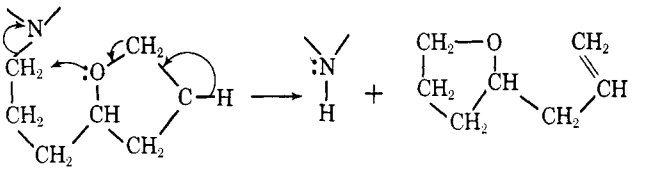
with the receptor surface in the same way as pethidine itself. Consideration of the role of the nitrogen substituent leads to two hypotheses: (a) that the chain is fully extended, and (b) that it simulates a ring.

If the side chain is fully extended, then any interaction between it and the receptor surface will be distinct from the norpethidine–receptor interaction, *i.e.*, it seems likely that two different areas of the receptor are involved with the two different portions of the molecule. Further, the attraction at the second site, due mainly to the electron-donating portion of the side chain, may be further enhanced by Van der Waals' forces involving a flat ring system such as phenyl or tetrahydrofuryl.

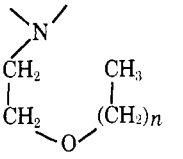
Alternatively, if the electron-donating portion of the side chain is attracted by the piperidino-nitrogen atom, which will carry some positive charge *in vivo*, then the side chain will be held in the form of a ring. In this case the side-chain "ring" might afford a wider area of interaction with that region of the receptor surface occupied by the methyl group of pethidine. In addition, the effect of the side chain upon the charge carried by the nitrogen atom may increase the lipid solubility of the molecule and so facilitate transfer across the aqueous–lipid barrier.

It has been suggested that analgesic action in compounds of this type is due to the secondary base produced by oxidative dealkylation *in vivo*.[26] There is little evidence for this hypothesis[27]; normorphine and norpethidine are considerably less active than the N-methyl homologs when given by any but the intracisternal route, and the validity of the results of drug administration by this route has been questioned.[28] If the side chain in our compounds does simulate a ring, however, it is possible that N-dealkylaiion may occur by a process of the type VI → VII (**25**, series F). Similar



VI VII

schemes may be written for other N-substituents, and such an hypothesis would predict that in series D (VIII) there would be no wide-spread activity.[29]



VIII

Acknowledgment.—We wish to thank Miss M. Bradley for technical assistance in the pharmacological evaluations.

(26) A. H. Beckett, A. F. Casy, and N. J. Harper, *J. Pharm. Pharmacol.*, **8**, 874 (1956).
(27) C. Elison, H. W. Elliott, M. Look, and H. Rapoport, *J. Med. Chem.*, **6**, 237 (1963).
(28) J. Dobbing, *Physiol. Rev.*, **41**, 130 (1961).
(29) Suggested by a referee.

4-Substituted Piperidines. II. Reaction of 1-Benzyl-4-cyano-4-*t*-aminopiperidines with Organometallic Compounds

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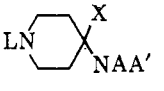
The reaction of 1-benzyl-4-cyano-4-*t*-aminopiperidines with organomagnesium and organolithium compounds is described. Reaction of these α-aminonitriles with Grignard reagents results in replacement of the nitrile group, whereas with the organolithium compounds normal ketone formation takes place. The resulting products are debenzylated, whereafter other substituents are introduced. Some of the obtained products show CNS-depressant activity.

Continuing our program on 4-substituted piperidines of possible therapeutic interest we prepared piperidines of the general formula I. As in the preceding paper,[1]



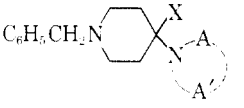
I

NAA′ represents a dialkylamino group or a saturated heterocyclic moiety; X stands for alkyl, aryl, alkanoyl, or aroyl; and L can represent any substituent retaining the basic character of the piperidine ring system.

Chemistry.—In the preceding paper[1] the peculiar properties of α-aminonitriles were pointed out.[2] This behavior is also demonstrated by their reaction with Grignard reagents. Several authors have investigated the reaction of α-aminonitriles with Grignard reagents and found that "normal" ketone formation takes place infrequently and that in most cases nitrile replacement occurs. Welvart[3] explained these anomalies by suggesting that the α-aminonitriles react in the form of the immonium ion II. In this ion the chemical bond between α-C and CN is electrovalent as well as covalent, allowing both C atoms to react with a nucleophilic reagent as RMgX.

