with 5% aqueous sodium hydroxide. Acidification of the alkaline extract gave 0.4 g. (67%) of product which was recrystallized once from water and twice from benzene, m.p. 132–133°.

Anal. Calcd. for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98. Found: C, 59.89; H, 5.18.

Method B.—A solution of 8 g. of 5-nitro-*o*-cresol[2] in 30 ml. of ethanol was hydrogenated over platinum oxide catalyst. The product was isolated by evaporation to dryness and benzenesulfonated in pyridine. The reaction mixture was poured into water and the product was recrystallized from boiling water; 8 g. (45%). After further purification by recrystallization from benzene the substance melted at 131–132°, and the melting point of a mixture with the product of method A was not depressed. The infrared spectra of the products were essentially identical.

N-Benzenesulfonyl-3-dicarbethoxymethyl-4-phenylaniline.—To a suspension of diethyl sodiomalonate in 30 ml. of ether, prepared by the interaction of 4 ml. of diethyl malonate and 1.3 g. of sodium, 2.0 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate was added. The reaction mixture boiled and became homogeneous. It was extracted with water and the aqueous layer upon acidification precipitated 1.0 g. (45%) of product. It was recrystallized from ethanol, m.p. 143–144°.

Anal. Calcd. for $C_{25}H_{25}NO_6S$: C, 64.23; H, 5.39. Found: C, 64.56; H, 5.39.

N-Benzenesulfonyl-3-dicarbethoxymethyl-4-methylaniline.—The procedure above was applied to 1.0 g. of 4-methyl-*o*-quinolbenzenesulfonimide acetate, and 0.6 g. (50%) of sulfonamide was obtained. The substance was purified by recrystallization from ethanol, m.p. 105–106°.

Anal. Calcd. for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72. Found: C, 58.95; H, 5.44.

N-Benzenesulfonyl-3-diacetylmethyl-4-phenylaniline.—To a suspension of sodioacetylacetone in 10 ml. of ether, prepared by adding 0.5 g. of sodium methoxide and 1.0 g. of acetylacetone, 1.2 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate was added. After standing overnight the ether was allowed to evaporate, and the residue was washed with water leaving a brown crystalline residue. Recrystallization from ethanol gave 0.6 g. (45%) of the sulfonamide, m.p. 182–183°.

Anal. Calcd. for $C_{23}H_{21}NO_4S$: C, 67.80; H, 5.20. Found: C, 67.99; H, 5.24.

N-Benzenesulfonyl-3-diacetylmethyl-4-methylaniline.—The procedure above was applied to 4-methyl-*p*-quinolbenzenesulfonimide acetate and yielded 0.6 g. (50%) of adduct, m.p. 169–170°.

Anal. Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.55. Found: C, 62.77; H, 5.57.

N-Benzenesulfonyl-3-cyano-4-phenylaniline.—A mixture of 1.0 g. of 4-phenyl-*p*-quinolbenzenesulfonimide acetate, 0.5 g. of sodium cyanide and 15 ml. of ethanol was gently warmed and shaken for a few minutes. A fluffy-yellow precipitate formed. After standing one day at room temperature the mixture was filtered, and the precipitate, after being washed with water and dried, weighed 0.3 g. (30%). The substance was purified by recrystallization from ethanol, m.p. 182–183°.

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22; N, 8.38. Found: C, 68.49; H, 4.22; N, 8.34.

The infrared spectrum shows C=N at 1550 cm.$^{-1}$, $-SO_2-$ at 1450 cm.$^{-1}$, C≡N at 2220 cm.$^{-1}$, and no N-H.

The filtrate above was acidified with concd. hydrochloric acid, and 0.7 g. (70%) of tan solid was collected and recrystallized from benzene and from ethanol, m.p. 162–163°. The product presumably is quinol imide acetate with the acetate group replaced by the cyano group.

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22. Found: C, 68.54; H, 4.16.

The infrared spectrum shows C≡N at 2220 cm.$^{-1}$ and the usual features of benzenesulfonimides.

