Synthesis of Varied Heterocyclic and Substituted Aryl Alkyl Secondary Amines, Related Schiff Bases, and Amides

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Following an investigation[1] of basic α,β-diarylpropionitriles (I) as potential steroid 11-hydroxylation inhibitors, it appeared advisable to extend the work in the direction of some similar benzanilide (II) and benzylaniline (III) analogs having structural similarity, with special reference to compounds in which Ar_1 and Ar_2 were aminophenyl and pyridyl groups.

$Ar_1CH_2CH(CN)Ar_2$ (I) $\quad$ $Ar_1CONRAr_2$ (II)

$Ar_1CH_2NRAr_2$ (III) $\quad$ $Ar_1(CHR)_nNH(CHR)_nAr_2$ (IV)

Accordingly, some basic amides (II) and their derivatives, listed in Table I, were first synthesized by standard procedures, the *p*-aminophenyl compounds being prepared by hydrogenation of the corresponding *p*-nitroamides. These substances were found to be devoid of interesting effects in endocrine and other pharmacological tests.

More interesting results were encountered in a series of amines (III; see Table II) which were prepared using the widely applicable method, sodium borohydride reduction of corresponding arylidenamines.[2,3] One compound in particular, an amide (III, Ar_1 = 3-pyridyl; Ar_2 = *p*-aminophenyl; R = $COCH_3$), was obtained by condensation of pyridine-3-aldehyde with *p*-nitroaniline followed by the sequence (1) sodium borohydride reduction, (2) acetylation of the resulting secondary amine, and (3) catalytic hydrogenation (Pd) of the nitro group. This substance showed effects on dog adrenocortical steroid output similar to, although weaker than, those exerted by compounds described earlier,[1] and thus appeared to mimic structurally the amphenone and metapyrone-related basic nitriles (I) reported previously. As in the latter series, the adrenocortical action was limited specifically to the 3-pyridyl analog.

Anils and benzylanilines resemble in molecular shape the numerous azo compounds, stilbenes, etc., long known to have various chemotherapeutic effects. Systems comprised of certain Schiff bases, notably those derived from pyridoxal and capable of triad prototropy,[4] have been implicated in biological mechanisms of transamination and oxidation. With these thoughts in mind, one may imagine that a program, based on general screening of a series of benzyl and benzylidene anilines substituted with a broad assortment of groups, might turn up some new directions in drug design. At least during the time (1957–1959) of our effort, and perhaps to a large extent at present as well, there is little predicting accurately what particular compounds, chosen at random from a series not previously much investigated, will alter biological oxidation or other reactions, nor on what cellular systems *in vivo* they will chance to exert a specific effect. Encouraged by reports[5] implying chemotherapeutic efficacy of unsaturated compounds incorporating the *p*-aminosalicylic acid, nicotinoyl and isonicotinoyl hydrazides, and dialkylamino (N-mustard) moieties, we commenced to prepare a series of Schiff bases and corresponding amines derived from these and other similar groups.

TABLE I

AMIDES

$Ar_1CONHAr_2$

Ar_1	Ar_2	Mp, °C	Recrystn solvent[a]	Form[b]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3-Pyridyl	3-Pyridyl	188–190	C		66.32	4.55	21.10	66.22	4.47	21.01
3-Pyridyl	2-Pyridyl	138–139[c]	C		...	...	...	...	...	...
3-Pyridyl	3-Pyridyl	240–244	A–D	G	32.32	3.13	8.70	32.65	3.44	8.82
3-Pyridyl	*o*-Hydroxyphenyl	224–226	A–C	F	57.59	5.64	11.20	57.66	5.36	11.58
p-Nitrophenyl	3-Pyridyl	228–231	A	F	...	...	15.05	...	...	14.84
p-Nitrophenyl	*p*-Hydroxyphenyl	263–265	A		60.46	3.90	10.85	60.28	4.03	11.08
p-Nitrophenyl	*p*-Nitrophenyl	265–267	A		54.36	3.16	14.63	54.60	3.24	14.93
p-Nitrophenyl	4-Pyridyl	248–250	A	E	55.17	4.24	16.09	55.09	3.60	15.91
p-Aminophenyl	3-Pyridyl	234–236	A	F	57.82	6.07	16.86	57.89	5.63	16.43
p-Aminophenyl	*p*-Hydroxyphenyl	252–254	A		68.41	5.30	12.27	67.77	5.29	12.21
p-Aminophenyl	*p*-Aminophenyl	205–207	B		68.70	5.77	18.49	68.78	5.67	18.79
p-Aminophenyl	4-Pyridyl	266–268	A	E	62.32	5.67	18.17	62.54	5.35	18.11

[a] A, methanol; B, ethanol; C, ethyl acetate; D, water. [b] Characterized as: E, monohydrate; F, dihydrate; G, methiodide. [c] C. O. Badgett, R. C. Provost, C. L. Ogg, and C. F. Woodward [*J. Am. Chem. Soc.*, **67**, 1135 (1945)] reported mp 136–137°; mp 138–139° was also reported: *Chem. Abstr.*, **29**, 2535 (1935); **36**, 3512 (1942). The corresponding 4-aminopyridineamide is also known: see *Chem. Abstr.*, **32**, 4285 (1938).

(1) G. N. Walker, *J. Med. Chem.*, **8**, 583 (1965).

(2) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).

(3) (a) G. N. Walker and M. A. Moore, *ibid.*, **26**, 432 (1961); (b) G. N. Walker, M. A. Moore, and B. N. Weaver, *ibid.*, **26**, 2740 (1961).

(4) C. H. Stammer and J. D. McKinney, *ibid.*, **30**, 3436 (1965), have reviewed this subject. See also L. F. Fieser and M. Fieser, "Topics in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1963, pp 285–286. For reduction of pyridoxal Schiff bases, see D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 1670, 3669 (1948).

(5) See, *inter alia*, H. H. Fox, *Science*, **118**, 497 (1953); C. T. Bahner, *J. Org. Chem.*, **22**, 1109, 1110 (1957); F. D. Popp, *ibid.*, **26**, 1566 (1961); H. Priewe, German Patent 859,154 (1952); *Chem. Abstr.*, **52**, 11906 (1958). The idea of chemotherapeutic compounds incorporating semilabile $-\overset{|}{N}=\overset{|}{N}-$, $-\overset{|}{N}\overset{|}{C}\overset{|}{N}-$, $-\overset{|}{O}\overset{|}{C}\overset{|}{N}-$, or $\overset{|}{C}=\overset{|}{N}-$ structural moieties which, having reached an appropriate site, may release an active aldehyde or amine, is at least as old as 4-′sulfamyl-2,4-diaminoazobenzene hydrochloride (Prontosil®); see, for example, recently, M. E. Kuehne and E. A. Konopka, *J. Med. Pharm. Chem.*, **5**, 257, 281 (1962), and J. H. Billman and J. L. Meisenheimer, *ibid.*, **6**, 682 (1963).