(1) C. van de Westeringh, P. Van Daele, B. Hermans, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *J. Med. Chem.*, **7**, 619 (1964).
(2) For a more detailed discussion of this class of compounds, see V. Migrdichian in "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, covering the literature up to 1947, and a review by P. Van Daele, *Mededel. Vlaam. Chem. Ver.*, **23**, 163 (1961), covering more recent literature.
(3) Z. Welvart, *Compt. rend.*, **238**, 2536 (1954).

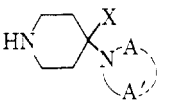
TABLE I



Compd.	N(A)(A′)[a]	X	Method	Yield, %	M.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., % Neut. equiv.	Found, % N	Found, % Cl⁻	Found, % Neut. equiv.
1	$N(CH_3)_2$	C_6H_5	A	27	87.4–88	$C_{20}H_{26}N_2$	9.52	...	147	9.31	...	147
2	$N(CH_3)_2$	COC_2H_5	B	65	225–226	$C_{17}H_{26}N_2O\cdot 2HCl$	8.07	20.42	174	8.35	20.21	175
3	C_4H_8N	C_6H_5	A	60	100–101	$C_{22}H_{28}N_2$	8.74	...	160	8.65	...	161
					224–226.5	$\cdot 2HCl$	7.12	18.03	197	6.88	17.84	200
4	C_4H_8N	COC_2H_5	B	47	237–239	$C_{19}H_{28}N_2O\cdot 2HCl$	7.50	18.99	187	7.71	18.61	188
5	$C_5H_{10}N$	CH_3	A	27	287.5–288	$C_{18}H_{28}N_2\cdot 2HCl$	8.11	20.53	173	8.16	20.47	174
6	$C_5H_{10}N$	C_6H_5	A	65	79–80	$C_{23}H_{30}N_2$	8.38	...	167	8.48	...	169
7	$C_5H_{10}N$	4-$CH_3C_6H_4$	A	35	104–108	$C_{24}H_{32}N_2$	8.04	...	174	8.05	...	179
8	$C_5H_{10}N$	$COCH_3$	B	33	57.5–60	$C_{19}H_{28}N_2O$	9.33	...	150	9.37	...	152
9	$C_5H_{10}N$	COC_2H_5	B	62	207.6–210.4	$C_{20}H_{30}N_2O\cdot HCl$	7.98	10.10	176	8.15	9.81	175
10	$C_5H_{10}N$	CO-*n*-C_3H_7	B	57	191.2–193	$C_{21}H_{32}N_2O\cdot HCl$	7.70	9.72	182	7.73	10.06	178
11	$C_5H_{10}N$	COC_6H_5	B	70	137–140	$C_{24}H_{30}N_2O$	7.73	...	181	7.43	...	185
					246–253	$\cdot HCl$	7.02	8.89	200	6.82	9.02	198
12	C_4H_8NO	COC_2H_5	B	54	176.5–183 dec.	$C_{16}H_{28}N_2O_2\cdot 2HCl$	7.20	18.21	195	7.20	18.41	201

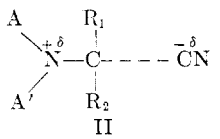
[a] C_4H_8N = pyrrolidino, $C_5H_{10}N$ = piperidino, C_4H_8NO = morpholino.

