Tricyclic Analogs of the Prodines

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A search for an analgesic with the potency of β-prodine and with the quality of analgesia associated with the benzomorphans led to the preparation of the octahydrobenz[*f*] isoquinoline system, a system where β-prodine is bridged in a manner related to the benzomorphans. Three different syntheses of this system are described. They permit access to a variety of substitution patterns as well as to the possible stereoisomers. The hybrid β-prodine–benzomorphan system displayed interesting CNS activity.

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La recherche d'un analgésique aussi puissant que la β-prodine mais d'une pureté d'action correspondant à celle des benzomorphanes nous a amené à préparer le système tricyclique octahydrobenz[*f*]isoquinoline. Dans ce système les deux cycles de la β-prodine sont pontés à la manière des benzomorphanes. Trois synthèses ont été développées permettant l'accès aux différents stéréoisomères et à une variété de substitution. Ce système hybride β-prodine–benzomorphane possède des propriétés pharmacologiques intéressantes.

The enhanced analgesic activity of β-prodine **1** over its α-isomer **2** (1) (Fig. 1) has been discussed in terms of increased contact with the receptor surface due to axial phenyl group conformation (2), restricted rotation favoring coplanarity of the phenyl and piperidine rings (3), and increased ability of the β-isomer to penetrate the blood–brain barrier (4). Extensive structure–activity relationship in this area has shown that these explanations cannot fully account for the observed difference in potency. At present the accepted view (5) is that the analgesic receptor, although unique, is flexible enough to accommodate a wide variety of structures, the observed analgesia being related to the ability of the drug to reach the receptor site and to achieve ionic binding with the receptor.

In an attempt to obtain an analgesic with a level of activity equal or superior to β-prodine but with a quality of analgesia associated with many benzomorphans (*e.g.* **3**; low physical dependance) we have prepared two series of compounds, **4** and **24**, in which the phenyl and methyl groups of the prodines are incorporated into an additional ring thus fixing both the conformation of the phenyl group and the angle between the phenyl and the piperidine planes. The two rings become linked in a manner similar to the benzomorphans, the junction being shifted by one carbon atom. In addition, a change in the

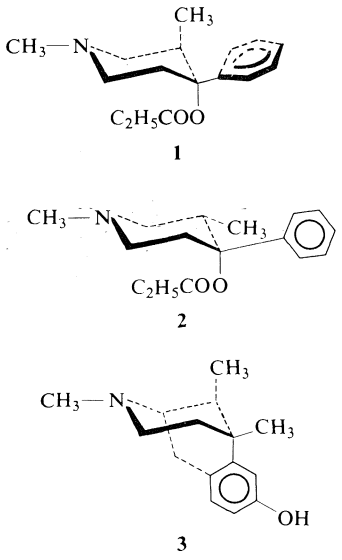


FIG. 1. Analgetic potency of the prodines and benzomorphans.

ED_{50}: 1.2 mg/kg (1)

ED_{50}: 5 mg/kg ED_{50}: 8.9 mg/kg (6)

stereochemistry of the new ring junction as well as an increase in the number of methylenes linking the methyl and phenyl groups result in a convenient variation of the angle between the two planes (Fig. 2).

