The Synthesis and Biological Activity of Piperidylindanes

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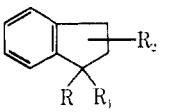
A variety of N-methylpiperidylindanes and -indenes were prepared and evaluated for analgetic activity by the phenylquinone writhing and Haffner's assays. Of these, 2-(1-methyl-4-piperidyl)-3-phenylindene (**20**) was found to be quite active in the phenylquinone-induced writhing assay, but inactive in Haffner's assay. Compound **20** is possibly an aspirin-type analgetic.

The analgetic activity of molecules containing the N-alkyl- or N-aralkylpiperidine nucleus (meperidine, morphine, fentanyl) and similar activity reported for some aminoindanes[1] prompted us to prepare a number of novel N-alkylpiperidylindanes and evaluate their analgetic activity. The compounds prepared are listed in Tables I and II.

stabilizing influence on the products of this reaction, since similar cyclizations in the absence of the nitrile led to extensive decomposition. Compound **3** was hydrolyzed and decarboxylated to the desired ketone **4** in 80% yield by refluxing in 18% HCl.

The corresponding 3-piperidyl-1-indanone **7** was prepared as shown in Scheme II.

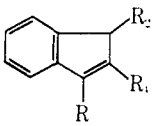
TABLE I



No.	R	R_1	R_2	Method	Mp, °C	Yield, %	Solvent	Formula	Analyses	ED_{50} writhing, mg/kg po	LD_{50}, mg/kg po
9	H	H	2-(1-Me-4-piperidyl)	C	220–221	73	MeOH	$C_{15}H_{21}N \cdot C_4H_4O_4$[a]	C, H, N	Inactive	500
10	H	OH	2-(1-Me-4-piperidyl)	D	179–180	84	MeOH–H_2O	$C_{15}H_{21}NO$	C, H, N	50	250
11	H	C_6H_5	2-(1-Me-4-piperidyl)	C	125–126	31	Heptane	$C_{21}H_{25}N$	C, H, N	Inactive	600
12	OH	C_6H_5	2-(1-Me-4-piperidyl)	A	185–186	78	MeOH–H_2O	$C_{21}H_{25}NO$	C, H, N	50	60
13	OH	*p*-ClC_6H_4	2-(1-Me-4-piperidyl)	A	221–222	45	EtOH	$C_{21}H_{24}ClNO$	N	50	150
14	H	OH	3-(1-Me-4-piperidyl)	D	210–211	40	EtOH	$(C_{15}H_{21}NO)_2 \cdot C_4H_4O_4$[a]	C, H, N	Inactive	150
15	H	C_6H_5	3-(1-Me-4-piperidyl)	C	168–169	55	EtOH–Et_2O	$C_{21}H_{25}N \cdot C_4H_4O_4$[a]	C, H, N	Inactive	150
16	OH	C_6H_5	3-(1-Me-4-piperidyl)	A	171–172	84	MeOH–H_2O	$C_{21}H_{25}NO$	C, H, N	100	300
17	OH	2-Piperidyl	3-C_6H_5	C	133–134	56	MeOH–H_2O	$C_{20}H_{23}NO$	C, H, N	Inactive	300
18	H	OH	3-(4-Piperidyl)	C	166–167	61	MeOH–Et_2O	$C_{14}H_{19}NO \cdot C_4H_4O_4$[a]	C, H, N	Inactive	600

[a] Characterized as the fumarate salt.