N-Benzenesulfonyl-3-cyano-4-methylaniline. A.—The procedure above was applied to 1.0 g. of 4-methyl-*p*-quinolbenzenesulfonimide acetate, and no water-insoluble precipitate was formed. Acidification of the solution gave 0.7 g. (75%) of sulfonamide which was recrystallized from ethanol and from benzene, m.p. 140–141°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.74; H, 4.44. Found: C, 62.16; H, 4.30.

B.—A suspension of 1.8 g. of 5-nitrotoluamide[3] in 30 ml. of ethanol was hydrogenated over platinum oxide catalyst, and the product was isolated by evaporation to dryness. The amine was dissolved in 5 ml. of pyridine, and 3 ml. of benzenesulfonyl chloride was added. After heating one hour on the steam-bath, the mixture was poured into water, taken up in ether, and extracted with dilute hydrochloric acid and aqueous sodium hydroxide. The alkaline extract was acidified, and the precipitated sulfonamide was again taken up in ether and dried. When the solution was concentrated to 15 ml., a white precipitate was filtered off (1.0 g.) and the filtrate was evaporated to dryness. The residue, recrystallized from ethanol–water and from benzene–petroleum ether (b.p. 90–100°), weighed 15 mg., m.p. 138–139°.

The melting point of a mixture with the product of method A showed no depression and the infrared spectra are identical.

Oxidation of N-Benzenesulfonyl-2,6-dimethylaniline.—A mixture of 10 g. of N-benzenesulfonyl-2,6-dimethylaniline, 17 g. of lead tetraacetate, and 100 ml. of chloroform was allowed to stand two days at room temperature. The mixture was shaken with water, filtered to remove lead dioxide, washed, concentrated, extended to 100 ml. with ether, and extracted four times with 5% aqueous sodium hydroxide. The amount of material recovered by acidification of the extract was 4.0 g. The ether layer was evaporated to an oil which partially crystallized, and addition of 20 ml. of benzene caused further crystallization. The substance was recrystallized from ethanol to give 3.0 g. (25%) of white crystals, m.p. 176–177°.

Anal. Calcd. for $C_{32}H_{32}O_8N_2S_2$: C, 60.34; H, 5.07. Found: C, 60.11; H, 5.28.

The infrared spectrum shows the usual features of quinol imide acetates.

(2) O. Michel and E. Grandmougin, *Ber.*, **26**, 2351 (1893).

(3) L. Van Scherpenzeel, *Rec. trav. chim.*, **20**, 171 (1901).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Strong Analgesics. The Preparation of Some Ethyl 1-Aralkyl-4-phenylpiperidine-4-carboxylates[1]

BY BILL ELPERN, LORRAINE N. GARDNER AND LEONARD GRUMBACH

RECEIVED OCTOBER 9, 1956

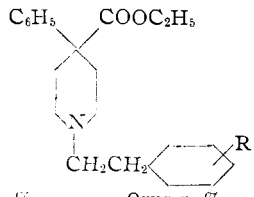
A series of ethyl 1-aralkyl-4-phenylpiperidine-4-carboxylates has been prepared and evaluated for analgesic potency by the rat thermal stimulus method. The most effective aralkyl groups were those having a three-carbon unsaturated chain.

The study of synthetic analgesics in this Laboratory during the past few years has been concerned with modifying the structure of meperidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate.

(1) This paper was presented at the 130th A.C.S. Meeting in Atlantic City, N. J., September, 1956.