In structure **4***b* the aromatic and piperidine

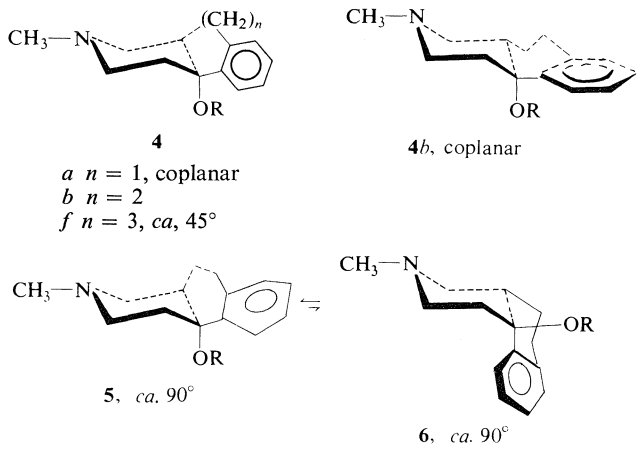


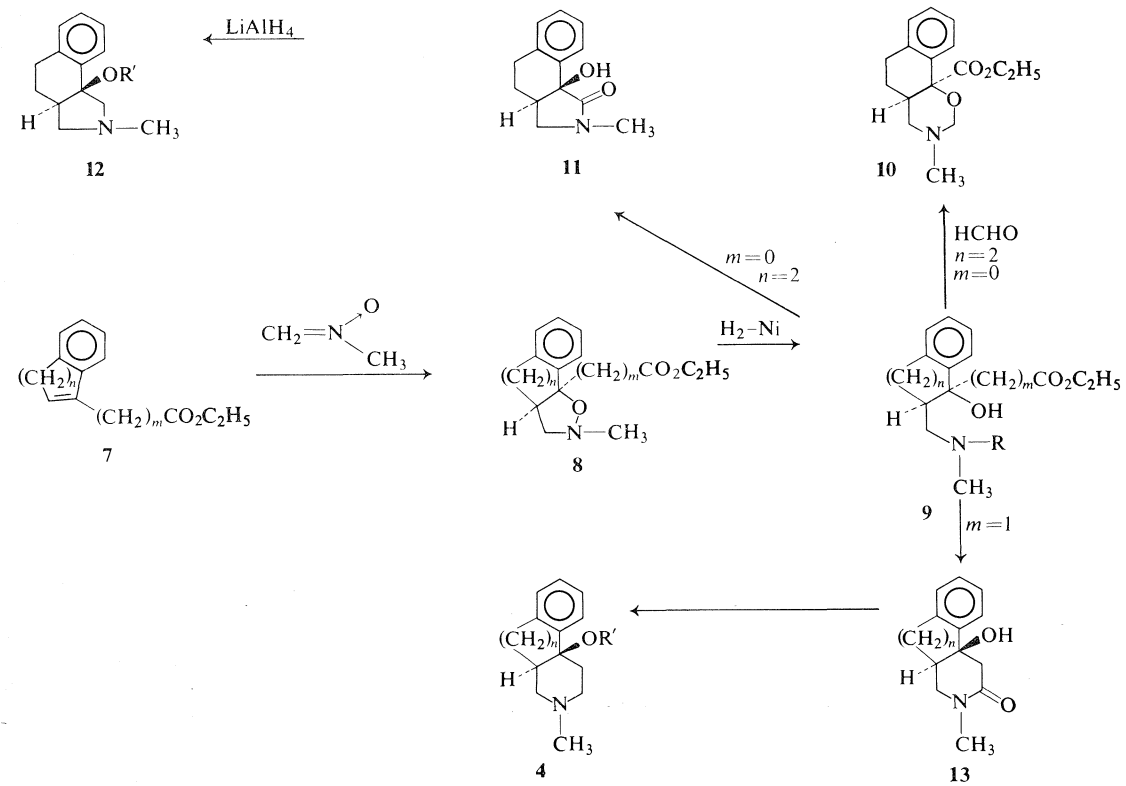
FIG. 2. The approximate angle between the planes of the aromatic and piperidine ring (from Drieding models) in tricyclic prodine analogs.

rings are frozen in a spatial arrangement that is almost identical to the conformation of β-prodine believed to confer the higher potency to the β-isomer (4). In **4***a* the two rings are still roughly parallel but the aromatic group is pushed backward in the plane as compared to **4***b*. The angles between the two planes in **4***f* and in the *cis* compound **5** are roughly 45 and 90°, thus providing the whole range of spatial arrangement. The conformation represented by **6** would mimic the phenylpiperidine arrangement found in the benzomorphans **3** but, at least in solution in deuteriochloroform, there is spectral evidence that the *cis* series exists exclusively in the conformation depicted by structure **5**. Structures such as **4** and **5** bearing an axial 4-OH would be stabilized, through the corresponding skew-boat conformation, by bonding of the OH to the lone pair of the nitrogen (3).

The 1,3-dipolar cycloaddition reaction of nitrones to conjugated olefins (7) provided a facile entry to compounds of type **4** as shown in Scheme 1 (Table 1). Since this type of cylcoaddition is stereospecific (8), the *trans* ring fusion desired for **4** was established at this early stage. Yields of the cycloaddition of *N*-methyl nitrone to unsaturated esters **7** were reasonable (60–80%) with the exception of **7***f* (17%). The seven-membered ring series *f* was abandoned after unfruitful attempts to improve this yield. The resulting isoxazolidines **8** were found to be versatile intermediates since they also provided other analogs, **10** and **12**, of meperidine and prodilidine. Reductive cleavage of the N—O bond afforded a quantitative yield of the aminoesters **9**. Although they are stable for short periods at room temperature the amino esters **9** spontaneously underwent cyclization to the lactams **11** and **13** upon warming. Treatment with a formaldehyde solution converted the aminoester **9***d* to the oxazine **10**, an analog of meperidine where the C-3 carbon atom of the piperidine moiety is replaced by an oxygen atom. When the reductive cleavage of **8***d* was carried out in the presence of formaldehyde the tertiary amine **9***e* was the sole product of the reaction. The lactams **11** and **13** were readily reduced by lithium aluminum hydride to the aminoalcohols **12** and **4**.

Esterification of the aminoalcohols **12** and **4** proved to be quite difficult and could not be achieved in the case of **4***a*. Under the conventional acylation conditions for tertiary alcohols (9) attempted esterification resulted in elimination to unsaturated amines as exemplified by **14** (Scheme 2). However we finally found out that the alcohols **12***a* and **4***b* were readily acylated by propionyl chloride, without base, in benzene solution at or below room temperature to give the esters **12***c* and **4***c* as hydrochlorides which could be precipitated from the reaction mixture by the addition of anhydrous ether.