TABLE II



No.	R	R_1	R_2	Method	Mp, °C	Yield, %	Solvent	Formula	Analyses	ED_{50} writhing, mg/kg po	LD_{50}, mg/kg po
19	H	1-Me-4-piperidyl	H	B	204–205	30	MeOH	$C_{18}H_{23}N \cdot C_4H_4O_4$[a]	C, H, N	Inactive	200
20	C_6H_5	1-Me-4-piperidyl	H	B	209–210	80	MeOH–Et_2O	$C_{24}H_{27}N \cdot C_4H_4O_4$[a]	C, H, N	25	100
21	*p*-ClC_6H_4	1-Me-4-piperidyl	H	B	237–238	64	EtOH–Et_2O	$C_{24}H_{26}ClN \cdot HCl$[b]	N	30	300
22	*p*-$CH_3OC_6H_4$	1-Me-4-piperidyl	H	B	218–219	58	EtOH–Et_2O	$C_{25}H_{29}NO \cdot HCl$[b]	N	Inactive	1000
23	C_6H_5	H	1-Me-4-piperidyl	B	174–175	80	MeOH–Et_2O	$C_{24}H_{25}N \cdot C_4H_4O_4$[a]		100	250
24	C_6H_5	$CH_2CH_2N(CH_3)_2$	H	See Exptl	209–210	60	EtOH–Et_2O	$C_{19}H_{21}N \cdot HBr$[c]		Inactive	100
25	C_6H_5	$CH_2CH_2CH_2N(CH_3)_2$	H	B	183–184	30	EtOH–Et_2O	$C_{20}H_{23}N \cdot HCl \cdot 0.5H_2O$[b]	C, H, N, H_2O	Inactive	300

[a] Characterized as the fumarate salt. [b] Characterized as the hydrochloride salt. [c] Characterized as the hydrobromide salt.

Chemistry.—The common intermediate for the synthesis of 2-piperidylindanes and -indenes was the ketone **4**, prepared by the series of reactions outlined in Scheme I. The cyanoacetate **1**, obtained from the corresponding α,β-unsaturated cyanoacetate[2] by catalytic hydrogenation, was alkylated with benzyl chloride. The product (**2**) was saponified and the resulting cyano acid (**2a**) was cyclized with polyphosphoric acid to the keto amide **3** in good yield. The presence of the nitrile group in **2** (and the amide group in **3**) seems to exert a

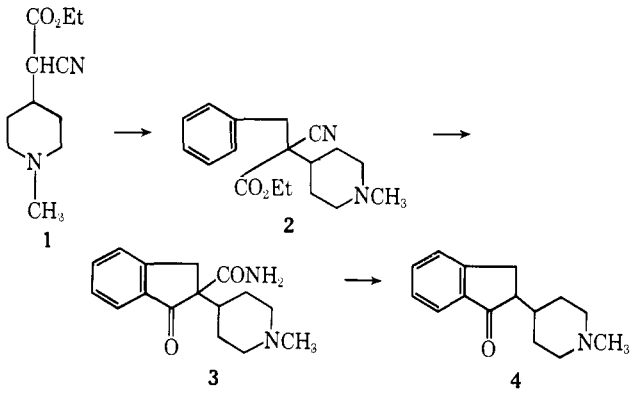
The acrylate **5** was obtained from 4-benzoylpyridine by reaction with triethyl phosphonoacetate in base. Quaternization with methyl iodide, followed by catalytic hydrogenation, gave the ester **6** which was saponified and cyclized with polyphosphoric acid to the ketone **7**.

The compounds listed in the tables were obtained from **4** and **7** by standard techniques. Although phenylmagnesium bromide failed to react with **4**, phenyl- and substituted phenyllithium reacted smoothly. Dehydrations of the resulting alcohols led to indenes. Compounds **10** and **14** were obtained by catalytic or sodium borohydride reductions.

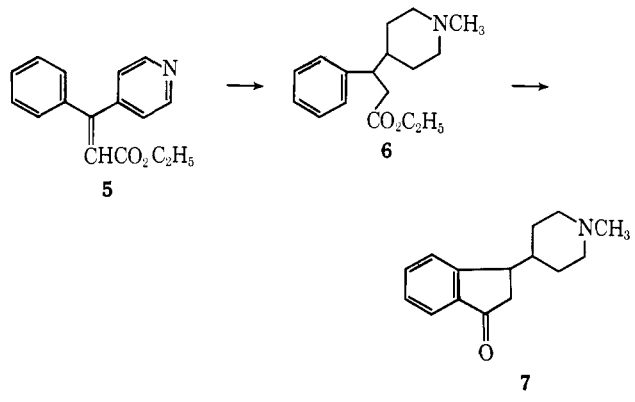
(1) L. B. Witkin, C. F. Heubner, F. Galdi, E. O'Keefe, P. Spitaletta, and A. J. Plummer, *J. Pharmacol. Exptl. Therap.*, **133**, 400 (1961).

