Hydrogenated Benzo[f]quinolines and Benz[e]indoles as Analgetics. 1

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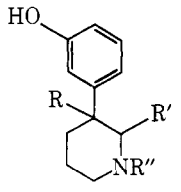
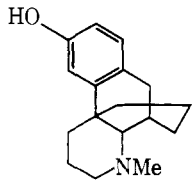
A series of octahydrobenzo[f]quinolines (IIIa) and hexahydro-1H-benz[e]indoles (IIIb), rigid structures related to 3-phenylpiperidine and pyrrolidine analgetics, has been synthesized. Structure–activity relationships were investigated by varying the structural parameters including a change in the stereochemistry of the ring junction. Several of the resulting compounds had analgetic activity on the order of meperidine.

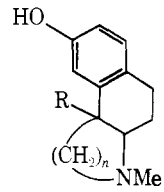
The research in the field of 3-alkyl-3-phenylpiperidine derivatives I in this laboratory has disclosed that a good analgetic activity with a low addiction liability resided in this type of compounds.[1] 3-Hydroxy-*N*-methyl-8-azades-*N*-morphinan (II), prepared also in our earlier work, proved to have codeine level activity.[2] Therefore, it became of interest for us to synthesize the octahydrobenzo[f]quinoline system IIIa, which may be looked upon as a relative of I with increased rigidity of the molecule. In structure IIIa, the aromatic and piperidine rings of I become linked in a manner related to the benzomorphans. Because two dia-



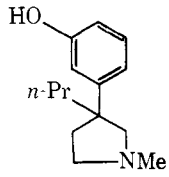
I



II



IIIa, $n = 3$
b, $n = 2$



IV

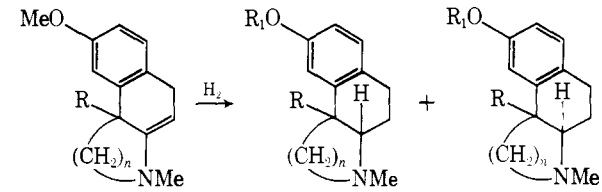
stereoisomeric forms differing at the junction of rings B and C are possible, it is of further interest to compare the analgetic activities of those isomers.

Described herein are the synthesis and analgetic activities of the cis and trans isomers of IIIa as well as the pyrrolidine analog, hexahydro-*H*-benz[e]indole derivative IIIb, bearing various alkyl groups at the quaternary carbon. IIIb may be considered a "bridged" version of profadol (IV), an interesting analgetic with mixed antagonist–agonist properties.[3,4]

Chemistry. The synthesis of the heterocyclic enamines Va,b, suitable precursors of IIIa,b, has been described in our previous paper.[7] Platinum-catalyzed hydrogenation of Va,b in EtOH gave, in each instance, a mixture of cis and trans isomers. The hydrochlorides of the cis isomers VIa,b were less soluble than those of the trans counterparts VIIa,b and the reverse was true for their picrates. Therefore, separation of the mixture was conveniently effected via these salts (Scheme I).

Stereochemical assignments for these isomers were made from the NMR spectra of their methiodides. While the chemical shifts of the two *N*-methyl signals of the trans-octahydrobenzo[f]quinoline (VIIa·MeI) were similar, the cis counterpart (VIa·MeI) displayed two distinct *N*-methyl signals, regardless of the size of alkyl groups, at about 3.0 and 2.25 ppm, respectively. The large separation of the signals of VIa·MeI (about 0.75 ppm) and the unusual high-field position of one of the signals are consistent with the

Scheme I



Va,b

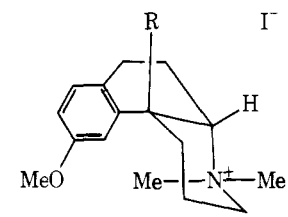
VIa,b, R_1 = Me
VIIIa,b, R_1 = H

VIIa,b, R_1 = Me
IXa,b, R_1 = H

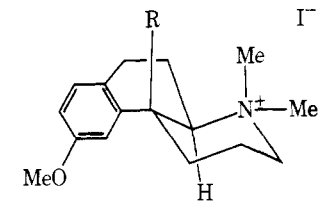
a, $n = 3$; b, $n = 2$

methiodides of cis isomer VIa having the conformation A with one *N*-methyl group falling well within the aromatic shielding zone.[8] A shielding factor difference of about 0.6 ppm between the two *N*-methyl groups in A was anticipated on the basis of Johnson and Bovey's equation.[9,10]

The methiodides of the pyrrolidine analog behaved similarly, the separation (about 0.45 ppm) of the two *N*-methyl signals invariably being observed for the cis isomer VIb·MeI.