TABLE I

ETHYL 1-(SUBSTITUTED-PHENETHYL)-4-PHENYLPIPERIDINE-4-CARBOXYLATES

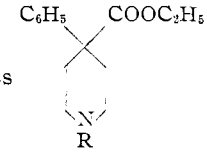


R	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Oxygen, % Calcd.	Found	Activity[b]
H-	193–195	$C_{22}H_{27}NO_2 \cdot HCl$	70.68	70.95	7.55	7.76	9.48[a]	9.32	2
3-OH	128–138	$C_{22}H_{27}NO_3$	74.75	74.81	7.70	7.57	13.56	13.00	1
3-OCH_3	151–155	$C_{23}H_{29}NO_3 \cdot HCl$	68.40	68.70	7.49	7.74	8.78[a]	8.89	3
4-OCH_3	77–78	$C_{23}H_{29}NO_3$	75.19	75.23	7.95	7.74	13.06	13.00	3
3,4-Di-OCH_3	180–185	$C_{24}H_{31}NO_4 \cdot HCl$	66.42	66.36	7.43	7.49	14.71	15.05	6
2-NO_2	188–191	$C_{22}H_{26}N_2O_4 \cdot HCl$	63.09	63.04	6.50	6.41	15.28	15.10	1
2-NH_2	235–238	$C_{22}H_{28}N_2O_2 \cdot 2HCl$	62.12	62.22	7.11	6.97	7.53	7.50	5
4-NO_2	113–114	$C_{22}H_{26}N_2O_4$	69.09	69.38	6.85	7.00	16.73	17.05	6
4-NH_2	247 dec.	$C_{22}H_{28}N_2O_2 \cdot 2HCl$	62.12	62.03	7.11	6.91	16.67[a]	16.48	11
4-CH_3CONH-	266–268	$C_{24}H_{30}N_2O_3 \cdot HCl$	66.88	66.80	7.25	7.06	8.23[a]	8.33	7
4-C_2H_5NH-	218–>240	$C_{24}H_{32}N_2O_2 \cdot 2HCl$	63.58	63.49	7.56	7.28	7.06	7.05	7
Meperidine									1

[a] Analysis for chlorine. [b] By intraperitoneal injection in rats.

TABLE II

ETHYL 1-ARALKYL-4-PHENYLPIPERIDINE-4-CARBOXYLATES



R	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Chlorine, % Calcd.	Found	Activity[d]
$C_6H_5CH(CH_3)CH_2$-	214–215	$C_{23}H_{29}NO_2 \cdot HCl$	71.21	71.68	7.80	8.07	9.14	8.69	0.5
$C_6H_5CH_2CH(CH_3)$-	214–215	$C_{23}H_{29}NO_2 \cdot HCl$	71.21	71.19	7.80	7.43	9.14	8.95	0
2-(C_5H_4N)CH_2CH_2-[b]	172–173	$C_{21}H_{26}N_2O_2 \cdot 2HCl$	61.31	60.84	6.86	6.74	17.24	17.11	5
4-(C_5H_4N)CH_2CH_2-[b,c]	205–209	$C_{21}H_{26}N_2O_2 \cdot 2HCl$	61.31	61.07	6.86	6.41	17.24	17.06	9

[a] Analyzed for oxygen. [b] (C_5H_4N) represents pyridyl. [c] Free base, m.p. 64–66°. [d] By intraperitoneal injection in rats.

Two recent publications[2,3] in this field have prompted us to report our findings.

A number of aralkyl halides were prepared and treated with ethyl 4-phenylpiperidine-4-carboxylate by refluxing in butanol in the presence of sodium carbonate.

The N-phenethyl compound could be alternatively prepared by the catalytic reduction of a mixture of phenylacetaldehyde and ethyl 4-phenylpiperidine-4-carboxylate.

Vinylpyridines condensed readily with ethyl 4-phenylpiperidine-4-carboxylate to give the corresponding ethyl 4-phenyl-1-pyridylethylpiperidine-4-carboxylates.

When the aralkyl group carried an aromatic nitro group this could be reduced catalytically to the corresponding amine which in turn could be acylated or reductively ethylated with acetaldehyde.