TABLE II



Compd.	N(A)(A′)[a]	X	Method	Yield, %	B.p. (mm.) or m.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., % Neut. equiv.	Found, % N	Found, % Cl⁻	Found, % Neut. equiv.
13	$N(CH_3)_2$	C_6H_5	D	25	189–205	$C_{13}H_{20}N_2\cdot 2HCl\cdot H_2O$[b]	9.49	24.02	148	9.31	23.63	154
14	$N(CH_3)_2$	COC_2H_5	C	84	Oil[c]	$C_{10}H_{20}N_2O$	...	...	92	...	...	100
15	C_4H_8N	C_6H_5	D	27	125–130 (0.05)	$C_{15}H_{22}N_2$	12.15	...	115	12.11	...	119
16	C_4H_8N	COC_2H_5	C	87	Oil[c]	$C_{12}H_{22}N_2O$	...	...	105	...	...	109
17	$C_5H_{10}N$	CH_3	C	87	297–298	$C_{11}H_{22}N\cdot 2HCl\cdot H_2O$[d]	10.25	25.95	137	10.08	25.97	138
18	$C_5H_{10}N$	C_6H_5	D	66	235–237	$C_{16}H_{24}N_2\cdot 2HCl$	8.82	22.35	159	8.79	22.15	163
19	$C_5H_{10}N$	4-$CH_3C_6H_4$	D	46	149–154	$C_{17}H_{26}N_2$	10.84	...	129	10.77	...	133
20	$C_5H_{10}N$	$COCH_3$	C	86	Oil[c]	$C_{12}H_{22}N_2O$	...	...	105	...	...	107
21	$C_5H_{10}N$	COC_2H_5	C	60	120–124 (0.1)	$C_{13}H_{24}N_2O$	12.49	...	112	12.40	...	113
22	$C_5H_{10}N$	CO-*n*-C_3H_7	C	77	Oil[c]	$C_{14}H_{26}N_2O$	...	...	119	...	...	115
23	$C_5H_{10}N$	COC_6H_5	C	30	134–136	$C_{17}H_{24}N_2O$	10.28	...	136	10.11	...	135
24	$C_5H_{10}N$	$CHOHC_2H_5$[e]		64	149–151	$C_{13}H_{26}N_2O$	12.37	...	113	12.19	...	118
					232–233	$\cdot 2HCl$	9.34	23.69	150	9.12	23.39	151
25	C_4H_8NO	COC_2H_5	C	90	Oil[c]	$C_{12}H_{22}N_2O_2$	...	...	113	...	...	118

[a] C_4H_8N = pyrrolidino, $C_5H_{10}N$ = piperidino, C_4H_8NO = morpholino. [b] *Anal.* Calcd.: H_2O, 6.10. Found: H_2O, 6.72 (Karl Fischer). [c] Used without purification. [d] *Anal.* Calcd.: H_2O, 6.59. Found: H_2O, 6.65 (Karl Fischer). [e] Obtained by reduction of **21**.



II

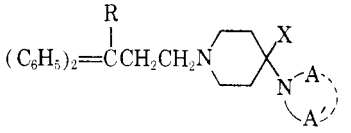
The course of the reaction is largely dependent on the nature of A, A′, R_1, and R_2. In cases where the immonium ion predominates (*i.e.*, where R_1 and R_2 are different from hydrogen) the nitrile group is replaced by the radical of the Grignard complex. This course of events depends not only on the nature of the nitrile, but also on the type of Grignard reagent used.[4]

(4) Z. Welvart, *Compt. rend.*, **250**, 1870 (1960).

In the case of 1-benzyl-4-cyano-4-*t*-aminopiperidines to be discussed here, a second amine function is present in the molecule, which might be a further implicating factor. It was found that in the reaction of these α-aminonitriles with Grignard reagents (aromatic as well as aliphatic) only nitrile replacement occurs (method A). Since the preparation of ketones by this method was unsuccessful we turned our attention to other possibilities. Indeed it was known that in the few instances where the reaction of α-aminonitriles with organolithium compounds is reported,[5] only normal ketone

(5) (a) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953); (b) N. H. Cromwell and P. H. Hess, *J. Am. Chem. Soc.*, **83**, 1237 (1961); (c) P. Duhamel, M. Miocque, and J. A. Gautier, *Compt. rend.*, **258**, 227 (1964); (d) G. Chauvière, B. Tchoubar, and Z. Welvart, *Bull. soc. chim. France*, 1428 (1963).