TABLE II
AROMATIC SECONDARY AMINES
$Ar_1CH_2NHAr_2$

No.	Ar_1	Ar_2	Mp, °C	Calcd, %			Found, %		
				C	H	N	C	H	N
1	3-Pyridyl	*m*-Nitrophenyl	114–115	62.87	4.84	18.33	63.04	4.91	18.00
2	4-Pyridyl	*o*-Hydroxyphenyl	176–178	71.98	6.04	13.99	72.18	6.21	13.95
3	*o*-Chlorophenyl	*p*-Dimethylaminophenyl	45	69.08	6.57	10.75	69.02	6.62	11.02
4	2-Pyridyl	*p*-Hydroxyphenyl	164–166	71.98	6.04	13.99	71.72	5.98	14.24
5	3-Pyridyl	*p*-Hydroxyphenyl	145–146	71.98	6.04	13.99	71.93	5.99	13.17
6	3-Pyridyl	*o*-Hydroxyphenyl	177–178	71.98	6.04	13.99	72.06	6.09	14.22
7	3-Pyridyl	4-Carboxyphenyl	220–222	68.41	5.30	12.27	67.93	5.38	12.45
8	*p*-Dimethylaminophenyl	*p*-Hydroxyphenyl	130–132	74.35	7.49	11.56	74.47	7.49	11.66
9	2-Pyridyl	4-Carboxyphenyl	207–209	68.41	5.30	12.27	68.38	5.42	12.51
10	3-Pyridyl	3-Carboxyphenyl	190–192	68.41	5.30	12.27	68.24	5.21	12.37
11	4-Pyridyl	4-Carboxyphenyl	244–247 dec	68.41	5.30	12.27	68.27	5.40	12.31
12	3,4-Dimethoxyphenyl	3-Hydroxy-4-carboxyphenyl	170–171	63.36	5.65	4.62	63.04	5.66	4.58
13	3,4-Dimethoxyphenyl	*p*-Hydroxyphenyl	164–166	69.48	6.61	5.40	69.25	6.29	5.65
14	*p*-Nitrophenyl	3-Pyridyl	92–94	62.87	4.84	18.33	62.60	5.06	18.34
15	*p*-Hydroxyphenyl	3-Pyridyl	191–192	71.98	6.04	13.99	72.12	6.30	13.79
16	*p*-Hydroxyphenyl	*p*-Aminophenyl	164	72.87	6.59	13.08	72.92	6.75	13.39
17	*p*-Dimethylaminophenyl	*p*-Aminophenyl	78	74.65	7.94	17.41	74.94	8.11	17.30
18	*o*-Hydroxyphenyl	*p*-Hydroxyphenyl	123	72.54	6.09	6.51	72.05	6.05	6.50
19	*o*-Hydroxyphenyl	*p*-Chlorophenyl	123	66.81	5.18	5.99	66.30	5.12	6.13
20	*o*-Hydroxyphenyl	3-Pyridyl	190	71.98	6.04	13.99	72.09	6.43	13.83
21	3,4-Dimethoxyphenyl	*p*-Aminophenyl	88	69.74	7.02	10.85	69.59	6.95	11.13
22	*o*-Hydroxyphenyl	*m*-Chlorophenyl	111	66.81	5.18	5.99	66.40	5.18	6.17
23	*p*-Hydroxyphenyl	*p*-Dimethylaminophenyl	105	74.35	7.49	11.56	74.80	7.48	11.8
24	*o*-Hydroxyphenyl	*p*-Dimethylaminophenyl	101	74.35	7.49	11.56	74.40	7.59	11.33
25	*p*-Chlorophenyl	*p*-Dimethylaminophenyl	89	69.08	6.57	10.75	68.78	6.61	11.05
26	*o*-Hydroxyphenyl	3-Hydroxy-4-carboxyphenyl	147	64.86	5.05	5.40	64.74	5.17	5.42
27	3-Indolyl	*p*-Dimethylaminophenyl	127	76.94	7.22	15.84	77.02	7.43	15.80
28	*p*-Chlorophenyl	*p*-Aminophenyl	140	67.09	5.63	12.04	66.61	5.70	11.69
29	3,4-Dimethoxyphenyl	*p*-Dimethylaminophenyl	123	71.30	7.74	9.78	71.33	7.73	10.64
30	*p*-Chlorophenyl	*o*-Chlorophenyl	42	61.92	4.40	5.56	61.48	4.34	5.63
31	*o*-Hydroxyphenyl	*p*-Nitrophenyl	138	63.92	4.95	11.47	64.23	5.02	11.75
32	*p*-Chlorophenyl	*p*-Chlorophenyl	70	61.92	4.40	5.56	61.77	4.30	5.57
33	*o*-Hydroxyphenyl	2,4-Dichlorophenyl	83	58.23	4.14	5.22	58.25	4.21	5.12
34	3,4-Dimethoxyphenyl	*p*-Chlorophenyl	123	64.86	5.81	5.04	65.06	5.99	5.14
35	*p*-Hydroxyphenyl	*m*-Nitrophenyl	124	63.92	4.95	11.47	63.68	5.01	11.71
36	*p*-Chlorophenyl	3-Pyridyl	106	65.90	5.07	12.81	66.21	5.34	13.09
37	*p*-Chlorophenyl	3-Hydroxy-4-carboxyphenyl	169	60.54	4.36	5.04	60.43	4.41	5.20
38	*p*-Chlorophenyl	4-Pyridyl	137	65.90	5.07	12.81	65.38	5.47	12.38
39	*p*-Chlorophenyl	*p*-Iodophenyl	101	45.44	3.23	4.08	45.46	3.24	3.96
40	*o*-Hydroxyphenyl	*p*-Iodophenyl	122	48.02	3.72	4.31	48.10	3.93	4.15
41	*p*-Chlorophenyl	*p*-Hydroxyphenyl	101	66.81	5.18	5.99	66.45	5.14	5.71
42	*p*-Chlorophenyl	*m*-Nitrophenyl	114	63.92	4.95	11.47	64.11	5.02	11.20
43	*p*-Dimethylaminophenyl	4-Carboxyphenyl	188 dec	71.09	6.71	10.36	70.74	6.80	10.44
44	*o*-Hydroxyphenyl	4-Sulfamylphenyl	182	56.09	5.07	10.07	55.73	5.07	9.84
45	*o*-Hydroxyphenyl	2,5-Dichlorophenyl	92	58.23	4.14	5.22	58.19	4.18	5.22
46	*o*-Hydroxyphenyl	2-Thiazolyl	129	58.23	4.89	13.58	57.96	4.81	13.63
47	2,4-Dichlorophenyl	*p*-Chlorophenyl	74	54.48	3.52	4.89	53.87	3.57	4.51
48	*p*-Chlorophenyl	*o*-Hydroxyphenyl	109	66.81	5.18	5.99	66.62	5.08	5.99
49	*p*-Chlorophenyl	2-Thiazolyl	131	53.45	4.04	12.47	53.71	4.14	12.68
50	3,4,5-Trimethoxyphenyl	1,2,3,4-Tetrahydro-5-naphthyl	112	73.36	7.70	4.28	73.04	7.45	4.16
51	3,4,5-Trimethoxyphenyl	1,2,3,4-Tetrahydro-6-naphthyl (·HCl)	196	66.01	7.20	3.85	66.09	7.13	3.96
52	3,4,5-Trimethoxyphenyl	3,4-Dimethoxyphenyl (·HCl)	202	58.45	6.54	3.78	58.38	6.41	3.77
53	3,4,5-Trimethoxyphenyl	2-Thiazolyl (·HCl)	190	49.28	5.41	8.64	49.62	5.64	8.58
54	3,4,5-Trimethoxyphenyl	*p*-Dimethylaminophenyl	98	68.33	7.65	8.85	68.50	7.70	9.04
55	*p*-Dimethylaminophenyl	2-Thiazolyl	149	61.77	6.48	18.01	61.53	6.72	17.89
56	*p*-Dimethylaminophenyl	*p*-(2-Hydroxyethyl)phenyl	82	75.52	8.20	10.36	75.25	8.21	10.67
57	*p*-Dimethylaminophenyl	3,4-Dimethoxyphenethyl	74	71.30	7.74	9.78	71.70	7.87	10.03
58	*p*-Dimethylaminophenyl	*p*-Dimethylaminophenyl	99	75.79	8.61	15.60	75.65	8.23	16.11
59	*p*-Dimethylaminophenyl	*p*-Methoxyphenyl	98	74.96	7.86	10.93	75.22	7.83	10.81
60	3,4-Dimethoxyphenyl	*p*-Diethylaminophenyl	66	72.58	8.34	8.91	72.75	8.29	9.19
61	3,4-Dimethoxyphenyl	*p*-Carboethoxyphenyl	120	68.55	6.71	4.44	68.11	6.61	4.39
62	3,4-Dimethoxyphenyl	1-Naphthyl	136	77.79	6.53	4.77	78.00	6.30	4.81
63	3,4-Dimethoxyphenyl	1,2,3,4-Tetrahydro-6-naphthyl	98	76.73	7.80	4.71	76.99	7.72	4.69
64	3,4-Dimethoxyphenyl	*p*-(2-Hydroxyethyl)phenyl	94	71.05	7.37	4.87	71.21	7.16	5.11
65	3,4-Dimethoxyphenyl	2-Thiazolyl	126	57.59	5.64	11.20	57.85	5.74	10.91

