. J. Bower and J. B. Kopp, *ibid.*, **7**, 147 (1965).

(12) Melting points are uncorrected. Nmr spectra were obtained with the Varian A-60 instrument at 60 Mcps using tetramethylsilane as internal reference. Infrared spectra were determined in KBr on a Perkin-Elmer 21 spectrophotometer.

171°; infrared spectrum, 3.1 (NH, OH), 5.91 μ (carbonyl); nmr peaks ($CDCl_3$) at δ 2.5–3.0 (3 H, multiplet), 3.8–4.2 (1 H, multiplet), 4.2 (3 H, singlet, OH and NH_2, disappears on deuteration), and 7.1–7.9 (8 H, multiplet, aromatic protons).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; Cl, 11.71; N, 9.26. Found: C, 63.31; H, 4.80; Cl, 11.4; N, 9.02.

B. From 4a.—A mixture of 15 g (0.053 mole) of **4a** and 100 ml of 50% hydrochloric acid was heated until a clear solution formed. Solid began to precipitate immediately. The mixture was warmed for an additional 15 min and the cooled. The solid was separated by filtration, washed with cold 50% ethanol, and recrystallized from ethanol to obtain 12 g (66.7%) of **6a** hydrochloride, mp 243–245° dec.

Anal. Calcd for $C_{16}H_{16}Cl_2N_2O_2$: C, 56.64; H, 4.76; Cl, 20.91; N, 8.26. Found: C, 56.42; H, 4.79; Cl, 20.9; N, 8.23.

Conversion of **6a** hydrochloride to the base afforded **6a** identical by the usual criteria with that obtained above (A).

Attempted Cyclization of 6a to 4a.—Attempted cyclizations of **6a** by refluxing in pyridine, ethylenediamine, and *o*-dichlorobenzene, and without solvent (200°) were unsuccessful. The recovered material was shown to be identical with the starting compound by the usual criteria.

3-(*p*-Chlorophenyl)-3-hydroxy-2-(2-methylaminoethyl)phthalimidine (6b). A. Acid Chloride Method.—A solution of 42 g (0.15 mole) of pseudo acid chloride of *o*-(*p*-chlorobenzoyl)-benzoic acid and 50 ml of benzene was added dropwise to a stirred solution of 35 g of N-methylethylenediamine and 150 ml of benzene. Stirring and heating were continued for 1 additional hr. The mixture was evaporated to dryness, the residue was extracted with water and ethyl acetate, and the ethyl acetate portion was evaporated to dryness and cooled, leaving a solid residue. Recrystallization from 80% ethanol afforded 26 g (54.9%) of **6b**, mp 112–115°. The analytical sample melted at 114–116°: infrared spectrum, 3.1 (NH, OH), 5.85 μ (carbonyl); nmr peaks ($CDCl_3$) at δ 2.4 (3 H, singlet, NCH_3), 2.6–3.0, (3 H, multiplet), 4.0–4.4 (1 H, multiplet), 5.75 (2 H, broadened peak, NH and OH, disappears on deuteration), and 7.1–8.0 (8 H, multiplet, aromatic protons).

Anal. Calcd for $C_{17}H_{16}ClN_2O_2$: C, 64.66; H, 5.10; Cl, 11.23; N, 8.87. Found: C, 64.51; H, 4.95; Cl, 11.1; N, 8.61.

B. From 4b.—A mixture of 3 g (0.01 mole) of **4b** and 10 ml of 50% hydrochloric acid was warmed in a steam bath for 20 min. The mixture was cooled and the solid was separated by filtration. The hydrochloride, mp 218–220° dec, was dissolved in water and neutralized with saturated sodium carbonate solution. The mixture was extracted with ethyl acetate and the extract was evaporated to dryness. Recrystallization of the residue from 80% ethanol afforded 2.5 g (80%) of **6b**, mp 113–115°, identical by the usual criteria with that obtained above (A).

Attempted Cyclization of 6b to 4b.—Attempted cyclizations of **6b** by refluxing in pyridine and heating without solvent (200°) were unsuccessful. The recovered material was shown to be identical with the starting compound by the usual criteria.

1-(*p*-Chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (8a).—To a stirred suspension of 7.6 g (0.2 mole) of lithium aluminum hydride and 1 l. of anhydrous ether, 28.5 g (0.1 mole) of **4a** was added in portions over a period of 0.5 hr. The mixture was stirred and refluxed for 22 hr and was then hydrolyzed by cautious addition of water. The ether layer was separated and dried over magnesium sulfate and the solution was evaporated to dryness. The residue was recrystallized from an ethyl acetate–hexane mixture to obtain 15 g (55%) of **8a**, mp 106–108. The analytical sample melted at 108–109°.

Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.29; Cl, 13.0; N, 10.27. Found: C, 70.28; H, 6.29; Cl, 13.0; N, 9.99.

The hydrochloride was prepared by dissolving the base in absolute ethanol and saturating the solution with anhydrous hydrgen chloride. The solid was separated by filtration and washed with ethanol. Recrystallization from 90% ethanol afforded **8a** dihydrochloride melting at 318° dec.

Anal. Calcd for $C_{16}H_{17}ClN_2 \cdot 2HCl$: C, 55.59; H, 5.54; ionic Cl, 20.51; N, 8.11. Found: C, 55.61; H, 5.60; ionic Cl, Cl, 20.3; N, 7.83.