The change in the n.m.r. chemical shift of the H-10 proton in **14***c*, **4***b*, and **4***c* constitutes a further confirmation of the correctness of these structures. In **14***c*, H-10 is part of the bulk of the 4 aromatic protons centered at 2.38 δ. The axial OH at position 10b in **4***b* shifts the H-10 proton downfield to 7.328. In **4***c* this shift is even more pronounced and H-10 appears as a multiplet centered at 7.72 δ.



a $n = 1$; $m = 1$; R′ = H
b $n = 2$; $m = 1$; R = R′ = H
c $n = 2$; $m = 1$; R = CH_3; R′ = C_2H_5CO
d $n = 2$; $m = 0$; R = H
e $n = 2$; $m = 0$, R = CH_3
f $n = 3$; $m = 1$; R′ = H

SCHEME 1

Alternatively the tertiary alcohols of type **4***b* could be produced cheaply as shown in Scheme 2 by aminomethylation (10) of 1-methyl-3,4-dihydronaphthalene (**15**) followed by hydrobromic acid addition across the double bond of the unsaturated amines **14**. Solvolysis in water at low temperature afforded the alcohols **18** (**18***c* = **4***b*). Yields of the aminomethylation reaction were considerably lower with ammonium chloride (17%) than with methylamine hydrochloride (51%) but the former has the advantage of providing the secondary amine **14***a* which can be alkylated with the desired alkyl halide. The aminoalcohol **18***e* obtained in this manner posseses pharmacological properties related to those of haloperidol.

The *cis*-fused tricyclic analogs of prodine (**5**) were prepared as outlined in Scheme 3. In fact this scheme provides higher yields of the *trans*-isomer. This suited our purposes because at this stage we had found out that the presence of the axial proton at position 4a in **4** in a *trans* configuration with respect to the alcohol or ester group at 10b, rendered elimination so easy that the pharmacological activity of the ester **4***c* represented the resultant of the combined activities of the ester **4***c* and its elimination product **14***c*. Accordingly we wished to block this elimination by incorporating an angular methyl group at 4a in the original structure **4**. Also at this time we were interested in finding how the presence of a phenolic group in the aromatic ring would affect the activity. In the benzomorphan class of analgesics a phenolic group at position 3 enhances the analgesic potency severalfold (5). Since there was some uncertainty

TABLE 1. Physical constants of compounds outlined in Scheme 1

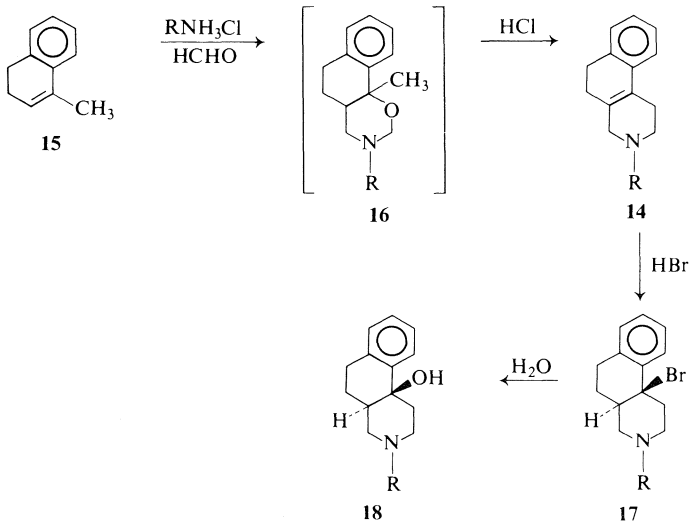
Compound	Melting or boiling point (°C)	Solvent	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4*a*	167–168	EtOAc		$C_{13}H_{17}NO$	76.81	8.43	6.89	76.36	8.47	7.00
4*b*	163–165	Petroleum ether	85	$C_{14}H_{19}NO$	77.38	8.81	6.45	76.95	8.76	6.42
4*c*[a]	174–175	EtOH–Et_2O	42	$C_{17}H_{24}ClNO_2$	65.90	7.81	4.52	65.82	7.73	4.65
8*a*[c]	96–97	C_6H_{12}	65	$C_{14}H_{17}NO_3$	68.00	6.93	5.66	67.57	6.61	5.51
8*b*	117–8/0.2		80	$C_{16}H_{21}NO_3$	69.79	7.69	5.09	70.38	7.79	4.93
8*d*	71–73	EtOH–H_2O	80	$C_{15}H_{19}NO_3$	68.94	7.33	5.36	68.82	7.28	5.42
8*f*	138–40/0.3		17	$C_{17}H_{23}NO_3$	70.56	8.01	4.84	70.31	8.08	5.47
11	184–186	EtOAc	45	$C_{13}H_{15}NO_2$	71.86	6.96	6.45	71.77	6.87	6.45
12*a*	145–146	EtOAc	90	$C_{13}H_{17}NO$	76.81	8.43	6.89	77.32	8.48	6.84
12*c*[b]	156–158	EtOH–Et_2O	45	$C_{18}H_{23}NO_6$	61.87	6.63	4.09	61.62	6.61	3.94
13*a*	216–217	EtOH		$C_{13}H_{15}NO_2$	71.86	6.96	6.45	71.65	6.91	6.38
13*b*	225–227	EtOH	89	$C_{14}H_{17}NO_2$	72.70	7.41	6.06	72.76	7.42	5.95
13*f*	166–167	MeOH–H_2O		$C_{15}H_{19}NO_2$	73.44	7.81	5.71	73.30	7.81	5.60

[a]HCl salt.
[b]Oxalic acid salt.
[c]Methyl ester.