TABLE III
ALDIMINES AND SECONDARY AMINES
$R_1{=}NR_2$ and R_1NHR_2

No.	R_1[a]	R_2	M.p., °C	Calcd., %			Found, %		
				C	H	N	C	H	N
1	3-Py-CH=	$4\text{-MeOC}_6H_4CHOHCH_2$	115	70.29	6.29	10.93	70.51	6.40	11.10
2	3-Py-CH_2	$4\text{-MeOC}_6H_4CHOHCH_2$[b,c]	153	54.39	6.08	8.45	54.28	6.06	8.22
3	4-Py-CH_2	$4\text{-MeOC}_6H_4CH_2CH(CH_3)$[b,c]	190	58.36	6.74	8.51	58.33	6.70	8.65
4	3-Py-CH_2	$4\text{-MeOC}_6H_4CH_2CH(CH_3)$[b,c]	216	58.36	6.74	8.51	58.63	7.02	8.51
5	4-Py-CH=	$4\text{-MeOC}_6H_4CHOHCH_2$	122	70.29	6.29	10.93	70.25	6.07	11.01
6	4-Py-CH_2	$4\text{-MeOC}_6H_4CHOHCH_2$[b,c]	161	54.39	6.08	8.45	54.68	6.39	8.44
7	4-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3(CH_2)_2$[b]	210	55.65	6.42	8.12	55.52	6.52	8.19
8	3-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3(CH_2)_2$[c]	226	55.65	6.42	8.12	55.57	6.69	8.01
9	2-Py-CH_2	$4\text{-MeOC}_6H_4CH_2CH(CH_3)$[b]	197 dec	58.36	6.74	8.51	58.39	6.78	8.48
10	3-Py-CH_2	$C_6H_5CH_2CH(CH_3)$[b]	203 dec	60.20	6.73	9.36	59.80	6.83	9.41
11	4-Py-CH_2	$C_6H_5(CH_2)_2$	198 dec	58.95	6.36	9.82	59.26	6.60	9.91
12	4-Py-CH_2	$3,4\text{-(CH}_2O_2)C_6H_3CH_2CH(CH_3)$[b,c]	168	55.98	5.87	8.16	55.96	6.08	8.29
13	3-Py-CH_2	$3,4\text{-(CH}_2O_2)C_6H_3CH_2CH(CH_3)$[b,c]	232	55.98	5.87	8.16	55.33	5.89	8.18
14	2-Py-CH_2	$3,4\text{-(CH}_2O_2)C_6H_3CH_2CH(CH_3)$[b,d]	210	55.10	6.21	8.03	55.14	6.06	8.26
15	4-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3CH_2CH(CH_3)$[b,c]	153	56.83	6.73	7.80	56.40	7.38	7.45
16	3-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3CH_2CH(CH_3)$[b]	202	56.83	6.73	7.80	56.75	6.77	7.72
17	3-Py-CH_2	$C_6H_5(CH_2)_2$[b]	205	58.95	6.36	9.82	59.12	6.40	9.96
18	2-Py-CH_2	$C_6H_5(CH_2)_2$[b]	170	58.95	6.36	9.82	59.16	6.38	10.07
19	2-Py-CH_2	$C_6H_5CH(CH_3)$[b]	224	58.95	6.36	9.82	58.80	6.44	9.60
20	3-Py-CH_2	$C_6H_5CH(CH_3)$[b,c]	199	58.95	6.36	9.82	58.42	6.57	9.30
21	4-Py-CH_2	$C_6H_5CH(CH_3)$[b]	232	58.95	6.36	9.82	58.77	6.34	9.64
22	$C_6H_5CH{=}CHCH_2$	$C_6H_5CHOHCH_2$	116–118	80.57	7.56	5.53	80.50	7.67	5.48
23	2-Py-CH_2	$4\text{-(MeO)C}_6H_4CHOHCH_2$	78	69.74	7.02	10.85	69.47	7.13	10.59
24	4-Py-CH_2	$4\text{-MeC}_6H_4CHOHCH_2$[b,d]	201	56.34	6.46	8.76	56.40	6.80	8.38
25	4-Py-CH_2	$4\text{-HOC}_6H_4CH_2CH(CH_3)$[b]	230 dec	57.15	6.40	8.89	56.72	6.52	8.61
26	4-Py-CH_2	$3,4,5\text{-(MeO)}_3C_6H_2(CH_2)_2$[b]	210 dec	54.40	6.45	7.47	53.99	6.51	7.44
27	3-Py-CH_2	$4\text{-MeC}_6H_4CHOHCH_2$[b]	198	57.15	6.39	8.88	56.93	6.45	9.12
28	2-Py-CH_2	$4\text{-MeC}_6H_4CHOHCH_2$[b,c]	115	57.15	6.39	8.88	56.58	6.54	8.85
29	3-Py-CH_2	$4\text{-HOC}_6H_4CH_2CH(CH_3)$[b]	228 dec	57.15	6.39	8.88	56.85	6.42	8.71
30	2-Py-CH_2	$C_6H_5CH_2CH(CH_3)$[b]	203	60.20	6.73	9.36	60.80	6.82	9.34
31	4-Py-CH_2	$C_6H_5CHOHCH(CH_3)$[b]	228	57.15	6.39	8.88	57.05	6.37	8.84
32	3-Py-CH_2	$C_6H_5CHOHCH(CH_3)$[b]	227	57.15	6.39	8.88	57.41	6.26	8.86
33	2-Py-CH_2	$C_6H_5CHOHCH(CH_3)$[b]	218	57.15	6.39	8.88	57.01	6.51	8.91