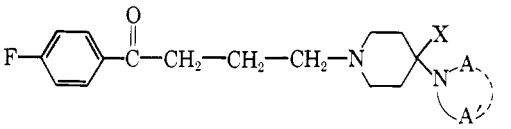
Table III



Compd.[a]	N(A)(A′)	X	R	M.p., °C.	Formula	Calcd., % N	Cl⁻	H_2O	Neut. equiv.	Found, % N	Cl⁻	H_2O	Neut. equiv.
26	$N(CH_3)_3$	C_6H_5	CN	231–234	$C_{29}H_{33}N_3\cdot 2HCl\cdot H_2O$	8.17	13.78	3.50	257	8.01	13.67	4.10	258
27	$N(CH_3)_2$	COC_2H_5	CN	235–238	$C_{26}H_{33}N_3O\cdot 2HCl$	8.82	14.89	...	238	8.67	15.14	...	235
28	C_4H_8N	C_6H_5	CN	250–253	$C_{31}H_{35}N_3\cdot 2HCl\cdot H_2O$	7.77	13.12	3.33	270	7.92	12.93	3.23	272
29	$C_5H_{10}N$	CH_3	CN	280–282	$C_{27}H_{35}N_3\cdot 2HCl$	8.86	14.95	...	237	8.62	15.27	...	232
30	$C_5H_{10}N$	CH_3	OH	294–295	$C_{26}H_{36}N_2O\cdot 2HCl$	6.02	15.24	...	233	5.89	15.10	...	232
31	$C_5H_{10}N$	C_6H_5	CN	251–254	$C_{32}H_{37}N_3\cdot 2HCl$	7.83	13.22	...	268	7.68	12.99	...	271
32	$C_5H_{10}N$	C_6H_5	OH	121–124	$C_{31}H_{38}N_2O$[c]	6.16	...	...	227	6.01	...	...	223
33	$C_5H_{10}N$	4-$CH_3C_6H_4$	CN	217–220	$C_{33}H_{39}N_3\cdot 2HCl$	7.63	12.88	...	275	7.49	13.12	...	273
34	$C_5H_{10}N$	$COCH_3$	CN	230–235	$C_{28}H_{35}N_3O\cdot 2HCl$	8.36	14.11	...	251	8.40	14.25	...	248
35	$C_5H_{10}N$	COC_2H_5	CN	171–175	$C_{29}H_{37}N_3O\cdot 2HCl$	8.14	13.73	...	258	8.20	13.37	...	255
36	$C_5H_{10}N$	COC_2H_5	$CONH_2$[d]	156–157	$C_{29}H_{39}N_3O_2$[e]	9.10	...	...	231	9.27	...	...	232
37	$C_5H_{10}N$	COC_6H_5	CN	241–242	$C_{33}H_{37}N_3O\cdot HCl$	7.96	6.71	...	264	8.23	6.68	...	264
38	C_4H_8NO	COC_2H_5	CN	213–215	$C_{28}H_{35}N_3O_2\cdot HCl$	8.72	7.36	...	241	8.93	7.24	...	242

[a] Most of these compounds were synthesized only once and probably not in optimum conditions; therefore, no yield is given. [b] C_4H_8N = pyrrolidino, $C_5H_{10}N$ = piperidino, C_4H_8NO = morpholino. [c] *Anal.* Calcd.: C, 81.89; H, 8.43. Found: C, 81.55; H, 8.39. [d] Obtained by hydrolysis of **35**. [e] *Anal.* Calcd.: C, 75.45; H, 8.52. Found: C, 75.23; H, 8.34.