In the case of ethyl 4-phenyl-1-(3-phenyl-2-propynyl)-piperidine-4-carboxylate, use was made of the Mannich reaction between ethyl 4-phenylpiperidine-4-carboxylate, formaldehyde and phenylacetylene.[4]

The pharmacological evaluation of these compounds for analgesic potency by the Bass, Vander Brook modification[5] of the D'Amour, Smith[6] rat thermal stimulus method will be reported more fully elsewhere but a brief summary can be given here. When ethyl 4-phenylpiperidine-4-carboxylate bore a substituted phenethyl group on the nitrogen, the potency was equal to or greater than when the nitrogen bore a methyl group. The most potent of this group of substituents was 4-aminophenethyl. The replacement of the phenethyl by pyridylethyl enhanced the potency with 4-pyridylethyl being more effective than 2-pyridylethyl. Lengthening the distance between the aryl group and the nitrogen results in peak activity with three methylene groups. The activity is increased still further if a double bond is included in the three carbon chain, but the activity is abolished when a triple bond is included. This was not unexpected since phenylpropargyl resembles benzyl in its spatial requirements and this latter group results in a very weak analgesic. Since the 4-pyridylethyl group gave a much more potent compound than did the phenethyl group and the phenylpropyl group also gave a much more potent compound, it was surprising to find that the 4-pyridylpropyl compound was no more potent than the phenethyl compound. As with the unsubstituted aralkyl

(2) T. D. Perrine and N. B. Eddy, *J. Org. Chem.*, **21**, 125 (1956).

(3) J. Weijlard, P. D. Orahovats, A. P. Sullivan, G. Purdue, F. D. Heath and K. Pfister, THIS JOURNAL, **78**, 2342 (1956).

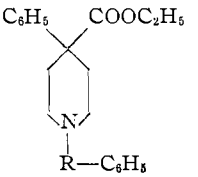
(4) C. Mannich and F. T. Chang, *Ber.*, **66**, 418 (1933).

(5) W. B. Bass and M. J. Vander Brook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1952).

(6) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

TABLE III

ETHYL 1-PHENYLALKYL-4-PHENYLPIPERIDINE-4-CARBOXYLATES

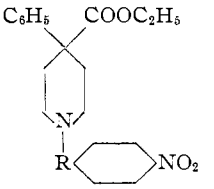


R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[a]
$-CH_2-$		$C_{21}H_{25}NO_2 \cdot HCl$							0.25
$-CH_2CH_2-$	193–195	$C_{22}H_{27}NO_2 \cdot HCl$	70.68	70.95	7.55	7.76	9.48	9.32	2
$-CH_2CH_2CH_2-$	170–171	$C_{23}H_{29}NO_2 \cdot HCl$	71.21	71.19	7.80	7.91	9.14	9.10	13
$-CH_2CH_2CH_2CH_2-$	146–148	$C_{24}H_{31}NO_2 \cdot HCl$	71.72	71.51	8.03	7.72	8.82	8.79	2
$-CH_2CH{=}CH-$	211–213	$C_{23}H_{27}NO_2 \cdot HCl$	71.59	71.32	7.31	7.43	9.19	8.90	29
$-CH_2C{\equiv}C-$	167–169	$C_{23}H_{25}NO_2 \cdot HCl$	71.97	71.82	6.83	6.70	9.24	9.22	0
$4\text{-}(C_5H_9N)CH_2CH_2CH_2$[b]	95–96	$C_{22}H_{28}N_2O_2 \cdot 2HCl$	62.12	62.26	7.11	7.06	7.53[c]	7.35	2

[a] By intraperitoneal injection in rats. [b] (C_5H_4N) represents pyridyl. [c] Analyzed for oxygen.