(2) S. M. McElvain and R. E. Lyle, *J. Am. Chem. Soc.*, **72**, 384 (1950).

SCHEME I



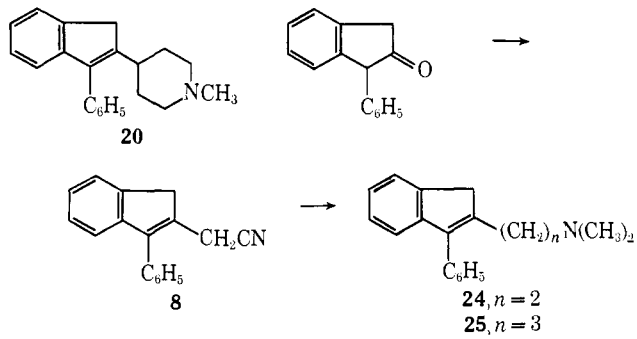
SCHEME II



Alternative approaches to some of the compounds listed in the tables proved either unsuccessful or too tedious. For example, attempted additions of N-methyl-4-piperidylmagnesium chloride[3] to 1-phenyl-2-indanone[4] and 3-phenyl-1-indanone[5] failed.

Addition of 4-pyridyllithium to the latter ketone gave only a poor yield of the corresponding hydroxypyridylindane and subsequent reactions (*e.g.*, dehydration, hydrogenation) of this material proved unsuccessful.

Since the pharmacologically most interesting compound was the indene **20**, its unbranched analogs **24** and **25** were prepared for comparison. The synthesis of **25**



followed very much the same path as the synthesis of **20**.

Compound **24** was prepared from 1-phenyl-2-indanone by reaction with diethyl cyanomethylphosphonate to give **8**. A small amount of the α,β-unsaturated analog of **8** was also isolated from this reaction. The nitrile **8** was reduced and the resulting amine dimethylated by the Eschweiler–Clarke technique to give **24**.

Pharmacology.—Analgetic activity was measured by the ability of test compounds to block phenylquinone-induced writhing in mice. In this procedure,[6] compounds were administered orally to groups of ten mice, 30 min prior to the injection of phenylquinone. The total number of animals not writhing starting at time zero (after phenylquinone) and continuing for three 15-min intervals (total time 45 min) was recorded and compared to that of a control group. The dose required to prevent 50% of the animals from writhing (ED_{50}) was determined.

The most active compound in this series, **20** in Table II, was compared to known analgetics in both the writhing (Table III) and Haffner's assays.[7] In the latter test, mice are given the test compounds orally and after 30 min an artery clip is applied to the root of the tail for 30 sec. The animals make continuous attempts to remove the noxious stimulus by biting the clip. Analgesia is determined by the insensitivity to the stimulus as shown by the absence of attempts at biting the clip.

TABLE III

Compd	ED_{50} writhing, mg/kg *po*
20	25
d-Propoxyphene HCl	50
Aspirin	250
Codein	35
Morphine	8

In the writhing assay, **20** was the most active member of this series. While its *p*-chloro analog **21** was also active, the *p*-methoxy derivative (**22**) was not. The indane **11** (Table I) as well as the unbranched analogs **24** and **25** were inactive.

In Haffner's assay **20** was inactive while the other analgetics tested (Table III), except aspirin, were active. Compound **20** was free of CNS side effects at the doses tested and had no antihistaminic activity. It was, therefore, assumed that antiwrithing properties of **20** were due to an analgetic effect, possibly of the aspirin type. Thus, the N-methylpiperidylindanes studied did not possess the potent analgetic activity of other N-methylpiperidine derivatives.

Experimental Section[8]

Ethyl Cyano(1-methyl-4-piperidyl)acetate (1).—A 200-ml EtOH solution of 41 g (0.19 mole) of ethyl (1-methyl-4-piperidylidene)-cyanoacetate containing 1 g of PtO_2 was hydrogenated at room temperature at an initial pressure of 3.5 kg/cm². After 20 min the H_2 uptake stopped, the catalyst was removed by filtration, the filtrate was concentrated, and the residual liquid was distilled to give 32.7 g of a light yellow liquid, bp 123–125° (0.7 mm). Its hydrochloride salt had mp 163–164°. *Anal.* ($C_{11}H_{18}N_2O_2\cdot$HCl) N.