Table IV



Compd.[a]	N(A)(A′)	X	M.p., °C.	Formula	Calcd., % N	Cl⁻	F	Neut. equiv.	Found, % N	Cl⁻	F	Neut. equiv.
39	$N(CH_3)_2$	COC_2H_5	224–225	$C_{20}H_{29}FN_2O_2\cdot 2HCl$	6.65	16.83	4.51	211	6.68	16.66	4.27	213
40	C_4H_8N	COC_2H_5	88–91	$C_{22}H_{31}FN_2O_2$	7.48	...	5.08	187	7.70	...	5.10	191
41	$C_5H_{10}N$	CH_3	270–271	$C_{21}H_{31}FN_2O\cdot 2HCl$	6.68	16.90	4.53	210	6.64	16.70	4.31	210
42	$C_5H_{10}N$	C_6H_5	99–101	$C_{26}H_{33}FN_2O$	6.86	...	4.65	204	7.06	...	4.48	202
43	$C_5H_{10}N$	4-$CH_3C_6H_4$	159–161	$C_{27}H_{35}FN_2O\cdot 2HCl$	5.66	14.32	3.83	248	5.61	14.35	3.72	247
44	$C_5H_{10}N$	$COCH_3$	250–252	$C_{22}H_{31}FN_2O_2\cdot 2HCl$	6.26	15.85	4.25	224	6.44	15.65	4.12	220
45	$C_5H_{10}N$	COC_2H_5	95–96.5	$C_{23}H_{33}FN_2O_2$	7.21	...	4.89	194	7.14	...	4.85	193
			208–210	$\cdot 2HCl$	6.07	15.37	4.13	231	6.31	15.38	4.06	228
46	$C_5H_{10}N$	CO-*n*-C_3H_7	195–198	$C_{24}H_{35}FN_2O_2\cdot 2HCl$	5.88	14.92	4.00	238	5.73	14.64	3.98	238
47	$C_5H_{10}N$	COC_6H_5	107–108	$C_{27}H_{33}FN_2O_2$	6.42	...	4.35	218	6.44	...	4.36	221
48	$C_5H_{10}N$	$CHOHC_2H_5$	195–197	$C_{23}H_{35}FN_2O_2\cdot 2(COOH)_2$[c]	4.91	...	3.33	285	4.77	...	3.17	291
49	C_4H_8NO	COC_2H_5	197–199	$C_{22}H_{31}FN_2O_3\cdot 2HCl$	6.05	15.30	4.10	232	6.10	15.30	4.04	232

[a] Most of these compounds were synthesized only once and probably not under optimum conditions; therefore, no yield is given. [b] C_4H_8N = pyrrolidino, $C_5H_{10}N$ = piperidino, C_4H_8NO = morpholino. [c] *Anal.* Calcd.: oxalic acid, 31.56. Found: oxalic acid, 31.98.

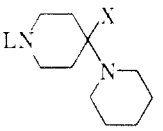
formation was observed. We therefore applied this latter reaction to compounds of type I (X = CN; L = $C_6H_5CH_2$) and without exception the expected ketones, both aromatic and aliphatic, were obtained in good yields (method B). The compounds prepared by the above methods are presented in Table I.

Reductive debenzylations were achieved for most of the N-benzyl compounds (method C); in the case of the 4-aryl derivatives (**1, 3, 6,** and **7**), however, 2 moles of hydrogen were observed. This is probably due to the fact that this part of the molecule is an α,α-disubstituted benzylamine. Even if the reductions were stopped after absorption of only 1 mole of hydrogen, none of the desired secondary amines could be isolated. For this reason another method of debenzylation, the von Braun cyanogen bromide reaction,[6] was applied (method D). Reaction of the tertiary amines with cyanogen bromide gave the corresponding N-cyanopiperidines, which were hydrolyzed to the corresponding secondary amines by boiling in dilute hydrochloric acid. Compound **21** was reduced to the corresponding alcohol (**24**) by means of sodium borohydride. A survey of the debenzylated products is offered in Table II.

Introduction of various substituents on these secondary amines was accomplished by conventional methods. A representative number of these is listed in Tables III–V. Each type of reaction discussed above is illustrated in the Experimental Section by one example.

(6) H. A. Hageman in *Org. Reactions*, **7**, 198 (1953).