TABLE IV

ETHYL 1-(4-NITROPHENYLALKYL)-4-PHENYLPIPERIDINE-4-CARBOXYLATES

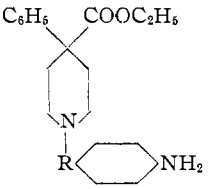


R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Oxygen, % Calcd.	Oxygen, % Found	Activity[a]
$-CH_2-$	83–85	$C_{21}H_{24}N_2O_4$	68.46	68.36	6.57	6.66	17.38	17.30	0
$-CH_2CH_2-$	113–114	$C_{22}H_{26}N_2O_4$	69.09	69.38	6.85	7.00	16.73	17.05	6
$-CH_2CH_2CH_2-$	172–174	$C_{23}H_{28}N_2O_4 \cdot HCl$	63.82	63.34	6.75	7.08	14.78	14.40	5
$-CH_2CH_2CH_2CH_2-$	171–173	$C_{24}H_{30}N_2O_4 \cdot HCl$	64.49	64.45	6.99	6.77	14.32	14.11	0.5
$-CH_2CH{=}CH-$	128–131	$C_{23}H_{26}N_2O_4$	70.04	70.35	6.65	6.32	16.23	16.04	10

[a] By intraperitoneal injection in rats.

TABLE V

ETHYL 1-(4-AMINOPHENYLALKYL)-4-PHENYLPIPERIDINE-4-CARBOXYLATES



R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Activity[c]
$-CH_2-$	196–203	$C_{21}H_{26}N_2O_2 \cdot 2HCl$	61.33	61.74	6.86	6.77	7.78[a]	7.63	1
$-CH_2CH_2-$	247 dec.	$C_{22}H_{28}N_2O_2 \cdot 2HCl$	62.12	62.03	7.11	6.91	16.67	16.48	11
$-CH_2CH_2CH_2-$	190–192	$C_{23}H_{30}N_2O_2 \cdot 2HCl \cdot H_2O$	60.80	60.71	7.49	7.76	15.50	15.06	6
$-CH_2CH_2CH_2CH_2-$	225–227	$C_{24}H_{32}N_2O_2 \cdot HCl$	69.14	69.25	7.98	8.19	8.50	8.49	2
$-CH_2CH{=}CH-$	167–170	$C_{23}H_{28}N_2O_2 \cdot 2HCl$[b]			13.52[a]	13.20	14.96	14.85	12

[a] Analyzed for oxygen. [b] Analyzed as dihydrate. [c] By intraperitoneal injection in rats.

groups, the nitro and aminoaralkyl groups both showed a peak in activity when the aryl group was separated from the nitrogen by a three-carbon chain having a double bond; however, the 4-aminocinnamyl group was less than half as effective as the unsubstituted cinnamyl group, whereas the 4-aminophenethyl group was about five times as effective as the unsubstituted phenethyl group.

Experimental[7]

The following intermediates were either commercially available or were prepared by methods reported in the literature: benzyl chloride, phenylacetaldehyde, phenethyl bromide, 3-methoxyphenethyl bromide, 4-methoxyphenethyl bromide, 3,4-dimethoxyphenethyl bromide, 2-nitrophenethyl bromide, phenylpropyl bromide, phenylbutyl bromide, cinnamyl bromide, phenylacetylene, 4-pyridylpropanol, 4-nitrobenzyl chloride, 4-nitrophenethyl bromide, 4-nitrophenylpropyl bromide, 4-phenylbutanol and 4-nitrocinnamyl alcohol.

3-Hydroxyphenethyl Bromide.—3-Methoxyphenethyl alcohol (10.8 g., 0.07 mole) was added to a mixture of 37.8 g. of 48% hydrobromic acid and 7.1 g. of concentrated sulfuric acid. After refluxing for six hours, the mixture was allowed to stand at room temperature overnight, then diluted with 75 ml. of water and extracted with benzene. The benzene solution was washed first with sulfuric acid then with water to remove any unreacted alcohol. The benzene solution was extracted with 10% aqueous sodium hydroxide solution to remove the phenol. The alkaline extract was treated with decolorizing carbon and then acidified with acetic acid. The pink oil that formed gave a strong test for phenol and was used without further purification.

(7) Melting points corrected.