TABLE 2. Physical constants of compounds outlined in Scheme 3

Compound	Melting or boiling point (°C)	Solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
20*a*			Not purified[d]						
20*b*	126–127.5		Not purified[d]						
20*c*	101–102	MeOH	$C_{16}H_{19}NO_4$	66.42	6.62	4.84	66.44	6.66	4.71
20*d*	106–107	MeOH	$C_{16}H_{19}NO_4$	66.42	6.62	4.84	66.53	6.64	4.79
21*a*	211–213	*i*-PrOH–EtOAc	$C_{14}H_{17}NO_2$	72.70	7.41	6.06	72.69	7.37	5.84
21*b*	240–242	EtOH–H_2O	$C_{15}H_{19}NO_3$	68.94	7.33	5.36	69.29	7.45	5.40
21*c*	166–167	EtOAc	$C_{15}H_{19}NO_3$	68.94	7.33	5.36	68.69	7.34	5.50
21*d*	216–217	EtOAc	$C_{15}H_{19}NO_3$	68.94	7.33	5.36	68.70	7.29	5.66
22*a*			Not purified[d]						
22*b*	170–171	EtOAc – Petroleum ether	$C_{15}H_{21}NO_2$	72.84	8.56	5.66	72.42	8.49	5.59
22*c*	166–167	EtOAc	$C_{15}H_{21}NO_2$	72.84	8.56	5.66	73.40	8.71	5.77
22*d*	Oil[d]								
23*a*			Not purified[d]						
23*b*[c]	221–222	MeOH–Et_2O	$C_{16}H_{24}ClNO_2$	64.53	8.12	4.70	64.46	8.26	4.63
23*c*	152–153	MeOH–H_2O	$C_{16}H_{23}NO_2$	73.53	8.87	5.36	73.61	9.03	5.35
23*d*[c]	210–211	MeOH–Et_2O	$C_{16}H_{24}ClNO_2$	64.53	8.12	4.70	64.55	8.20	4.53
24*a*[c]	194–196[a]	MeOH–Et_2O	$C_{18}H_{26}ClNO_2$	66.76	8.09	4.33	66.96	8.14	4.29
24*b*[c]	164–166[b]	MeOH–Et_2O	$C_{19}H_{28}ClNO_3$	64.49	7.98	3.96	64.61	8.07	3.86
24*c*[c]	195–196	MeOH–Et_2O	$C_{19}H_{28}ClNO_3$	64.49	7.98	3.96	64.46	8.02	4.17
24*d*[c]	167–168	MeOH–Et_2O	$C_{19}H_{28}ClNO_3$	64.49	7.98	3.96	64.57	8.04	3.99

[a]Melts with evolution of a gas, resolidifies, and melts again at 210–230°.
[b]Melts with evolution of a gas, resolidifies, and melts again at 231–232°.
[c]Hydrochloric acid salt.
[d]Crude product used in the next step.



a R = H
b R = C_6H_5CO
c R = CH_3
d R = CH_2—CH_2—3-indolyl
e R = *p*-$FC_6H_4CO(CH_2)_3$

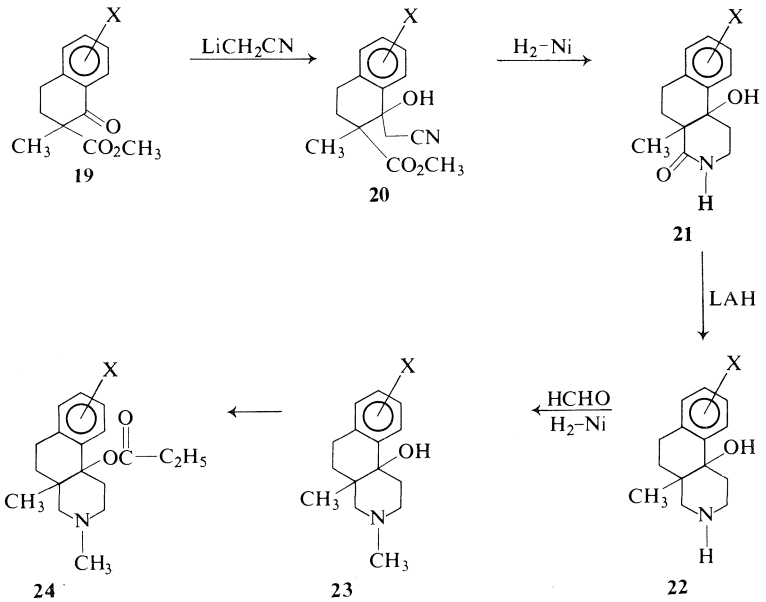
SCHEME 2

as to which of the position 7 or 9 in **4** would correspond to the 3 position of **3** an example of both series was desired. All of these were available through Scheme 3.