34	4-Py-CH_2	$C_6H_5CH_2CH(CH_3)$[b,c]	185	60.20	6.73	9.36	59.99	6.81	9.50
35	2-Pyr-CH_2	$3,4\text{-(MeO)}_2C_6H_3CHOHCH_2$	148[e]	57.59	6.77		57.66	6.99	
			104[f]	...	...	10.14	...	...	10.04
36	2-Quin-CH_2	$3,4\text{-(MeO)}_2C_6H_3CHOHCH_2$[b]	190	58.40	5.88	6.81	58.10	6.04	6.92
37	4-Quin-CH_2	$3,4\text{-(MeO)}_2C_6H_3CHOHCH_2$[b,c,g]	129	53.90	6.28	6.28	54.10	6.66	6.16
38	4-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3CHOHCH_2$[b]	203	53.19	6.14	7.76	53.13	6.31	7.78
39	2-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3CHOHCH_2$[b,h]	145	51.90	6.23	7.57	51.99	6.46	7.82
40	3-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3CHOHCH_2$[b]	197	53.19	6.14	7.76	53.32	6.28	7.73
41	4-Quin-CH_2	$4\text{-HOC}_6H_4CH_2CH(CH_3)$[b,i]	168 dec	59.35	6.36	7.30	59.05	6.50	7.28
42	2-Pyr-CH_2	$4\text{-HOC}_6H_4CH_2CH(CH_3)$	141	73.01	7.88	12.17	72.72	8.06	11.89
43	2-Quin-CH_2	$4\text{-HOC}_6H_4CH_2CH(CH_3)$[b]	217	62.47	6.07	7.67	62.31	6.21	7.62
44	2-Pyr-CH_2	$4\text{-MeC}_6H_4CHOHCH_2$[e]	165	63.03	7.18	10.51	62.60	7.24	10.55
45	2-Pyr-CH_2	$4\text{-MeOC}_6H_4CHOHCH_2$[e]	160	59.46	6.77	9.91	59.66	7.06	10.03
46	2-Pyr-CH=	$4\text{-MeC}_6H_4CHOHCH_2$[j]	185	...	...	12.27	...	...	12.11
47	2-Pyr-CH=	$4\text{-MeOC}_6H_4CHOHCH_2$[j]	164	68.83	6.60	11.47	68.87	6.94	11.66
48	2-Pyr-CH_2	$3,4\text{-(CH}_2O_2)C_6H_3CH_2CH(CH_3)$[e]	167	61.32	6.52	9.54	60.77	6.58	9.44
49	4-Quin-CH_2	$3,4\text{-(CH}_2O_2)C_6H_3CH_2CH(CH_3)$[b]	205	63.66	5.88	7.43	63.46	6.07	7.28
50	2-Quin-CH_2	$3,4\text{-(CH}_2O_2)C_6H_3CH_2CH(CH_3)$[b,i]	191	60.8	6.08	7.10	61.27	5.74	7.14
51	2-Pyr-CH_2	$4\text{-MeOC}_6H_4CH_2CH(CH_3)$[e]	149	64.16	7.54	9.98	64.41	7.71	10.00
52	4-Quin-CH_2	$4\text{-MeOC}_6H_4CH_2CH(CH_3)$[b]	210 dec	63.32	6.38	7.39	62.84	6.60	7.18
53	2-Quin-CH_2	$4\text{-MeOC}_6H_4CH_2CH(CH_3)$[b,h]	190 dec	61.80	6.45	7.23	61.52	6.71	7.27
54	2-Pyr-CH_2	$C_6H_5CH(CH_3)$[e]	153	67.05	7.64	11.17	67.19	7.93	11.02
55	2-Pyr-CH_2	$3,4\text{-(MeO)}_2C_6H_3(CH_2)_2$[e]	147	60.70	7.13	9.44	60.33	7.32	9.07
56	2-Pyr-CH_2	$C_6H_5CHOHCH(CH_3)$	81	73.01	7.88	12.17	72.73	7.95	12.23
57	4-Quin-CH_2	$3,4\text{-(MeO)}_2C_6H_3(CH_2)_2$[b,h]	148	59.5	6.18	6.93	59.6	6.59	6.60
58	2-Quin-CH_2	$3,4\text{-(MeO)}_2C_6H_3(CH_2)_2$[b]	187	60.76	6.11	7.08	60.58	6.33	7.10
59	2-Py-CH_2	$3,4\text{-(MeO)}_2C_6H_3(CH_2)_2$[b]	204	55.66	6.42	8.11	55.63	6.45	8.30
60	2-Pyr-CH_2	$C_6H_5CHOHCH_2$[e]	161	61.77	6.78	11.09	61.97	6.80	10.89
61	2-Pyr-CH=	$C_6H_5CHOHCH_2$	157	72.89	6.59	13.08	72.91	6.80	13.10
62	4-Quin-CH_2	$4\text{-MeOC}_6H_4CHOHCH_2$[b]	148	59.85	5.82	7.35	59.74	6.10	7.40
63	2-Quin-CH_2	$4\text{-MeOC}_6H_4CHOHCH_2$[b]	158	59.85	5.82	7.35	60.00	6.35	7.00
64	4-Quin-CH_2	$C_6H_5CH_2CH(CH_3)$[b,c]	150	65.33	6.35	8.02	64.91	6.83	7.94
65	4-Quin-CH_2	$C_6H_5CHOHCH(CH_3)$[b,c,i]	201 dec	59.5	6.28	7.31	59.79	6.90	7.09
66	4-Quin-CH_2	$C_6H_5CHOHCH_2$[b,c,g]	139	55.82	5.96	7.58	55.64	6.46	7.40

TABLE III (*Continued*)