1-Phenyl-2-propyl Bromide.—Phenylacetone was reduced catalytically, using Raney nickel, to the corresponding alcohol in 90% yield (b.p. 113–115° (25 mm.), $n^{27}D$ 1.5180). This was then converted to the bromide using the procedure described in the first example. A 75% yield of bromide was obtained boiling at 115–118° (30 mm., $n^{27}D$ 1.5378.

2-Phenyl-1-propyl Bromide.—α-Phenylpropionaldehyde was reduced catalytically using Raney nickel to the corresponding alcohol in 80% yield (b.p. 121–124° (25 mm.), $n^{25}D$ 1.5221). This was then converted to the bromide using the procedure described in the first example. A 61% yield of bromide was obtained boiling at 113–118° (30 mm.), $n^{27}D$ 1.5421.

4-Pyridylpropyl Bromide.—3-(4-Pyridyl)-propanol (27.4 g., 0.2 mole) was refluxed four hours with 350 ml. of 48% hydrobromic acid. After concentrating the reaction mixture to dryness *in vacuo* on a steam-bath, the red-brown solid was crystallized from alcohol–ether twice; yield 34.4 g. (61%), m.p. 123–124°.

Anal. Calcd. for $C_8H_{11}Br_2N$: Br, 56.9. Found: Br, 56.3.

4-(4-Nitrophenyl)-butyl Bromide.—The nitration of phenylbutyl bromide was carried out by a procedure identical to that used in the nitration of phenylpropyl bromide to give a 70% yield of material boiling at 122–135° (0.2 mm.), $n^{28}D$ 1.5664.

Anal. Calcd. for $C_{10}H_{12}BrNO_2$: Br, 30.96; O, 12.40. Found: Br, 30.75; O, 12.58.

4-Nitrocinnamyl Bromide.—4-Nitrocinnamyl alcohol (29 g., 0.16 mole) was suspended in 200 ml. of carbon tetrachloride. Fifteen grams of phosphorus tribromide (0.06 mole) in 100 ml. of carbon tetrachloride was added while maintaining the temperature below 10°. When the addition was completed stirring was continued at 10° for one hour, then one hour at room temperature and one hour at reflux. The mixture was next poured onto ice, the organic layer separated, washed with dilute sodium hydroxide, dilute hydrochloric acid and finally with water. The organic solution was evaporated *in vacuo* on a steam-bath to give an oil that solidified on cooling. Crystallization from 50 ml. of methanol gave 26.5 g. (67%) melting at 58–62°.

Anal. Calcd. for $C_9H_8BrNO_2$: Br, 33.02. Found: Br, 32.40.

Reaction between Ethyl 4-Phenylpiperidine-4-carboxylate and Various Halides.—The following general procedure is typical. A mixture of 13.4 g. (0.05 mole) of ethyl 4-phenylpiperidine-4-carboxylate hydrochloride, halide (0.05 mole), 20 g. of sodium carbonate anhydrous and 100 ml. of dry butanol was refluxed for 24 hours. The hot suspension was filtered free of inorganic salts and a small piece of Dry Ice was added to the clear filtrate. The absence of a precipitate indicated that all of the ethyl 4-phenylpiperidine-4-carboxylate had reacted since it forms a precipitate rapidly with carbon dioxide, even in the air. The clear filtrate was concentrated *in vacuo* on a steam-bath to an oil.

A slight excess of dilute aqueous hydrochloric acid was added and the mixture was heated to boiling, decolorizing charcoal added, filtered hot and the filtrate allowed to stand. The crystalline hydrochloride that came down was recrystallized from water or absolute ethanol. The yields were generally better than 60%.

Reaction between Ethyl 4-Phenylpiperidine-4-carboxylate and Vinylpyridines.—Ethyl 4-phenylpiperidine-4-carboxylate hydrochloride (13.4 g., 0.05 mole) was converted to its free base form by dissolving in 200 ml. of *n*-butyl alcohol, adding 2 g. (0.05 mole) of sodium hydroxide in a minimum of water and 100 ml. of saturated aqueous sodium chloride solution. The aqueous layer was quickly separated and the organic layer was added to 5.3 g. (0.05 mole) of freshly distilled vinylpyridine. The resulting solution was refluxed 24 hours, cooled, filtered, treated with carbon dioxide and then saturated with hydrogen chloride. Ether (200 ml.) was added and the resulting white precipitate was collected and crystallized from isopropyl alcohol and then absolute ethanol in 30–70% yields.