Ethyl α-Benzyl-α-cyano-1-methyl-4-piperidineacetate (2).—To a 7.0-g (0.145 mole) NaH (52% in mineral oil) suspension in 100 ml of 1,2-dimethoxyethane was added ethyl cyano(1-methyl-4-piperidyl)acetate (30 g, 0.143 mole) dissolved in 100 ml of 1,2-

(3) E. L. Engelhardt, U. S. Patent 3,014,911 (Dec 26, 1961).
(4) A. C. B. Smith and W. Wilson, *J. Chem. Soc.*, 1342 (1955).
(5) D. B. Bruce, A. J. S. Sorrie, and R. H. Thomson, *ibid.*, 2403 (1953).
(6) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).
(7) F. Haffner, *Deut. Med. Wochschr.*, **55**, 731 (1929); for an evaluation of this method, see C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(8) All melting points are corrected (capillary tubes in oil bath) and all boiling points are uncorrected. Ir spectra were obtained on a Perkin-Elmer Model 21 spectrometer and uv spectra on a Cary Model 14 spectrometer. Absorption bands or peaks of the ir and uv spectra were as expected. Where the analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. $MgSO_4$ was the drying agent used throughout.

dimethoxyethane. After the evolution of H_2 stopped, benzyl chloride (20 g, 0.158 mole) was added and the resulting mixture was refluxed for 3 hr. It was concentrated to half its volume, diluted (H_2O), made acidic with dilute HCl, and washed (Et_2O). The aqueous layer was made basic with K_2CO_3 and extracted with ether. Drying and removal of the solvent left 34 g (79%) of a light orange oil. Its hydrochloride salt had mp 208–209° after one recrystallization from EtOH–Et_2O. *Anal.* ($C_{23}H_{27}N_2O_2$·NCl) C, H, N.

α-Benzyl-α-cyano-1-methyl-4-piperidineacetic Acid (2a).—Compound **2** (72 g, 0.24 mole) was hydrolyzed by refluxing in aqueous MeOH in the presence of 9.6 g (0.24 mole) of NaOH for 2.5 hr. After cooling, the reaction solution was acidified to pH 5 and the separated solid was collected by filtration, washed (H_2O), and dried to give 60.3 g (94%) of a white solid, mp 244° dec. *Anal.* ($C_{16}H_{20}N_2O_2$) C, H, N.

2-(1-Methyl-4-piperidyl)-1-oxo-2-indanecarboxamide (3).—To warm (60°) polyphosphoric acid (600 g) was added to 60 g (0.22 mole) of **2a** over a period of 45 min. The resulting mixture was stirred at 90–100° for 4 hr. It was then poured onto ice and the solution was made basic with solid KOH and extracted with $CHCl_3$. Drying and removal of the solvent left 47 g (78%) of a tan solid, mp 163–165°. Two recrystallizations from hexane–ethyl acetate gave white prisms, mp 165–165.5°. *Anal.* ($C_{16}H_{20}N_2O_2$) C, H, N.

2-(1-Methyl-4-piperidyl)-1-indanone (4).—2-(1-Methyl-4-piperidyl)-1-oxo-2-indanecarboxamide (31 g, 0.11 mole) was hydrolyzed (and decarboxylated) by refluxing for 3 hr in 180 ml of 18% HCl. After basification with NaOH, the product was extracted with ether and concentrated. Recrystallization of the residual solid (20.3 g, 79%, mp 91–95°) from hexane–EtOAc gave the product as white prisms, mp 99.5–101°. *Anal.* ($C_{15}H_{19}NO$) C, H, N.

Ethyl 1-Methyl-α-phenyl-4-piperidinepropionate (6).—A solution of 11 g of 4-[(β-carbethoxy-α-phenyl)vinyl]-1-methylpyridinium iodide in 150 ml of EtOH was hydrogenated in the presence of 1 g of PtO_2 catalyst at room temperature at an initial pressure of 3.5 kg cm^{-2}. After filtration from the catalyst, the crude product was converted to its fumarate salt which was recrystallized from EtOH–Et_2O to give 6.2 g (65%) of the product as white crystals, mp 123–124.5°. *Anal.* ($C_{17}H_{23}NO_2 \cdot C_4H_4O_4$) C, H, N.