2,5-Diacetyl-1-(*p*-chlorophenyl)-1,2,3,4,5,6-hexahydro-2,5-benzodiazocine (8b).—A mixture of 15 g (0.055 mole) of **8a** and 25 ml of acetic anhydride was shaken until a clear solution formed (10 min). The solution was evaporated to dryness, the residue was dissolved in ethanol, and water was added to the point of cloudiness. After standing overnight, the precipitated solid was separated by filtration. Recrystallization from 95% ethanol afforded 9 g (46%) of a white, crystalline solid: mp 137–139°, infrared spectrum, 6.1 μ (single carbonyl).

Anal. Calcd for $C_{20}H_{21}ClN_2O_2$: C, 67.31; H, 5.93; Cl, 9.93; N, 7.85. Found: C, 66.99; H, 5.77; Cl, 9.9; N, 7.78.

Resolution of 8a.—A solution of 32 g (0.14 mole) of *d*-10-camphorsulfonic acid and 250 ml of absolute ethanol was added to a solution of 19 g (0.07 mole) of **8a** in 250 ml of ethanol. After 4 hr, the solid was separated by filtration and recrystallized from ethanol. The solid (20 g) was dissolved in water and made basic with 20% sodium hydroxide solution. The mixture was extracted with ether and the extract was evaporated to dryness. Recrystallization of the residue in ether afforded 6 g (63.2%) of base: mp 121–123°, $[\alpha]^{25}D$ −105.7° (1%, EtOH). The hydrochloride melted at 303° dec, $[\alpha]^{25}D$ −118.3 (1%, H_2O).

Anal. Calcd for $C_{16}H_{17}ClN_2 \cdot 2HCl$: C, 55.59; H, 5.54; Cl, 30.76; N, 8.11. Found: C, 55.27; H, 5.64; Cl, 30.4; N, 8.08.

The original mother liquor remaining after the separation of the salt was evaporated to one-third volume. The solution was cooled and a small amount of solid was separated by filtration. The solution was evaporated to dryness and the viscous residue was dissolved in water and made basic with 20% sodium hydroxide solution. The mixture was extracted with ether and the extract was evaporated to dryness. Recrystallization of the residue in ether afforded 5 g (52.6%) of base: mp 121–123°, $[\alpha]^{25}D$ +105.8° (1%, EtOH). The hydrochloride melted at 303° dec, $[\alpha]^{25}D$ +115.9 (1%, H_2O).

Anal. Calcd for $C_{16}H_{17}ClN_2 \cdot 2HCl$: C, 55.59; H, 5.54; Cl, 30.76; N, 8.11. Found: C, 55.40; H, 5.63; Cl, 30.4; N, 8.11.

***o*-Aroylbenzoic Acids.**—The keto acids which were not commercially available were prepared either by a Friedel–Crafts reaction or reaction of a Grignard reagent with a phthalic anhydride.[13]

***o*-(*m*-Chlorobenzoyl)benzoic Acid.**—The Grignard reagent prepared from 12.6 g of magnesium turnings and 95 g of *m*-bromochlorobenzene in 500 ml of ether was added to a suspension of 74 g (0.5 mole) of phthalic anhydride in 1 l. of benzene and 500 ml of ether at a rate adjusted to maintain gentle reflux. The mixture was refluxed for an additional 2 hr and then hydrolyzed by the addition of 150 ml of saturated ammonium chloride solution. The organic layer was separated, evaporated to a volume of 500 ml, and cooled. The solid that precipitated was separated by filtration and recrystallized from ethyl acetate–hexane to afford 52 g (40%) of white solid, mp 162–164°.[14]

Anal. Calcd for $C_{14}H_9ClO_3$: C, 64.49; H, 3.48; Cl, 13.60. Found: C, 64.23; H, 3.46; Cl, 13.6.

***o*-(*m*-Trifluoromethylbenzoyl)benzoic Acid.**—The Grignard reagent prepared from 100 g (0.45 mole) *m*-bromobenzene trifluoride and 10.9 g of magnesium turnings in 500 ml of ether was added to a suspension of 66.6 g (0.45 mole) of phthalic anhydride in 1 l. of benzene and 500 ml of ether at a rate adjusted to maintain gentle reflux. Reflux was continued for 14 hr and the mixture was then hydrolyzed by addition of saturated ammonium chloride solution. The organic layer was separated and evaporated to one-half volume. The mixture was cooled and the solid was separated by filtration. Recrystallization from 95% ethanol afforded 49 g (37%) of yellow crystals, mp 166–168°.

Anal. Calcd for $C_{15}H_9F_3O_3$: C, 61.24; H, 3.09; F, 19.37. Found: C, 61.51; H, 3.42; F, 19.7.

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(13) (a) See Hahn and Reid, footnote *b*, Table I; (b) see Peters and Walker, footnote *c*, Table I; (c) see Arcus and Marks, footnote *e*, Table I; (d) see Topliss, *et al.*, footnote *d*, Table I; (e) see Phillips, footnote *h*, Table I; (f) W. A. Lawrence, *J. Am. Chem. Soc.*, **42**, 1871 (1920); (g) see Goldberg, footnote *i*, Table I.

(14) German Patent 621,980 (1936) [*Chem. Zentr.*, 1507 (1936)] reports the melting point of this acid as 149–152°.