Ethyl 1-Phenethyl-4-phenylpiperidine-4-carboxylate.—A mixture of 90 g. of ethyl 1-benzyl-4-phenylpiperidine-4-carboxylate, 176 ml. of 2B alcohol, 17.6 ml. of acetic acid, 2.6 g. of palladium chloride, 2.6 g. of sodium acetate, 13 g. of charcoal and 53 ml. of water was treated with hydrogen at 50 pounds pressure at room temperature. The reduction was complete in 30 minutes. Thirty-six grams of phenylacetaldehyde (freshly distilled) was added to the mixture and again treated with hydrogen. Reduction was completed in an hour. After removing the catalyst by filtration the filtrate was concentrated *in vacuo*. The residual oil was taken up in ether, gaseous hydrogen chloride added and the white hydrochloride collected and crystallized from acetone in 50% yields.

Reduction of Ethyl 4-Nitrophenylalkyl-4-phenylpiperidine-4-carboxylates.—The nitro compound was suspended in absolute ethanol and reduced with hydrogen in the presence of platinum oxide at room temperature at approximately 800 pounds pressure. When the reduction was completed, the catalyst was removed by filtration. The filtrate was concentrated down to about one-fourth of the original volume, an equivalent of concentrated hydrochloric acid added and the product crystallized out. Recrystallization from aqueous alcohol or aqueous acetone gave the product in yields better than 60%.

Ethyl 1-(4-Acetamidophenethyl)-4-phenylpiperidine-4-carboxylate Hydrochloride.—The corresponding amino compound (8.1 g., 0.02 mole) was dissolved in a mixture of 50 ml. of water and 50 ml. of acetic acid. Acetic anhydride (2.5 g., 0.025 mole) was added and the resulting solution was warmed for 30 minutes on a steam-bath. Two milliliters of concentrated HCl was added and the hydrochloride salt formed immediately, which was collected and crystallized from water in 48% yield.

Ethyl 1-(4-Ethylaminophenethyl)-4-phenylpiperidine-4-carboxylate Dihydrochloride.—The corresponding amino compound (17.7 g., 0.05 mole) was reductively alkylated with 2.35 g. (0.054 mole) of acetaldehyde in a mixture of 150 ml. of alcohol, 3.2 ml. of acetic acid, 0.5 g. of sodium acetate and 9.5 ml. of water using palladium chloride on charcoal as the catalyst. The reduction was completed in three hours at 500 pounds pressure. The mixture was filtered and the filtrate concentrated *in vacuo* to a gum which was taken up in ether, saturated with HCl gas and the resulting solid dihydrochloride crystallized from dilute alcohol in 10% yield.

Ethyl 4-Aminocinnamyl-4-phenylpiperidine-4-carboxylate.—Ethyl 4-nitrocinnamyl-4-phenylpiperidine-4-carboxylate (3.15 g., 0.008 mole) was added all at once to 6.4 ml. of 2 *N* sodium hydroxide in 20 ml. of ethanol saturated with hydrogen sulfide. The mixture was warmed on a steam-bath until boiling started, then the steam was turned off and the reaction mixture was allowed to stand overnight. Water was added to the mixture, and it was extracted with benzene. The organic layer was concentrated to a red tar which was taken up in ether, hydrogen chloride gas added and the solid obtained was crystallized from alcohol. There was obtained one gram (26%) of material giving a positive test for a primary aromatic amine and for a double bond.

Acknowledgments.—We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer and staff for the chemical analyses, to Mr. A. Soria for the preparation of some of these compounds in larger quantities, and to Miss V. Fuller for technical assistance in the pharmacological evaluations.

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