TABLE V



Compd.[a]	X	L[b]	M.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., % H₂O	Calcd., % Neut. equiv.	Found, % N	Found, % Cl⁻	Found, % H₂O	Found, % Neut. equiv.
50	CH_3	$C_6H_5(CH_2)_2$	273–274	$C_{18}H_{30}N_2 \cdot 2HCl$	7.80	19.73	...	180	7.85	19.36	...	184
51	C_6H_5	$C_6H_5O(CH_2)_2$	177–179	$C_{24}H_{32}N_2O \cdot 2HCl$	6.40	16.21	...	219	6.28	16.00	...	217
52	C_6H_5	$C_6H_5NH(CH_2)_2$	240–242	$C_{24}H_{33}N_3 \cdot 2HCl \cdot H_2O$	9.25	15.60	3.96	151	9.33	15.33	3.21	153
53	$COCH_3$	$CH_3(CH_2)_6$	214–217	$C_{19}H_{36}N_2O \cdot 2HCl$	7.34	18.63	...	191	7.44	18.71	...	189
54	COC_2H_5	CH_3[c]	260–263	$C_{11}H_{22}N_2O \cdot 2HCl$	9.00	22.77	...	156	8.77	22.44	...	158
55	COC_2H_5	$C_6H_5(CH_2)_2$	244–247	$C_{21}H_{32}N_2O \cdot 2HCl \cdot H_2O$	6.68	16.91	4.30	210	6.60	16.96	4.94	211
56	COC_2H_5	$C_6H_5CH_2CH{=}CHCH_2$	208–211	$C_{29}H_{32}N_2O \cdot 2HCl$	6.78	17.15	...	207	6.95	16.85	...	209
57	COC_2H_5	$C_6H_5O(CH_2)_2$	116.5–118	$C_{21}H_{32}N_2O_2 \cdot 2HCl \cdot 2H_2O$	6.18	15.64	7.90	227	6.20	15.29	7.30	229
58	COC_2H_5	$C_6H_5O(CH_2)_3$	208–210	$C_{22}H_{34}N_2O_2 \cdot 2HCl$	6.51	16.44	...	216	6.40	16.23	...	216
59	COC_2H_5	$C_6H_5CO(CH_2)_2$	207–210	$C_{22}H_{32}N_2O_2 \cdot 2HCl$	6.52	16.51	...	215	6.48	16.16	...	218
60	CO-*n*-C_3H_7	$C_6H_5CH(OH)(CH_2)_2$	76–77.5	$C_{23}H_{36}N_2O$[d]	7.52	...	...	186	7.57	...	...	188

[a] Most of the compounds were synthesized only once and probably not in optimum conditions; therefore, no yield is given. [b] In all cases, except for **54**, L is introduced as described in the Experimental Section for **45**. [c] Synthesized by reductive alkylation. [d] *Anal.* Calcd.: C, 74.15; H, 9.74. Found: C, 74.01; H, 9.78.

Pharmacology.—By analogy with the results in other series of 4-substituted piperidine derivatives it was hoped that introduction of the γ-(α,α-diphenylbutyronitrile) group, or of closely related substituents, might result in compounds exhibiting analgesic activity resembling piritramide[1] or antidiarrheal activity like diphenoxylate.[7] None of these compounds (Table III), however, was found to have any such activity.

In the butyrophenone series (only fluoro derivatives are listed) and in particular in the 4-alkanoyl compounds (Table IV, **39, 40, 44–46**) some CNS activity was encountered, although on the whole the compounds of this series were less potent neuroleptic agents than those of the haloperidol[8] or dipiperon[1] type. It was therefore unexpected that in some animal species, particularly in cats and the like, these compounds were found to be qualitatively superior to the cited reference compounds with respect to their CNS-depressant activity (see Table VI). In particular **45** (again a 4-fluorobutyrophenone derivative like haloperidol and dipiperon) showed interesting properties in this regard and further studies on the possible use of this compound in veterinary practice are underway.

TABLE VI

Compd.	Apomorphine antagonism in dogs PD_{50}, mg./kg. s.c.[a]	MED[b] against morphine-induced feline mania[c]
39	1.5	15
40	1.2	10
44	0.90	10
45	0.60	10
46	1.5	20
Haloperidol	0.020	Inactive at 20
Dipiperon	0.50	Inactive at 40

[a] P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, F. J. Verbruggen, and J. M. Van Nueten, *Arzneimittel-Forsch.*, **13**, 205 (1963). [b] Minimum effective dose in mg./kg. s.c. [c] R. W. Begley, W. R. Jones, and J. C. Weaver, *Arch. intern. pharmacodyn.*, **129**, 236 (1960).

Experimental Section[9,10]

1-Benzyl-4-phenyl-4-pyrrolidinopiperidine (3). Method A.—Starting from 10.8 g. (0.45 g.-atom) of magnesium and 70 g. (0.44 mole) of bromobenzene, a solution of phenylmagnesium bromide in 300 ml. of dry ether was prepared in the usual manner. To this solution was added dropwise a solution of 58.5 g. (0.215 mole) of 1-benzyl-4-cyano-4-pyrrolidinopiperidine[1] in 1200 ml. of dry ether. After the addition was complete, the mixture was refluxed for 12 hr. The reaction mixture was then decomposed at a temperature of about 10° with 400 ml. of a 10% NH_4Cl solution, containing a few milliliters of dilute HCl to obtain a good separation. The water layer was extracted with ether and the combined organic layers were washed successively twice with 200 ml. of a 20% NaOH solution and twice with water. The ethereal solution was dried (K_2CO_3), filtered, and evaporated. The residue was crystallized from diisopropyl ether to yield 42 g. of product **3**.