Nucleophilic addition of lithioacetonitrile to the ketones **19** gave mixtures of the isomeric *cis*-(OH, CH_3) and *trans*-cyano alcohols **20**, (Table 2) with the *trans*-isomer predominating in all cases. Although the isomers could be easily separated by fractional crystallization or column chromatography no effort was made to obtain the pure *cis*-isomers with the exception of **20***c*, which was selected to study the structure–activity relationships in relation to the stereochemistry of the new ring junction. Catalytic hydrogenation of the nitrile group resulted in spontaneous cyclization of the intermediate aminoesters to the lactams **21**. Reduction of **21** with lithium aluminum hydride afforded the aminoalcohols **22** which were methylated and acylated with propionyl chloride as described for **4***c*. The resulting esters **24**, with the angular 4a-methyl group, were considerably more stable than **4***c* but unfortunately not stable enough to resist the conditions required [HBr; pyridine·HCl (14); BBr_3 (11); $\phi_2\overline{P}$ (12); EtSNa (13)] to achieve their *O*-demethylation. Either no *O*-dealkylation was observed or the main reaction product was the unsaturated amine **25**.

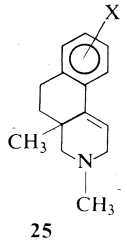
The stereochemistry of compounds **19**–**24** was assigned from a study of their n.m.r. spectra. The series **21***d*, **22***d*, and **23***d* shows a doublet for H-10 (J_{8-10} = 3 Hz) centered at the chemical shift indicated in Table 3. This doublet is shifted downfield in the series **21***c*, **22***c*, and **23***c* by *ca.* 17 Hz indicating a closer proximity of H-10 to the oxygen function at 10b. The doublets (J_{7-8} = 8.5 Hz) centered at 7–7.1 δ for H-7 and the doublets of doublets (J_{7-8} = 8.5 Hz; J_{8-10} = 3 Hz) centered at 6.7–6.8 δ for H-8 are not affected by the change of stereochemistry. Examination of molecular models reveals that H-10 and O-10b are in a *cisoid* conformation in a *cis* structure like **5** while the two groups are more remote in a *trans* structure like **4**. This deshielding of the H-10 proton in the *cis* series also provides some evidence that, in solution in deuteriochloroform, **5** and not **6** is the most stable conformation since there is no possible interaction between H-10 and O-10b in **6**. In the open-chain intermediates **20** a *cis* relation between the cyanomethyl group and methyl group at 2 deshields the 2-methyl by *ca.* 12 Hz. On the other hand, when it is the methoxy carbonyl group that is *cis* to the cyanomethyl group it is the ester-methyl which is shifted downfield by *ca.* 14 Hz.

Because of the instability of **4***c* it is difficult to



a X = H, *trans* (OH, CH_3)
b X^1 = 5-OCH_3, *trans* (OH, CH_3)
c X = 7-OCH_3, *cis* (OH, CH_3)
d X = 7-OCH_3, *trans* (OH, CH_3)

SCHEME 3



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assess its analgesic activity with certainty. Orally it is a potent antidepressant of the MAO inhibitor type which indicates that it is rapidly degraded to **14**. Parenterally it shows analgesia which slowly changes to the type of activity exhibited by **14**. The inclusion of a methyl group at position 4a of **4***c* does stabilize the molecule but it also reduces the analgesic potency (**4***a*, **24***a*). The presence of a methoxyl group on the aromatic moiety of **24***a* improves the potency but, unexpectedly, the position of substitution is not critical (**24***b*, **24***d*). Since the alcohol **23***b* is a stronger analgesic than the corresponding ester **24***b* this series seems to bear a closer relation to the benzomorphans than to the prodines.

[1]Numbering refers to 5- or 7-methoxytetralone as starting material.

TABLE 3. Nuclear magnetic resonance data. Chemical shifts, in δ units, (TMS)

Compound	C—CH_3	CO_2CH_3	CH_2CN	O—CH_3
20*a*	1.50	3.62	2.80[a]	—
20*b*	1.49	3.63	2.78[a]	3.80
20*d*	1.43	3.60	2.71[a]	3.80
20*c*	1.28	3.83	2.81[b]	3.83

Compound	C—CH_3	O—CH_3	H_7	H_8	H_{10}
21*c*	1.28	3.82	7.11	6.82	7.30
21*d*	0.99	3.78	7.11	6.82	7.02
22*c*	0.81	3.76	7.01	6.73	7.19
22*d*	0.81	3.76	7.08	6.73	6.90
23*c*	0.88	3.77	7.02	6.70	7.13
23*d*	0.95	3.70	7.03	6.70	6.88

[a]Multiplet.
[b]Singlet.

The most surprising observation is that a change from *trans* to *cis* in the stereochemistry of the ring bridging the piperidine and the phenyl ring does not alter the analgesic activity (**24***d*, **24***c*). This is in marked contrast with the prodine series where the superiority of the *cis* over the *trans* geometry for activity is well established (5). On the other hand compound **10**, where the

replacement of the carbon atom at position 3 of the piperidine ring by an oxygen atom is not likely to alter the conformation of the system with regard to **4***c* and **24***d*, is completely devoid of analgesic activity. Obviously, as already stressed out by Portoghese and Larson (4), factors other than the purely geometrical contribution play a major role in the ability of a molecule to reach and interact with the analgesic receptor (Table 4).

Other intermediates in this tricyclic series of compounds exhibited interesting CNS activity as shown in Table 5.

Experimental

Melting points, determined on a Fisher Mel-Temp, are not corrected. All compounds possessed i.r. and n.m.r. spectra consistent with their structure. The i.r. spectra were determined on a Unicam SP200-G grating spectrophotometer. The n.m.r. spectra were obtained on a Varian A-60A spectrometer with TMS as internal standard and in deuteriochloroform. Combustion analyses were performed by Microtech Laboratories.