3-(1-Methyl-4-piperidyl)-1-indanone (7).—A 110-g sample of **6** was hydrolyzed by refluxing with 16 g of NaOH in aqueous MeOH for 4.5 hr. After cooling, it was acidified with HCl and concentrated to dryness. The residue was added to 1000 g of polyphosphoric acid and the resulting mixture was stirred and heated on a steam bath for 2.5 hr. It was then poured into ice–water, made basic with KOH, and extracted with $CHCl_3$. Drying and removal of the solvent left a brown liquid which was distilled to give 37 g (45%) of a light yellow liquid, bp 160° (0.5 mm). A fumarate was prepared and recrystallized from EtOH–Et_2O to give white crystals, mp 179–180°. *Anal.* ($C_{15}H_{19}NO \cdot C_4H_4O_4$) C, H, N.

3-Phenyl-2-indeneacetonitrile (8).—A 21.6-g sample of NaH (50% on mineral oil) was washed with C_6H_6 to remove the mineral oil and suspended in dry 1,2-dimethoxyethane. To this suspension was added 80 g of diethyl cyanomethylphosphonate and the mixture was stirred until H_2 evolution stopped. A 1,2-dimethoxyethane solution of 80 g of 1-phenyl-2-indanone was then added and the resulting mixture was refluxed for 18 hr. It was then concentrated to one-third its volume and poured into H_2O and extracted (Et_2O). Drying and removal of the solvent left a brown oil which was crystallized in hexane and recrystallized from heptane–EtOAc to give 31 g (35%) of white prisms, mp 62–63°. *Anal.* ($C_{17}H_{13}N$) N.

1-Phenylindene-2-ethylamine.—To a 6-g suspension of $LiAlH_4$ in 100 ml of ether was added a solution of 30 g of 3-phenyl-3-indeneacetonitrile in 200 ml of ether and the resulting mixture was stirred at room temperature for 2 hr, then refluxed for 1 hr. H_2O was added to the reaction mixture and the inorganic solids were filtered. The filtrate was dried and concentrated and a hydrobromide salt of the residual oil was recrystallized three times from EtOH–Et_2O to give 10 g (32%) of a white solid, mp 248–250°. *Anal.* ($C_{17}H_{17}N \cdot HBr$) C, H, N.

The following experiments are representative of the methods used for the preparation of the compounds listed in Tables I and II. The physical constants of these products are listed in the tables.

Method A. 2-(1-Methyl-4-piperidyl)-1-phenyl-1-indanol (12). To an ether solution of PhLi (prepared from 21 g of PhBr and 1.8 g of Li) was added 17 g (0.07 mole) of 2-(1-methyl-4-piperidyl)-1-indanone, dissolved in 50 ml of ether. The resulting solution was refluxed for 18 hr and poured into ice–water and the separated solid was collected, dried, and purified.

Method B. 2-(1-Methylpiperidyl)-3-phenylindene (20). Compound **12** (32 g, 0.1 mole) was dehydrated by warming to 60° with 300 ml of 2 *M* H_2SO_4 for 20 min. The solution was then poured into a cold KOH solution and extracted with ether. Drying and removal of the solvent left 29 g of a clear yellow oil.

Method C. 1-Phenyl-2-(1-methyl-4-piperidyl)indane (11). Compound **20** (8 g, 0.028 mole) was hydrogenated at room temperature in 100 ml of glacial AcOH in the presence of PtO_2 catalyst (0.7 g) at an initial pressure of 3.5 kg cm^{-2}. After H_2 uptake stopped (3 hr), the catalyst was filtered, and the filtrate was concentrated, diluted (H_2O), made basic with K_2CO_3, and extracted with ether. Drying and removal of the solvent gave an oil which partially crystallized and was purified by recrystallization.