No.	R_1[a]	R_2	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
67	2-Quin-CH_2	4-$MeC_6H_4CHOHCH_2$[b]	174 dec	62.47	6.07	7.67	62.41	6.08	7.95
68	4-Py-CH=	$C_6H_5CHOHCH_2$[i]	110	74.31	6.24	...	74.76	6.02	...
69	4-Quin-CH_2	4-$MeC_6H_4CHOHCH_2$[b,h]	149	60.96	6.19	7.66	61.21	6.42	7. 0
70	2-Quin-CH_2	$C_6H_5CHOHCH_2$[b]	174	61.54	5.74	7.98	61.41	5.87	8.00
71	2-Quin-CH_2	$C_6H_5CHOHCH(CH_3)$[b]	210	62.47	6.07	7.67	62.62	6.18	7.52
72	2-Py-CH_2	4-$HOC_6H_4CH_2CH(CH_3)$[b]	221	57.15	6.40	8.89	57.07	6.54	8.54
73	2-Quin-CH_2	$C_6H_5CH_2CH(CH_3)$[b]	193	65.33	6.35	8.02	65.72	6.43	7.93
74	C_6H_5CH=$CHCH_2$	$C_6H_5CHOHCH(CH_3)$	96–99	80.86	7.92	5.24	80.60	8.00	5.32
75	2-Py-CH_2	$C_6H_5CHOHCH_2$[b]	166	55.82	6.02	9.30	55.88	6.12	9.54
76	3-Py-CH_2	$C_6H_5CHOHCH_2$[b]	179	55.82	6.02	9.30	56.12	6.21	9.61
77	4-Py-CH_2	$C_6H_5CHOHCH_2$[b]	143	55.82	6.02	9.30	55.84	6.17	9.14
78	C_6H_5CH=$CHCH_2$	4-$MeOC_6H_5CH_2CH(CH_3)$[e]	217–220	71.80	7.61	4.40	72.08	7.66	4.56
79	$C_6H_5CH_2CH(CH_3)$	4-$MeOC_6H_4CH_2CH(CH_3)$[e]	233	71.34	8.19	4.37	71.20	8.18	4.38
80	$C_6H_5CHOHCH(CH_3)$	4-$MeOC_6H_4CHOHCH_2$[e]	185	64.10	7.16	4.15	64.13	7.28	4.29
81	$C_6H_5CHOHC(CH_3)$=	4-$MeOC_6H_4CHOHCH_2$	119	72.21	7.07	4.68	72.26	6.75	4. 8
82	$C_6H_5CHOHCH(CH_3)$	4-$HOC_6H_4CH_2CH(CH_3)$[e]	227	67.17	7.52	4.35	67.13	7.70	4.45
83	$C_6H_5CH_2CH(CH_3)$	3,4-$(CH_2O_2)C_6H_3CH_2CH(CH_3)$[e]	167	67.59	6.93	4.38	67.68	7.13	4.12
84	$C_6H_5CH_2CH(CH_3)$	3,4-$(MeO)_2C_6H_3(CH_2)_2$[e]	150	67.94	7.80	4.17	68.25	7.96	4.31
85	$C_6H_5CHOHCH(CH_3)$	3,4-$(MeO)_2C_6H_3(CH_2)_2$	85–86[f]	72.35	7.99	4.44	72.15	7.92	4.37
			176[e]	64.85	7.44	3.98	64.39	7.48	4.05
86	$C_6H_5CHOHCH(CH_3)$	3,4-$(MeO)_2C_6H_3CH(OH)CH_2$[e]	183	62.03	7.13	3.81	61.86	7.22	3.90
87	$C_6H_5CHOHCH(CH_3)$	3,4-$(CH_2O_2)C_6H_3CH_2CH(CH_3)$[e]	237	65.23	6.92	4.00	65.18	7.00	4.03
88	3,4-$(MeO)_2C_6H_3CH_2$	4-$MeOC_6H_4CH(OH)CH_2$	111	68.12	7.31	4.41	67.86	7.27	4.38
89	3,4,5-$(MeO)_3C_6H_2CH_2$	4-$MeOC_6H_4CH_2CH(CH_3)$[e]	152	62.90	7.39	3.66	62.70	7.39	3.71
90	3,4,5-$(MeO)_3C_6H_2CH_2$	$C_6H_5CH(CH_3)$[e]	164	64.0	7.16	4.14	63.42	7.06	4.40
91	3,4,5-$(MeO)_3C_6H_2CH_2$	3,4-$(MeO)_2C_6H_3(CH_2)_2$[e]	157	60.37	7.09	3.52	60.19	7.18	3.41
92	3,4,5-$(MeO)_3C_6H_2CH_2$	$C_6H_5(CH_2)_2$[e,k]	166	...	7.16	4.14	...	7.16	4.39
93	3,4,5-$(MeO)_3C_6H_2CH_2$	$C_6H_5CH_2CH(CH_3)$[e]	166	64.88	7.45	3.98	64.80	7.52	4.12
94	3,4,5-$(MeO)_3C_6H_2CH_2$	$C_6H_5CHOHCH_2$[e]	201	61.09	6.84	3.95	60.99	6.89	4.03
95	3,4,5-$(MeO)_3C_6H_2CH_2$	$C_6H_5CHOHCH(CH_3)$[e]	218	62.03	7.13	3.81	62.07	7.28	3.93
96	3,4,5-$(MeO)_3C_6H_2CH_2$	4-$MeOC_6H_4CHOHCH_2$[e,h]	204	58.00	6.85	3.56	58.13	6.92	3.55
97	3,4,5-$(MeO)_3C_6H_2CH_2$	3,4-$(MeO)_2C_6H_3CHOHCH_2$[e]	185	58.03	6.82	3.38	58.07	6.94	3.09
98	3,4,5-$(MeO)_3C_6H_2CH_2$	Cyclohexyl[e]	147	60.84	8.29	4.43	60.87	8.21	4.58
99	3,4,5-$(MeO)_3C_6H_2CH_2$	$Et_2N(CH_2)_2$[b,c]	179	52.03	8.2	7.6	52.15	8.23	7.86
100	3,4,5-$(MeO)_3C_6H_2CH_2$	$Me_2N(CH_2)_3$[b,c]	207	50.7	7.95	7.9	50.67	7.89	7.84
101	3,4,5-$(MeO)_3C_6H_2CH_2$	$Et_2N(CH_2)_3$[b,i]	192	50.87	8.53	6.98	50.62	8.19	6.91
102	3,4-$(MeO)_2C_6H_3CH_2$	Cyclohexyl[e]	201	63.1	8.47	4.9	63.01	8.64	4.93
103	3,4-$(MeO)_2C_6H_3CH_2$	$Me_2N(CH_2)_3$[b,i]	203	51.69	8.06	8.61	51.46	8.06	8.14
104	3,4-$(MeO)_2C_6H_3CH_2$	$C_6H_5CH_2$	187	65.46	6.85	4.77	65.79	6.98	4.75
105	4-$Me_2NC_6H_4CH_2$	Cyclohexyl[b,c]	208 dec	59.01	8.58	9.17	58.81	8.40	9.43
106	4-$Me_2NC_6H_4CH_2$	$C_6H_5CH_2$[b,c]	194	61.34	7.08	8.94	61.14	7.09	9.11
107	4-$Me_2NC_6H_4CH_2$	$C_6H_5CH(CH_3)$[b]	184	62.38	7.4	8.57	62.17	7.40	8.71

[a] Py = pyridyl, Pyr = pyrryl, Quin = quinolyl. [b] Dihydrochloride. [c] Hygroscopic. [d] · $0.25H_2O$. [e] Monohydrochloride. [f] Crystalline base. [g] Dihydrate. [h] Hemihydrate. [i] Monohydrate. [j] Infrared: λ_{max} 6.07–6.08 μ. [k] *Anal.* Calcd: Cl, 10.49. Found: Cl, 10.68.