N-Methylnitrone (17)

A mixture of paraformaldehyde (9.3 g, 0.31 mol HCHO), *N*-methyl hydroxylamine hydrochloride (25.0 g, 0.30 mol), and anhydrous potassium carbonate (90.0 g, 0.65 mol) in dry benzene (500 ml) was stirred at room temperature for 5 h. The solids were removed by filtration and washed with methylene chloride. Concentration of the filtrates on the rotary evaporator left the crude nitrone as a yellowish semisolid.

TABLE 4. Analgesic potency[a]

Compound	ED_{50}[b] (mg/kg)
4*c*	20
22*b*	30
23*b*	3
24*a*	32
24*b*	13
24*c*	14
24*d*	11

[a]Phenylquinone writhing test, mice, subcutaneous administration (15).
[b]Effective dose: 50% of the mice under test.

TABLE 5. Antireserpine activity[a]

Compound	ED_{50}[b] (mg/kg)
4*b*	1
4*c*	1
14*a*	2.5
14*c*	<0.25

[a]Ability to reverse reserpine-induced hypothermia in mice (16).
[b]Effective dose, 50% of the mice under test, oral administration.

Cycloaddition of N-Methylnitrone to the Olefins 7

A mixture of the above crude nitrone and the olefin **7** (0.2 mol) (18) in benzene or toluene (500 ml) was stirred at room temperature or heated under reflux as specified below. The cooled solution was extracted with 10% hydrochloric acid and the aqueous layer made basic with concentrated ammonium hydroxide. Extraction with methylene chloride, drying, and concentration left an oily residue which was purified by crystallization or distillation. The unreacted olefin was recovered from the original benzene or toluene solution: **7***b* (18*a*) and **7***d* (18*b*); benzene, room temperature 48 h; **7***a* (18*a*), benzene, reflux, 6 days; **7***f* (18*c*), toluene, reflux, 60 h.

*Reductive Cleavage of the Isoxazolidines **8** to the Aminoalcohols **9***

The ixoxazolidine **8** (0.02 mol) in absolute ethanol (100 ml) was hydrogenated, in a Parr Shaker, at an initial pressure of 60 p.s.i. of hydrogen in the presence of Raney nickel (*ca.* 5 g). One equivalent of hydrogen was absorbed in a few minutes. The catalyst was removed by filtration over Celite and the filtrates were concentrated on the rotary evaporator at room temperature. The crude residue was used immediately without further purification.

An analytical sample of the oxalate salt of **9***d* was prepared in ether. Recrystallization of the solid from alcohol–water gave colorless crystals, m.p. 221–223°.

Anal. Calcd. for $C_{17}H_{23}NO_7$:C, 57.78; H, 6.56; N, 3.96. Found: C, 57.63; H, 6.54; N, 3.93.

*trans(2-Dimethylaminomethyl-1-hydroxy)-1-ethoxycarbonyl-1,2,3,4-tetrahydronaphthalene (**9e**)*

The isoxazolidine **8***b* (5.0 g, 0.019 mol) in absolute methanol (100 ml) was hydrogenated as described above in the presence of paraformaldehyde (3.0 g, 0.099 mol) and Raney nickel (*ca.* 5 g). The residue left after removal of the catalyst and solvent was crystallized in petroleum ether (90–120°) to give **9***e* as white crystals, m.p. 57–60°; yield 4.2 g, 79%.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.26; H, 8.36; N, 5.05. Found: C, 69.03; H, 8.38; N, 4.92.

4a,10b-cis-10b-Ethoxycarbonyl-3-methyl-3,4,4a,5,6,10b-hexahydro-2H-naphth[2,1-e]-1,3-oxazine (10)

The isoxazolidine **8***b* (5.0 g, 0.019 mol) was hydrogenated as described above. After removal of the catalyst, paraformaldehyde (2.0 g, 0.066 mol) was added to the filtrates and the solution was heated under reflux for 2 h. Concentration on the rotary evaporator, dissolution in ether, and treatment with an excess of dry hydrogen chloride afforded **10** as a crystalline hydrochloride, m.p. 228–230° (ethanol); yield 4.15 g, 70%.

Anal. Calcd. for $C_{16}H_{22}ClNO_3$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.42; H, 7.05; N, 4.48.

*Cyclization of the Aminoesters **9** to the Lactams **11** and **13***

The crude aminoester **9** was dissolved in toluene, a few millograms of *p*-toluenesulfonic acid were added, and the solution was heated under reflux for 3 h. After cooling, the solution was washed with 10% hydrochloric acid, dried, and concentrated on the rotary evaporator. The

solid residue was recrystallized in the solvent specified in Table 1.

*Reduction of the Lactams **11** and **13***

The lactam (0.05 mol) in dry THF or dioxane (75 ml) was added dropwise to a stirred slurry of lithium aluminum hydride (5.0 g, 0.13 mol) in the same solvent (75 ml). The mixture was heated under reflux for 18 h, cooled (0–5°), and treated in succession with water (5.0 ml), 20% sodium hydroxide solution (3.75 ml), and water (17.5 ml). The solids were removed by filtration and washed with methylene chloride. Concentration of the filtrates on the rotary evaporator left an oil which was crystallized in the solvent specified in Table 1.