Method D. 2-(1-Methyl-4-piperidyl)-1-indanol (10). To a 0.7-g suspension of $NaBH_4$ in 40 ml of *i*-PrOH was added **11** (3.7 g, 0.016 mole) dissolved in the same alcohol and the resulting solution was stirred at room temperature for 16 hr, then heated at 60° for 2 hr, poured into dilute HCl, washed with ether, made basic with K_2CO_3, and extracted with $CHCl_3$. Drying and removal of the solvent left the product as a solid which was purified by recrystallization.

2-(3-Phenyl-2-indenyl)-N,N-dimethylethylamine (24). A 9.4-g sample of 1-phenylindene-2-ethylamine was treated with 32 ml of HCO_2H and 6.5 ml of 37% aqueous HCHO by refluxing for 6 hr. After cooling, the solution was made strongly acidic with 2 *N* HCl, evaporated to dryness, diluted with water, made basic with KOH, and extracted with ether. The hydrobromide salt of the crude product was prepared and recrystallized twice from EtOH–Et_2O to give 7.5 g (60%) of white crystals, mp 209–210°. *Anal.* ($C_{19}H_{21}N \cdot HBr$; C, H, N.

2-Benzyl-2-cyano-5-dimethylaminovaleric Acid. A 40-g (0.2 mole) sample of ethyl α-cyanodihydrocinnamate was alkylated with 37.4 g (0.3 mole) of dimethylaminopropyl chloride in 1,2-dimethoxyethane in the presence of 9.6 g of 50% NaH (on mineral oil) according to the procedure for the preparation of **2**. The crude product, ethyl 2-benzyl-2-cyano-5-dimethylaminovalerate, amounted to 47.2 g (82%). A 15-g (0.05 mole) portion of this ester was hydrolyzed with 2.3 g (0.05 mole) of NaOH as described for the hydrolysis of **2**. The product was recrystallized from water to give 6.6 g (50%) of white crystals, mp 204–205°. *Anal.* ($C_{13}H_{20}N_2O_2$) C, H, N.

2-Carbamyl-2-dimethylaminopropyl-1-indanone. A 50-g sample of 2-benzyl-2-cyano-5-dimethylaminovaleric acid was cyclized with polyphosphoric acid (700 g) as described for the preparation of **3**. The product was recrystallized from EtOAc–hexane to give 32 g (64%) of white crystals, mp 118–119°. *Anal.* ($C_{15}H_{20}N_2O_2$) C, H, N.

2-Dimethylaminopropyl-1-indanone. A 75.5-g (0.3 mole) sample of 2-carbamyl-2-dimethylaminopropyl-1-indanone was hydrolyzed and decarboxylated in 18% HCl as described in the preparation of **4**. The oily crude product (58 g, 90% pure by vpc) was converted to its hydrochloride salt and recrystallized from EtOH–Et_2O to give 47 g (65%) of 2-dimethylaminopropyl-1-indanone hydrochloride, mp 167–168° (lit.[9] mp 117–118°). *Anal.* ($C_{14}H_{19}NO \cdot HCl$) C, H, N.

3-(4-Pyridyl)-1-indanone. Dimethyl (phenyl-4-pyridylmethyl)malonate (87 g, 0.28 mole) was hydrolyzed by refluxing with 23 g (0.56 mole) of NaOH in aqueous MeOH for 4.5 hr. After cooling, the solution was acidified to pH 5–6 and the precipitated solid [presumably (phenyl-4-pyridyl)methylmalonic acid] was filtered and dried. It amounted to 73 g (92%), mp >250°. A 70-g sample of this diacid was then treated with 800 g of polyphosphoric acid at 90° for 5 hr. The reaction mixture was poured onto ice and made basic with KOH. The separated solid was filtered and amounted to 39 g (72%) of a light tan solid, mp 106–109°. Two recrystallizations from hexane–EtOAc gave white needles, mp 111–112°. *Anal.* ($C_{14}H_{11}NO$) C, H, N.

Acknowledgment.—We wish to thank Dr. H. R. Almond and Mrs. M. C. Christie for many of the analytical and spectral results.

(9) C. F. Huebner, U. S. Patent 2,947,756 (Aug 2, 1960). We are unable to explain the discrepancy in melting points.