Inspection of Table II will indicate that hydride reduction of anils has such versatility with respect to functional group variation as is seldom encountered in other synthetic procedures, since there are very few rings or groups of possible prosthetic interest that will not survive treatment with methanolic borohydride. Contrary to certain recorded statements,[1] we encountered no great difficulty in isolating borohydride reduction products of arylaldimines bearing aromatic carboxylic acid, hydroxyl, or sulfonamide groups, provided that aqueous solutions were appropriately neutralized or acidified after the reactions, if necessary, and provided that sufficiently vigorous conditions and excess reagent were employed. This work incidentally gave a variety of new arylbenzylamines potentially useful in further synthetic work toward other pharmacologically interesting classes of compounds. Moreover some presently rather inexplicable biological effects were found in testing several of the compounds of Table II, as mentioned below.

Knowing that attachment of substituted or heterocyclic arylidene or arylmethyl groups to the nitrogen of an amine can change its biological properties, one is led to predict some profitable outcome in modifying along similar lines the catecholamines and phenethylamines.[6–8] Not only do β-pyridylethylamines[9] and selected arylethylamines,[10] particularly 1-(*p*-methoxyphenyl)- and 1-(3,4-methylenedioxyphenyl)-2-propylamines, show analgetic effects, but other modified arylethylamines[11] (aside from amphetamine) have been re-

(6) G. L. Jenkins and W. H. Hartung, "Chemistry of Organic Medicinal Products," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1953, pp 263–374.

(7) W. H. Hartung, *Chem. Rev.*, **9**, 389 (1931).

(8) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, Methuen and Co., Ltd., London, 1964, pp 282–343.

(9) A. Burger and G. E. Ullyot, *J. Org. Chem.*, **12**, 342 (1947); A. Burger and C. R. Walter, *J. Am. Chem. Soc.*, **72**, 1988 (1950).

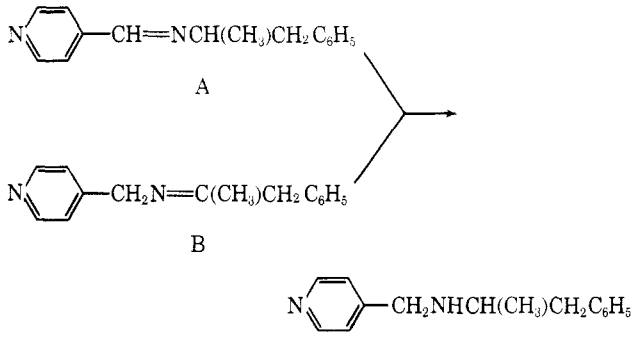
(10) E. J. Fellows and G. E. Ullyot in "Medicinal Chemistry," Vol. 1, C. M. Suter, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p 390.

(11) (a) A. L. Allewelt and A. R. Day, *J. Org. Chem.*, **6**, 384 (1941); (b) H. Corrodi, H. Persson, A. Carlsson, and J. Roberts, *J. Med. Chem.*, **6**, 751 (1963).

ported as having central or selective adrenergic blocking actions. Moreover, several relevant reports, appearing during the course of our own work, indicated that arylethylamines with appended heterocyclic groups such as pyridyl[12] and pyridylethyl[13] had, respectively, enhanced analgetic or central depressant activities, and also concurrently a number of new relatives of mescaline with altered pharmacology were reported.[14] Study of certain other phenolic N-γ-phenylpropyl-substituted phenethylamines earlier had revealed vasodilatory properties,[15] and substituted N-benzylephedrines[16] were known as useful bronchodilators. More recently N-β-phenoxyethyl derivatives of phenethylamines were reported as coronary dilators,[17] and interesting coronary effects have been described as well with N-(γ,γ-diphenylpropyl)phenethylamines.[18]

In the synthesis of the secondary amines (IV) listed in Table III, it was possible, as mentioned earlier,[3b] to obtain some products by borohydride reduction of two different Schiff bases, for example, see Scheme I.

SCHEME I



However, at least with pyridyl compounds, aldimines of type A were found to be more stable, obtainable in greater variety, and reduced in better yields than those of type B. Thus, nearly all of the heterocyclic-substituted secondary amines were prepared *via* A-type intermediate imines; of the latter, those which were obtained in crystalline form and purified during the course of the work are also listed in Table III. The yields of the borohydride reduction products ranged from 60–90%. The borohydride method has the advantage over alternative reductive alkylation[19] of amines in avoiding arylmethylamine hydrogenolysis as well as concurrent reduction of pyridyl and other heterocyclic moieties, both of which are likely to occur with platinum and other catalysts.

Schiff bases such as B and related ones from 1-hydroxy-1-phenyl-2- propanone and the aminomethylpyridines perhaps owe their lack of stability to a relatively great tendency for triad prototropic shift of the double bond under basic conditions.[20] No such difficulty was encountered with the more stable C=N compounds prepared from 2-phenylpropanone, 1-hydroxy-1-phenyl-2-propanone, or phenylpropanedione and the β-arylethylamines, reduction of which enabled preparation of compounds such as **79**, **80**, and **82**–**87** (Table III) in high yields.

Pharmacology.—Compounds were screened by procedures described or referred to in previous particles,[1,21] for adrenal, analgetic, CNS, and cardiovascular effects. Early in the work, interest centered on endocrine phenomena, and through use of a chromatographic technique[22] compounds **8** and **17** of Table II were found to increase somewhat the output of *all* the adrenocortical steroids being traced in dog experiments. This was attributed tentatively to increased ACTH production. Other methoxy, *p*-hydroxy, and *p*-amino compounds of the same type, however, did not seem to have measurable effects of this kind, but rather were found to act as motor stimulants in mice and dogs. The most active stimulant of Table II appeared to be compound **29**, which provoked marked and prolonged excitement and increase in aggressive behavior in dogs at 5–10 mg/kg but was also convulsive at the higher dose. Weaker effects of the same type were observed with several other related compounds, notably **16**, **21**, **23**, and **60**. The onset of toxic effects was slow (20 hr) and it would appear that the action of these compounds is not entirely a direct one on the central nervous system but may involve rather complex effects on the endocrine balance between the adrenal and pituitary glands. Further investigation of this possibility, although at present not warranted from a practical point of view, might be interesting.

At doses of *ca.* 3–10 mg/kg, compounds **8**, **24**, **25**, and **27** (Table II) evoked transient hypotensive effects in dogs, and at higher doses (25–100 mg/kg) they acted as stimulants in mice. Similar effects were observed with two compounds reported earlier, 3-(*p*-dimethylaminobenzylamino)pyridine[3b] and 3-(*p*-dimethylaminomethylamino)indole.[3a] However, the compounds of Table II having pyridyl, trimethoxyphenyl, and other substituent groups were practically devoid of interesting pharmacological effects, and halogen-containing molecules, while somewhat antifungal and antiparasitic in a number of instances, were usually quite sensitizing as well.