A (VIa·MeI)

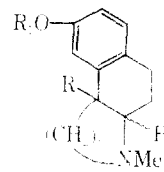


B (VIIa·MeI)

The proportion of the cis and trans isomers formed in hydrogenation of Va,b varied with size of the R group and ring size (n). Thus, when the size of the alkyl group is relatively small (R = Me, Et), the six-membered enamine Va was hydrogenated to give predominantly the cis isomer VIa with the uptake of hydrogen from the same side of the alkyl group. The reverse is true for Va with larger alkyl groups (R = Pr, Bu), the major products being the trans isomer VIIa. The five-membered enamine Vb, on the other hand, afforded invariably the cis isomer VIb as a major product. Hydrogenation of the six-membered enamine Va in EtOH containing 15% hydrochloric acid gave an increased yield of the trans isomer VIIa. This tendency is remarkable especially for Va with a small R group, the trans isomer being obtained as a predominant product. The stereochemistry of hydrogenation of the five-membered enamine Vb in acidic media was not materially different from that seen in neutral media. These results are summarized in the microfilm edition (see paragraph at end of paper regarding supplementary material). Finally, O-demethylation of VIa,b and VIIa,b gave the phenols VIIIa,b and IXa,b, respectively. The compounds prepared are listed in Table I.

Pharmacology. In Table II are given analgetic activities (mouse hot-plate method[11]) and acute (24 hr) toxicities of VIIIa,b and IXa,b. Comparative data for morphine, meperidine, and codeine are also presented. In general, both ben-

Table I. Hydrogenated Benzo[*f*]quinolines and Benz[*e*]indoles



No.	R_1	R	*n*	Isomerism	Mp, °C	Crystn solvent[a]	Formula[b]
1	CH_3	CH_3	2	Cis	197–198	A–B–C	$C_{15}H_{21}NO \cdot HCl$
2	CH_3	CH_3	2	Trans	204–206	A	$C_{15}H_{21}NO \cdot C_6H_3N_3O_7$
3	CH_3	C_2H_5	2	Cis	186–188	A–B–C	$C_{16}H_{23}NO \cdot HCl$
4	CH_3	C_2H_5	2	Trans	196–198	A	$C_{16}H_{23}NO \cdot C_6H_3N_3O_7$
5	CH_3	*n*-C_3H_7	2	Cis	190–191[c]	A	$C_{17}H_{25}NO \cdot HCl$
6	CH_3	*n*-C_3H_7	2	Trans	206–208	A	$C_{17}H_{25}NO \cdot C_6H_3N_3O_7$
7	CH_3	*n*-C_4H_9	2	Cis	168–170	A	$C_{18}H_{27}NO \cdot HCl$
8	CH_3	*n*-C_4H_9	2	Trans	179–181	A–B	$C_{19}H_{27}NO \cdot C_6H_3N_3O_7$
9	CH_3	CH_3	3	Cis	245–247	A–B–C	$C_{16}H_{23}NO \cdot HCl$
10	CH_3	CH_3	3	Trans	210–212	A–B	$C_{16}H_{23}NO \cdot C_6H_3N_3O_7$
11	CH_3	C_2H_5	3	Cis	190–192	A–B–C	$C_{17}H_{25}NO \cdot HCl \cdot H_2O$
12	CH_3	C_2H_5	3	Trans	231–233	B–D	$C_{17}H_{25}NO \cdot C_6H_3N_3O_7$
13	CH_3	*n*-C_3H_7	3	Cis	222–225	A	$C_{18}H_{27}NO \cdot HCl$
14	CH_3	*n*-C_3H_7	3	Trans	239–241	D	$C_{18}H_{27}NO \cdot C_6H_3N_3O_7$
15	CH_3	*n*-C_4H_9	3	Cis	207–208	A–B–C	$C_{19}H_{29}NO \cdot HCl$
16	CH_3	*n*-C_4H_9	3	Trans	209–211	D–E	$C_{19}H_{29}NO \cdot C_6H_3N_3O_7$
17	H	CH_3	2	Cis	208–210	E	$C_{15}H_{21}NO \cdot HBr \cdot 0.5H_2O$
18	H	C_2H_5	2	Cis	225–227	A–B–C	$C_{16}H_{23}NO \cdot HBr$
19	H	*n*-C_3H_7	2	Cis	199–201	A–B–C	$C_{17}H_{25}NO \cdot HBr$
20	H	*n*-C_3H_7	2	Trans	278–280	E	$C_{17}H_{25}NO \cdot HBr$
21	H	*n*-C_4H_9	2	Cis	188–190	E–C	$C_{18}H_{27}NO \cdot HBr$
22	H	*n*-C_4H_9	2	Trans	239–241	E–C	$C_{18}H_{27}NO \cdot HBr$
23	H	CH_3	3	Cis	243–245	B–F	$C_{15}H_{21}NO \cdot HBr$
24	H	CH_3	3	Trans	145–150[d]	G	$C_{15}H_{21}NO \cdot HCl \cdot H_2O$
25	H	C_2H_5	3	Cis	256–259	A–E–C	$C_{16}H_{23}NO \cdot HBr$
26	H	C_2H_5	3	Trans	253–255	E–C	$C_{16}H_{23}NO \cdot HBr$
27	H	*n*-C_3H_7	3	Cis	264–266	B–C	$C_{17}H_{25}NO \cdot HBr$
28	H	*n*-C_3H_7	3	Trans	268–270	B–C	$C_{17}H_{25}NO \cdot HCl$
29	H	*n*-C_4H_9	3	Cis	240–242	A–B–C	$C_{18}H_{27}NO \cdot HBr$
30	H	*n*-C_4H_9	3	Trans	261–263	E–C	$C_{18}H_{27}NO \cdot HBr$