*Esterification of the Alcohols **4b** and **12a***

A solution of the alcohol **4***b* or **12***a* (0.01 mol) and freshly distilled propionyl chloride (2.0 ml, 2.81 g, 0.03 mol) in dry benzene (15 ml) was stirred at room temperature for 2 h. Anhydrous ether was added to complete the crystallization of the ester hydrochloride. After standing at 0° for 1 h the hygroscopic solid was collected by filtration. The ester **4***c* was purified by recrystallization. The ester **12***c* was dissolved in methylene chloride and the solution neutralized at 0° with a saturated sodium carbonate solution, washed with brine, dried, and concentrated to leave an oil. The oil was dissolved in ether and treated with an excess of a solution of oxalic acid in ether to give the oxalic acid salt of **12***c* as a white nonhydroscopic solid.

*1,2,3,4,5,6-Hexahydrobenz[f]isoquinoline (**14a**)*

A mixture of 3,4-dihydro-1-methylnaphthalene (14.4 g, 0.1 mol), 37% formaldehyde solution (34.0 g, 0.43 mol), and ammonium chloride (10.8 g, 0.2 mol) in glacial acetic acid (35 ml) was stirred on the steam-bath for 18 h, diluted with ice-cold water (150 ml), washed with ether (3 × 75 ml), and neutralized with a 50% sodium hydroxide solution. Extraction with methylene chloride and concentration yielded 24.0 g of crude **16**.

The residue was dissolved in concentrated hydrochloric acid (250 ml), heated under reflux for 2 h, cooled, washed with ether (5 × 100 ml), and neutralized with a 50% sodium hydroxide solution. Extraction with ether, drying, and concentration gave an oil which was purified by distillation to afford pure **14***a*, b.p. 120°/0.1 mm; yield 3.2 g, 17%.

An hydrochloric acid salt was prepared for analytical purposes, m.p. 204–205° dec.

Anal. Calcd. for $C_{13}H_{16}ClN$: C, 70.41; H, 7.27; N, 6.32. Found: C, 70.60; H, 7.31; N, 6.47.

*1,2,3,4,5,6-Hexahydro-3-methylbenz[f]isoquinoline (**14c**)*

(*a*) A mixture of 3,4-dihydro-1-methyl naphthalene (86.0 g, 0.6 mol), 37% formaldehyde solution (200 g, 2.4 mol), and glacial acetic acid was stirred vigorously a 60–65° for 1/2 h. Monomethylamine hydrochloride (81.0 g, 1.4 mol) was added by small portions while keeping the temperature at 70°. After the end of the addition, the mixture was stirred for 3 h at 70°, diluted with ice-cold water, washed with ether (5 × 100 ml), made basic with a 50% sodium hydroxide solution, and extracted with ether (5 × 100 ml). Drying and concentration of the ether extracts gave crude **16***c* (116.2 g) as a yellow oil.

The above was dissolved in concentrated hydrochloric acid (100 ml) and heated under reflux for 2 h. Work-up as above gave an oil (99.5 g) which was purified by distillation to provide **14***c* as a slightly colored viscous oil b.p. 120–130°/0.05 mm; yield 61.5 g, 51%.

A solid hydrochloride was prepared for analytical purposes, m.p. 208–209° (ethanol–ether).

Anal. Calcd. for $C_{14}H_{18}ClN$: C, 71.32; H, 7.70; N, 5.94. Found: C, 71.18; H, 7.68; N, 6.00.

(*b*) By methylation of **14***a*: methylation of **14***a* by the normal formaldehyde – formic acid method (19) gave an oil identified as **14***c* by comparison (i.r., n.m.r., t.l.c.) with an authentic sample.

(*c*) By elimination from **4***b*: a mixture of the alcohol **4***b* (2.0 g, 0.0092 mol) and freshly distilled propionyl chloride (2.0 ml, 2.81 g, 0.03 mol) in benzene (25 ml) was heated under reflux for 18 h. Addition of ether gave a white solid which was recrystallized in isopropanol–ether to give crystals, m.p. 208–209° identical (i.r., mixture m.p.) with authentic **14***a*.

*3-Benzoyl-1,2,3,4,5,6-hexahydrobenz[f]isoquinolines (**14b**)*

A solution of benzoyl chloride (1.6 g, 0.0114 mol) in chloroform (10 ml) was added dropwise to a cooled (0–5°) and stirred mixture of the amine **14***a* (2.0 g, 0.0108 mol) and 10% sodium hydroxide solution (5 ml). After a 30 min stirring period at room temperature, the phases were decanted, the aqueous phase re-extracted with chloroform, and the combined chloroform extracts were dried and concentrated. The semisolid residue was recrystallized in ethylacetate – petroleum ether to give **14***b* as a white solid, m.p. 93–95°; yield 2.3 g, 73%.

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.76; H, 6.69; N, 4.79.