Considering the numerous precedents involved[6–18] and the number of substances examined, results with compounds in Table III were statistically rather disappointing. While many of the N-pyridylidene- and N-pyridylmethylamphetamines and phenethanolamines showed analgetic and/or central stimulant effects in preliminary screening, the percentage of compounds which on repeated testing had noteworthy activity was rather small. Reproducible analgetic (tail flick test) responses at doses ranging up to 100 mg/kg (subcutaneous) were obtained with compounds **31**, **48**, and **68**, and with Schiff bases corresponding to compounds **28**, **56**, and **75**. The best of these appeared to

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(13) S. L. Shapiro, I. M. Rose, F. C. Testa, and L. Freedman, *J. Org. Chem.*, **26**, 1323 (1961).

(14) F. Bennington, R. D. Morin, and L. C. Clark, *ibid.*, **20**, 102, 1292 (1955); **22**, 332 (1957); **23**, 1979, 2034 (1958); **25**, 2066 (1960).

(15) F. Külz and C. Schöpf, U. S. Patent 2,661,373 (1953); *Chem. Abstr.*, **49**, 1793 (1955). See also K. Wiemers, *Arch. Exptl. Pathol. Pharmakol.*, **213**, 283 (1951); *Chem. Abstr.*, **45**, 1252 (1951).

(16) M. Bockmühl, G. Ehrhart, L. Stein, and J. Hallensleben, U. S. Patent 2,088,941 (1937); German Patent 644,909 (1937); *Chem. Abstr.*, **31**, 6823, 6415 (1937), respectively.

(17) H. D. Moed and J. Van Dijk, *Rec. Trav. Chim.*, **75**, 1215 (1956).

(18) G. Ehrhart, *Arzneimittel Forsch.*, **295**, 196 (1962); K. Harsányi, D. Korbonits, and P. Kiss, *J. Med. Chem.*, **7**, 623 (1964).

(19) See W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).

(20) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(21) G. N. Walker, R. T. Smith, and B. N. Weaver, *J. Med. Chem.*, **8**, 626 (1965).

(22) J. J. Chart, H. Sheppard, T. Mowles, and N. Howie, *Endocrinology*, **71**, 479 (1962).

TABLE IV
ANILS
$Ar_1CH{=}NAr_2$

Ar_1	Ar_2	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
p-Nitrophenyl	2-Pyridyl	147–148 (+MeOH)	60.22	5.05	16.21	60.55	5.20	16.08
3-Pyridyl	*m*-Nitrophenyl	109–111	63.43	3.99	18.49	63.61	4.26	18.13
4-Pyridyl	*p*-Hydroxyphenyl	201–202	72.71	5.09	14.13	72.76	5.19	14.29
2-Pyridyl	*p*-Hydroxyphenyl	186–186	72.71	5.09	14.13	72.87	5.23	14.07
3-Pyridyl	*p*-Hydroxyphenyl	212–213	72.71	5.09	14.13	72.78	5.07	14.01
4-Pyridyl	*o*-Hydroxyphenyl	166–168	72.71	5.09	14.13	73.01	5.07	14.30
3-Pyridyl	4-Carboxyphenyl	241–243	69.01	4.46	12.38	69.30	4.60	12.23
3-Pyridyl	*o*-Hydroxyphenyl	87–88	72.71	5.09	14.13	73.11	5.38	13.79
2-Pyridyl	4-Carboxyphenyl	235–237	69.01	4.46	12.38	69.11	4.54	12.22
3-Pyridyl	3-Carboxyphenyl	219–221	69.01	4.46	12.38	69.01	4.33	12.37
4-Pyridyl	4-Carboxyphenyl	288–290	69.01	4.46	12.38	69.23	4.20	12.47
p-Nitrophenyl	3-Pyridyl	157–158	63.43	3.99	18.49	63.69	4.23	18.72
p-Hydroxyphenyl	3-Pyridyl	182–183	72.71	5.09	14.13	73.20	5.03	13.95
p-Nitrophenyl	*p*-Hydroxyphenyl	168	64.46	4.16	11.57	64.06	4.35	12.17
3,4-Dimethoxyphenyl	*p*-Hydroxyphenyl	150–151	70.02	5.88	5.44	69.94	5.88	5.49
3,4-Dimethoxyphenyl	4-Carboxyphenyl	176–178	63.78	5.02	4.65	63.26	5.05	4.78
p-Hydroxyphenyl	*p*-Aminophenyl	196	73.56	5.70	13.20	73.57	5.87	12.93
3-Pyridyl	*p*-Aminophenyl	144	73.07	5.62	21.31	72.91	5.71	21.03
o-Hydroxyphenyl	4-Sulfamylphenyl	214	56.50	4.38	10.14	56.43	4.45	10.28

be **48**, detectably active at *ca.* 20% of the toxic (70 mg/kg) dose, not antagonized, but rather apparently enhanced in its effect, by N-allylnormorphine, and not effective orally.

It is interesting that, whereas Schiff bases, notably those corresponding to compounds **10**, **30**, **34**, **42**, **48–52**, **54**, **64**, and **73**, as well as earlier reported N-(3-indolyl)methyleneamphetamines,[3a] tended to evoke central stimulation bordering on convulsive effects in mice at 2.5–10 mg/kg (subcutaneously), the secondary amines with heterocyclic groups more often affected blood pressure or produced mild analgetic or sedative effects. Marked to moderate, but transient, hypotensive action was exerted by **11**, **43**, and **58** at (intravenous) doses of about 10 mg/kg. As might be expected,[15,23] lowering of blood pressure in dogs also resulted with several of the di(β-arylalkyl)amines, especially compounds **80** and **85–87**. The most interesting of these, lower melting diastereoisomeric **85**, was strongly hypotensive in dogs and lacked sedative properties, although in mice the same compound behaved as a central depressant. The higher melting diastereoisomer of **85** (see Experimental Section), on the other hand, in dogs produced a sedative response and did not lower blood pressure. The trimethoxyphenyl compounds of Table III did not prove to be of interest, nor did the remaining (**102–107**) amines have any useful effects.

Broadly speaking, results of testing this array of amines tended to point up the well-known close (and sometimes inseparable) connection between central, cardiovascular, and analgetic pharmacological actions of the phenethylamines, and it cannot be claimed that any improvement was found over the efforts of others to deal with this intriguing but complex problem.

Experimental Section[24]

N-(*p*-Nitrophenyl)nicotinamide.—Preparation of nicotinamides listed in Table I is exemplified by synthesis of this compound. A mixture of 33.4 g of nicotinic acid and 52 ml of $SOCl_2$ was heated on a steam cone for 15 min allowing excess reagent to boil away, and finally the solid residue was warmed very briefly *in vacuo*. The residual solid, crude nicotinoyl chloride hydrochloride (58 g), was combined with 37.5 g of *p*-nitroaniline in 500 ml of toluene, and the suspension refluxed 3 hr. Evolution of HCl was complete after *ca.* 1.5 hr. The yellow, insoluble crystals were collected and treated with 450 ml of wet methanol, and the suspension boiled 15 min. The crude product was then collected, washed with methanol, and air dried; yield 40 g (56%) of solvated amide, mp 253–255° dec; purified further for analysis by recrystallization from methanol, it consisted of pale yellow needles of the hydrate, melting point as recorded in Table I.