1-Benzyl-4-propionyl-4-piperidinopiperidine (9). Method B.—A solution of ethyllithium, prepared from 10.4 g. (1.5 g.-atoms) of lithium and 90 g. (0.68 mole) of ethyl bromide in 900 ml. of petroleum ether (b.p. 40–60°),[11] was added dropwise to a solution of 71 g. (0.25 mole) of 1-benzyl-4-cyano-4-piperidinopiperidine in 1250 ml. of petroleum ether, while refluxing. The reaction mixture was further stirred and refluxed for 2 hr. The mixture was cooled in an ice bath and decomposed by dropwise addition of 200 ml. of water at a temperature below 10°. The organic layer was separated, dried (K_2CO_3), and filtered, and gaseous HCl was introduced. The precipitated sticky hydrochloride salt was filtered off and crystallized from water to yield 55 g. of the monohydrochloride **9**.

4-Propionyl-4-piperidinopiperidine (21). Method C.—A mixture of 75 g. (0.215 mole) of 1-benzyl-4-propionyl-4-piperidinopiperidine hydrochloride, 250 ml. of 2-propanol, and 250 ml. of water was debenzylated under atmospheric pressure and at a temperature of about 30° in the presence of 10 g. of 10% palladium on charcoal. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and boiled twice with 100 ml. of water and filtered again. The combined filtrates were evaporated. The residue was dissolved in 300 ml. of water, made alkaline, and extracted with ether. The organic solution was dried and evaporated. The residue was distilled *in vacuo*, to yield 28 g. of oily product **21**.

4-Phenyl-4-pyrrolidinopiperidine (15). Method D.—To a solution of 41.5 g. (0.39 mole) of BrCN in 700 ml. of chloroform was added dropwise a solution of 99 g. (0.32 mole) of 1-benzyl-4-phenyl-4-pyrrolidinopiperidine in the course of 6 hr. at room temperature. After the addition was complete, the whole was heated to reflux and stirred for 90 min. The mixture was

(7) P. A. J. Janssen, A. H. Jageneau, and J. Huygens, *J. Med. Pharm. Chem.*, **1**, 299 (1959).

(8) P. A. J. Janssen, C. van de Westeringh, A. H. M. Jageneau, P. J. A. Demoen, B. K. F. Hermans, G. H. P. Van Daele, K. H. L. Schellekens, C. A. M. Van der Eycken, and C. J. E. Niemegeers, *ibid.*, **1**, 281 (1959).

(9) All melting points were taken on a Tottoli melting point apparatus and are corrected.

(10) Consult tables for analytical data.

(11) H. Gilman, F. W. Moore, and O. Baine, *J. Am. Chem. Soc.*, **63**, 2479 (1941).

evaporated, and the oily residue was stirred into 900 ml. of 6% HCl. This mixture was slowly heated and then refluxed for 6 hr. It was then cooled to room temperature and stirring was continued overnight. Then the solution was boiled with activated charcoal and the filtrate was extracted three times with ether. The acidic aqueous layer was separated, made alkaline, and extracted with chloroform. The organic layer was dried and evaporated, and the oily residue was distilled *in vacuo* to yield 19 g. of oily **15**.

4-(1-Hydroxypropyl)-4-piperidinopiperidine (24).—To a heated solution (40°) of 6.7 g. (0.03 mole) of 4-propionyl-4-piperidinopiperidine in 100 ml. of 2-propanol was added portionwise 1.3 g. of $NaBH_4$. The whole was stirred for 6 hr. at the same temperature. After cooling in an ice bath, the reaction mixture was decomposed by dropwise addition of 60 ml. of 5 *N* HCl. The solution was filtered and evaporated, the residue was dissolved in 100 ml. of water, and the aqueous solution was made alkaline and extracted with chloroform. The organic layer was dried, filtered, and evaporated. The residue was triturated with diisopropyl ether to yield 4.3 g. of **24**.