[a] A, Me_2CO; B, EtOH; C, Et_2O; D, DMF; E, MeOH; F, H_2O; G, *i*-C_3H_7OH. [b] All compounds were analyzed for C, H, and N. [c] Lit.[6] mp 195°. [d] Turbid melt at 112–115°.

zo[*f*]quinolines and benz[*e*]indoles exhibit good analgetic potencies, ranging from morphine-like to codeine-like. For instance, the six-membered amine **23** is a more potent analgetic than meperidine. This is in contrast to simple 3-phenylpiperidines where the NCH_3 derivative I (R = R′ = R″ = CH_3) was analgetically inactive.[1] Therefore, the transformation of I into the more rigid structure IIIa enhanced the analgetic activity. Regarding the effect of the size of alkyl groups, the compounds with larger substituents than CH_3 are more active in the five-membered derivatives. This parallels the reported observation in the 3-alkyl-3-phenylpyrrolidine analgetics.[12] In the six-membered amines, C_2H_5 substitution is apparently optimal for analgetic effectiveness. The activity of cis isomers **19** and **21** surpasses that of the trans counterparts **20** and **22** in the pyrrolidine derivatives. However, in the six-membered amines, the relationship between analgetic activities and the stereochemistry of the ring junction is not uniform and apparently varies with the size of alkyl substituents. It seems that these results could be ascribed to a possible conformational change of the molecule due to the change of the size of the alkyl group in the cis isomer VIa. Although the conformation of VIa·MeI was established, no data are available for those of the corresponding free base or protonated salt.

The pyrrolidine **19**, a rigid structure related to profadol, will not suppress abstinence syndrome in morphine-dependent monkeys but does not exhibit antagonism.[13] Therefore, contrary to the experience in profadol, **19** seems to fall under the category of agonist–analgetics.[15]

Examination of analgetic activities of the optical isomers and the N-substituted derivatives would shed more light on the structure–activity relationships of this series of compounds. Further studies along these lines are in progress and will be the subject of a following paper.

Experimental Section

All melting points were determined with a Yamato apparatus are are uncorrected. GLC were obtained on a Perkin-Elmer 800 instrument using a 2% OV-17 column. NMR spectra were measured in CF_3CO_2H with a JEOL ME-60 spectrometer at ambient temperature and Me_4Si was used as an external standard. The organic solutions were dried over Na_2SO_4 and all evaporations were carried out in vacuo. Where analyses are indicated only by symbols of the elements, they are within ±0.4% of the theoretical values.