Other amides were prepared by standard procedure in the presence of pyridine.

3-(*p*-Aminobenzoylamino)pyridine. A.—Reaction of *p*-nitrobenzoyl chloride with 10.9 g of 3-aminopyridine in 500 ml of ethyl acetate for 0.5 hr afforded crude **3-(*p*-nitrobenzoylamino)pyridine,** mp *ca.* 200°, in 84% yield.

B. Reduction of this nitroamide typifies the procedure used in preparing the aminoamides of Table I. A suspension of 9.7 g of product from A in 200 ml of ethyl acetate and 150 ml of ethanol was shaken on the standard Parr apparatus in the presence of 2.5 g of 10% Pd–C under 3.1 kg/cm² of hydrogen at 65° for 3 hr; a pressure drop of 0.632 kg/cm² (in a 4-l. system) took place during the first hour, after which there was no further uptake. After filtration, the gray, solid mixture of catalyst and product was boiled with several portions (300 ml) of methanol to dissolve the product. Evaporation of the filtered methanol solutions gave 4.5 g (55%) of solvated product as pale yellow needles, mp 233–235° dec (sintering 220°).

Other aminoamides (Table I) obtained in comparable yields, similarly, were quite sparingly soluble in alcohols and other organic solvents, and several consisted of very tenacious hydrates for which exact analytical figures were very difficult to obtain. Corresponding hydrochlorides, examined with a few examples, were even less tractable.

Anils and Schiff Bases.—The compounds listed in Table IV and other secondary amine precursors were prepared by heating together equimolar amounts of requisite aldehyde and amine in an appropriate solvent, chosen in accordance with the solubility characteristics of the amine. Benzene or toluene was preferred so that customary azeotropic removal of water could be carried out through reflux for 1–3 hr under a water separator. With some of the less soluble nitroanilines, nitrophenols, and isatin, ethyl acetate gave better results, and for highly polar (sulfonamido and carboxy) compounds ethanol or ethyl acetate was occasionally used to advantage. Within the limits of experi-

(23) See J. S. Buck, *J. Am. Chem. Soc.*, **53**, 2192 (1931), and references therein.

(24) Melting points were obtained using a coil-heated, stirred, silicone oil bath with a calibrated 360° thermometer.

mental error and varying purity of commercial samples of the amines and aldehydes used, the yields of aldimines were nearly quantitative. Those which crystallized, were sufficiently stable, and could be purified successfully by recrystallization from ethyl acetate, benzene, or cyclohexane are listed in Tables III and IV.

Secondary Amines.—Reduction of aldimines was invariably carried out by treatment of a methanol solution or suspension of the compound in an open vessel with excess (usually 2–5 parts by weight or more if the reaction were relatively sluggish) solid $NaBH_4$, added in portions as described earlier.[3] After an additional period of heating (1–2 hr), concentration to a smaller volume, and treatment with water, the products were isolated as described earlier[3a] and either recrystallized from an appropriate solvent (ethanol, ethyl acetate, or aqueous alcohols) or converted as usual to hydrochlorides, which were then recrystallized from ethanol, methanol, or ethanol–ether.

N-(3-Pyridylmethyl)-*p*-aminoacetanilide. A.—After the usual $NaBH_4$ reduction of the anil prepared from 3-pyridinealdehyde and *p*-nitroaniline, the amine (17.7 g, mp 177–179°) was refluxed 0.5 hr with 250 ml of acetic anhydride. Evaporation of excess reagent and collection of the product with the aid of ethyl acetate gave 10.4 g of the *p*-nitroacetanilide, mp 90–92°.

B. Hydrogenation of 7.7 g of the nitroacetanilide in the presence of 3 g of 10% Pd–C in ethyl acetate (350 ml) at 3 atm for 1 hr, filtration, and evaporation of the solvent gave crude, oily amine, from which there was obtained 5.6 g of corresponding **dihydrochloride,** mp 177–180° dec; it crystallized from ethanol as the **monohydrate,** slightly unstable, pink crystals.

Anal. Calcd for $C_{14}H_{15}N_3O \cdot 2HCl \cdot H_2O$: C, 50.61; H, 5.77; N, 12.65. Found: C, 51.03; H, 6.06; N, 12.89.

N-(3-Pyridylmethylene)-1-phenyl-2-propylamine, prepared by reaction of pyridine-3-aldehyde and amphetamine in benzene, and dried *in vacuo*, was an oil; λ_{max}^{film} 6.07 μ; λ_{max}^{EtOH} 231 mμ (ϵ 13,960), with inflection 278 mμ (ϵ 2630).

N-(1-Phenyl-2-propylidene)-4-pyridylmethylamine, similarly prepared by reaction of 2-phenylpropanone and 4-aminomethylpyridine in benzene, was also an oil; λ_{max}^{film} 6.02 μ; λ_{max}^{EtOH} 250 mμ (ϵ 3310), with inflections 258 and 262 mμ (ϵ 3090 and 2670, respectively).

Reduction of the foregoing two compounds with $NaBH_4$ in methanol, as usual, gave identical samples of **10** (Table III) as the dihydrochloride in each case; λ_{max}^{EtOH} 258 mμ (ϵ 2650).

Other N-pyridylidene, N-pyrrylidene, and N-quinolylidene derivatives of amines, prepared using the appropriate heterocyclic aldehydes, showed infrared absorption at 6.08 μ.

N-Homoveratrylnorephedrine (Table III; isomers of 85). To a solution of 40.6 g of homoveratrylamine in 500 ml of benzene was added a solution of 34 g 1-phenyl-1,2-propanedione in 400 ml of benzene. After exothermic reaction was complete, the cloudy solution was refluxed under a water trap for 2 hr. Evaporation of the benzene gave brown oil. The crude imine was dissolved in *ca.* 600 ml of methanol and treated with excess $NaBH_4$ as usual; after the exothermic and effervescent reaction was finished, the solution was heated 1 hr on a steam cone until the excess reducing agent had been destroyed and most of the solvent removed. Treatment of the cooled suspension with water and extraction of the crude product with ether, followed by drying (K_2CO_3) and evaporation to a smaller volume, gave the higher melting diastereoisomer, mp 118–120°, collected in several crops totalling 21.6 g with the aid of ether. A pure sample was prepared by recrystallization from aqueous methanol: colorless crystals, mp 119.5–121°.

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.54; H, 8.09; N, 4.60.

From the ethereal mother liquor there was isolated, after standing and further trituration with ether, 2.9 g of the lower melting isomer, as colorless crystals, mp 84–86°, purified further by recrystallization from ether and also characterized as the corresponding hydrochloride, as noted in Table III

Compounds **80, 82, 86,** and **87** were obtained by reduction of corresponding imines prepared from 1-hydroxy-1-phenyl-2-propanone, and each was isolated in the form of a single diastereoisomer.

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