1-[γ-(4-Fluorobenzoyl)propyl]-4-propionyl-4-piperidinopiperidine (45).—A mixture of 5.6 g. (0.028 mole) of γ-chloro-4-fluorobutyrophenone,[12] 4.4 g. (0.02 mole) of 4-propionyl-4-piperidinopiperidine, 6.4 g. of Na_2CO_3, and some crystals of KI in 250 ml. of methyl isobutyl ketone was refluxed with stirring for 48 hr. The solution was filtered hot and evaporated. The residue was crystallized from diisopropyl ether to yield 5.1 g. of **45**, m.p. 95–96.5°. This product was converted to its dihydrochloride which, after recrystallization from 2-propanol, melted at 208–210°.

1-(3-Carboxamido-3,3-diphenylpropyl)-4-propionyl-4-piperidinopiperidine (36).—A solution of 6.2 g. (0.012 mole) of **35** in 8 ml. of 90% H_2SO_4 was heated for 3 hr. at 100°. After cooling, the reaction mixture was poured onto 30 g. of ice. The whole was made alkaline with NH_4OH and extracted with chloroform. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The solid residue was crystallized twice from acetone to yield 3.7 g. of **36**, m.p. 156–157°.

1-Methyl-4-propionyl-4-piperidinopiperidine (54).—A mixture of 4.5 g. (0.02 mole) of 4-propionyl-4-piperidinopiperidine, 0.7 g. of paraformaldehyde, 23.5 g. of formic acid, and 250 ml. of 2-propanol was stirred and refluxed for 2 hr. The reaction mixture was concentrated to 20 ml., and to this residue was added 20 ml. of water. This solution was made alkaline with NaOH and extracted with ether. The ethereal solution was dried (K_2CO_3) and filtered, and gaseous HCl was introduced into it. The precipitated hydrochloride was filtered off and recrystallized from ethanol to yield 2.5 g. of **54**, m.p. 260–263°.

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6-Hydroxyindoles and the Metabolism of Melatonin

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Different published data on investigations of the metabolism of melatonin are incongruous and one out of three metabolites formed has not been identified. One purpose of this study was to resolve the apparent ambiguities in the literature and to identify the third, unknown metabolite. 3-(2-Acetylaminoethyl)-6-hydroxy-5-methoxyindole (6-hydroxymelatonin) was synthesized and a study of the metabolism of melatonin was repeated. Comparison of chromatographic properties of metabolites confirmed earlier data that the major radioactive peak seen on chromatograms was 6-hydroxymelatonin sulfate. A previously unidentified spot was shown to be free 6-hydroxymelatonin by comparing it with our synthetic compound of unequivocal structure. Because of the past suggestion that 6-hydroxylated metabolites of psychotomimetic tryptamines should be more psychoactive than the nonhydroxylated parent compounds, 6-hydroxy-5-methoxytryptamine was synthesized. It was found less effective in depressing work rates of conditioned rats than 5-methoxytryptamine, thus failing to support the hypothesis in this instance.

Two representatives of indoles hydroxylated in the 6-position were synthesized to examine some of their biological and chemical properties. Such compounds are of interest for several reasons. Szara and Hearst[1] suggested that 6-hydroxylated metabolites of psychotomimetic tryptamines should be more psychoactive than the parent nonhydroxylated compounds.

Hydroxylation is an important means by which mammals detoxify aromatic compounds.[2] Indications are that indoles which cannot be metabolized through other functional groups are hydroxylated and eliminated by the kidney as glucuronides or sulfate esters.[3] Although tryptamines[4] and even chain N-methyltryptamines[5] are metabolized to the corresponding acids, chain N-acetylation[6] and chain N,N-dialkylation[7] prevent or slow down biochemical oxidation to the acids. In these instances an alternative pathway of aromatic hydroxylation can prevail.

The syntheses of compounds prepared in this study are given in Chart I. Reacting 6-benzyloxy-5-methoxyindole (I) with aqueous formaldehyde and dimethylamine produced the substituted gramine (II) in good yield. Since it has been shown previously that the quaternary salts react more efficiently in the following reaction than gramine itself,[8] 6-benzyloxy-5-methoxygramine methosulfate (III) was prepared. Reaction of the quaternary salt with sodium cyanide in aqueous

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