Catalytic Hydrogenation of Enamines V. A. Reduction in EtOH. In a typical reduction, a mixture of 10b-ethyl-9-methoxy-4-methyl-1,2,3,4,6,10b-hexahydrobenzo[*f*]quinoline (Va, R = Et) (regenerated from 10 g of the picrate), 0.25 g of PtO_2, and 80 ml of EtOH was shaken in H_2 atmosphere at room temperature for 2 hr. The catalyst was removed and the filtrate was concentrated to give 5.3 g of oil. GLC analysis showed two isomers (63:37). To this oil

Table II. Analgetic Activity of Benz[e]indoles and Benzo[f]quinolines

Compd[a]	ED_{50}, mg/kg[b]	LD_{50}, mg/kg
17	17.6 (13.8–22.6)[c]	334.0 (262.3–437.7)[c]
18	11.1 (7.7–16.0)	156.2 (104.5–233.5)
19	9.2 (6.7–12.7)	104.7 (81.7–134.4)
20	18.1 (15.7–24.3)	169.4 (144.0–199.2)
21	9.1 (6.6–12.7)	93.4 (78.7–110.8)
22	11.4 (6.7–19.7)	131.1 (110.5–155.5)
23	7.6 (4.8–12.0)	169.4 (144.0–199.2)
24	*d*	265.0 (205.0–342.4)
25	5.7 (4.6–7.1)	33.2 (22.0–50.1)
26	5.7 (3.6–9.1)	150.1 (126.7–177.8)
27	14.1 (12.6–20.3)	210.3 (131.7–335.9)
28	23.4 (18.6–30.5)	144.8 (118.7–176.6)
29	22.5 (9.1–55.7)	>338.0
30	11.5 (6.7–19.8)	89.7 (76.2–105.4)
Codeine[e]	24.3 (19.1–31.0)	231.2 (203.5–279.2)
Meperidine[f]	12.3 (9.1–16.9)	273.0 (221.0–331.0)
Morphine[f]	4.5 (3.8–5.3)	407.0 (351.2–461.5)

[a] Compounds were tested as the salts represented in Table I. [b] Tested sc in mice according to the hot-plate procedure.[11] [c] Confidence interval (95%). [d] No effect with a dose of 22.5 mg/kg. [e] Phosphate. [f] Hydrochloride.

was added a solution of picric acid (4.8 g) in 60 ml of Me_2CO and the mixture was allowed to stand overnight. The precipitate was filtered and washed with Me_2CO to give 3.46 g (34.4%) of *trans*-10b-ethyl-9-methoxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (12) picrate: mp 229–232°. The analytical sample was obtained from DMF–EtOH: mp 231–233°. The methiodide was prepared from the free base (regenerated from the picrate) in Me_2CO: mp 249–250° dec; needles from Me_2CO–EtOH–Et_2O; NMR δ 3.03 (6 H, s, $^+NMe_2$). Anal. ($C_{18}H_{28}NOI$) C, H, N. Solvent was removed from the picrate's mother liquor (Me_2CO). Regeneration of free base from the residue and its conversion to the HCl salt gave, after recrystallization from Me_2CO–EtOH–Et_2O, 3.71 g (61%) of *cis*-10b-ethyl-9-methoxy-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (11) HCl: mp 190–192°. The methiodide was recrystallized from Me_2CO–EtOH–Et_2O and had mp 201–203° dec: NMR δ 2.25 (3 H, s, ^+NMe) and 3.00 (3 H, s, ^+NMe). Anal. ($C_{18}H_{28}NOI$) C, H, N.

B. Reduction in EtOH Containing Hydrochloric Acid. In a typical procedure, a mixture of Va (R = Et) (regenerated from 27 g of the picrate), 0.5 g of PtO_2, 100 ml of EtOH, and 200 ml of 15% aqueous HCl was shaken in H_2 atmosphere at room temperature for 20 hr. The filtered solution was evaporated and the residue was made basic with NH_4OH. The resultant free base was extracted with Et_2O and washed with H_2O. Evaporation of the dried extracts gave 14.5 g of oil. Separation of this oil by the method described above gave 17.4 g (64.5%) of 12·picrate, mp 229–230°, and 5.25 g (32%) of 11·HCl, mp 189–191°.

O-Demethylation. In a typical procedure, a mixture of *cis*-8-methoxy-3-methyl-9b-*n*-propyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[e]indole (5) hydrochloride (2 g) and 10 ml of 47% HBr was refluxed for 1 hr. The mixture was evaporated to dryness and the residue was digested with 10 ml of Me_2CO. Filtration and recrystallization from Me_2CO–EtOH–Et_2O gave 2.07 g (93%) of *cis*-8-hydroxy-3-methyl-9b-*n*-propyl-2,3,3a,4,5,9b-hexahydro-1*H*-benz[e]indole (19) hydrobromide: mp 199–201°.

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Supplementary Material Available. A table of yields of the cis and trans isomers via hydrogenation of enamines V will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JMC-75-697.

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