*3-[4′-(p-Fluorophenyl)-4′-butyryl]-1,2,3,4,5,6-hexahydrobenz[f]isoquinoline (**14e**)*

A mixture of the amine **14***a* (2.0 g, 0.0108 mol), triethylamine (2.0 g, 0.0197 mol), γ-chloro-*p*-fluorobutyrophenone (2.5 g, 0.0125 mol), and dry toluene (10 ml) was stirred and heated under reflux for 18 h. After cooling the mixture was washed with water, the aqueous phase re-extracted with toluene, and the combined organic phases dried and concentrated to leave an oil. The oil was dissolved in ether and the hydrochloride of **14***e* was precipitated with dry hydrogen chloride. After washing with ether, the solid was dissolved in water, neutralized with a 10% sodium hydroxide solution, and extracted with methylene chloride. Drying and concentration left a yellow oil which was crystallized in petroleum ether to give **14***e* as a white solid, m.p. 73–74°; yield 1.9 g, 51%.

Anal. Calcd. for $C_{23}H_{24}FNO$: C, 79.05; H, 6.92; N, 4.01. Found: C, 79.10; H, 6.99; N, 4.05.

*10b-Hydroxy-1,2,3,4,4a,5,6,10b-octahydro-4a,10b-trans-benz[f]isoquinoline (**18a**)*

A solution of the amine **14***a* (5.0 g, 0.027 mol) in glacial acetic acid (35 ml) was cooled to 10° and saturated with dry hydrogen bromide during 4 h while maintaining the temperature at 10–20°. After standing at room temperature for 18 h the solution was diluted with ether (250 ml) and the precipitated solid was collected by filtration, dissolved in water (25 ml), stirred for 2 h at room temperature, cooled to 5°, neutralized with a 50% sodium

hydroxide solution, and extracted with methylene chloride. Drying and concentration left a solid which was crystallized in carbon tetrachloride to give **18***a* as white crystals, m.p. 173–175°; yield 2.25 g, 50%.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.20; H, 8.39; N, 6.99.

*3-(β-Ethyl-3′-indolyl)-10b-hydroxy-1,2,3,4,4a,5,6,10b-octahydro-4a,10b-trans-benz[f]isoquinoline (**18***d*)

A solution of 3-indoleglyoxylyl chloride (20) (2.0 g, 0.00965 mol) in chloroform (30 ml) was added dropwise to a cooled (0–5°) and stirred mixture of the amine **18***a* (2.0 g, 0.00985 mol), 20% sodium hydroxide solution (2 ml), water (5 ml), and chloroform (10 ml). The mixture was stirred 0.5 h at 0° and then 1 h at room temperature The solid was collected by filtration and recrystallized in ethanol to give the 3-indoleglyoxylamide as a white solid, m.p. 200–204°; yield 2.7 g, 75%.

The above solid was reduced in dioxane with lithium aluminum hydride (1.0 g) under the normal conditions (18 h, reflux). The oily reaction residue was dissolved in $CHCl_3$–ether and treated with an excess of dry hydrogen chloride. The solid was recrystallized in methanol–ether to give **18***d* as white crystals, m.p. 246–248° dec; yield 2.3 g, 61%.

Anal. Calcd. for $C_{23}H_{27}ClNO_2$: C, 72.14; H, 7.11; N, 7.32. Found: C, 72.24; H, 7.24; N, 7.02.

*3-[4′-(p-Fluorophenyl)-4′-butyryl]-10b-hydroxy-1,2,3,4,4a,5,6,10b-octahydro-4a,10b-trans-benz(f)-isoquinoline (**18***e*)

A mixture of the amine **18***a* (3 g, 0.0148 mol), γ-chloro-*p*-fluorobutyrophenone (4.0 g, 0.02 mol), potassium carbonate (3.0 g, 0.0217 mol), and dry toluene (30 ml) was stirred and heated under reflux for 48 h. After cooling the solids were removed by filtration, washed with toluene, and the combined filtrates concentrated. The residual oil was dissolved in ethanol and acidified with 10% hydrochloric acid. The solid hydrochloride was recrystallized in dilute ethanol to give **18***e* as white crystals, m.p. 211–221°; yield 3.7 g, 62%.

Anal. Calcd. for $C_{23}H_{27}ClFNO_2 \cdot \frac{1}{2}H_2O$: C, 66.90; H, 6.84; N, 3.39. Found: C, 67.00; H, 6.56; N, 3.50.

*1-Cyanomethyl-1-hydroxy-2-methoxycarbonyl-2-methyl-1,2,3,4-tetrahydronaphthalenes (**20**)*

A solution of acetonitrile (4.1 g, 0.1 mol) in dry THF (100 ml) was added dropwise under nitrogen to a solution of *n*-butyllithium (69 ml of a 1.6 *M* solution in hexane, 0.11 mol) in dry THF (70 ml) kept at −78°. After stirring at −78° for 1 h, a solution of the ketone **19***a* (21), **19***b* (22), or **19***c* (23) (0.1 mol) in THF (150 ml) was added rapidly (5 min), the cooling bath removed, and the solution stirred for 0.5 h, poured into a mixture of crushed ice (*ca.* 400 g) and concentrated hydrochloric acid (100 ml), and the layers separated. The aqueous phase was extracted with ether (4 × 75 ml) and the combined organic layers dried and concentrated to leave an oil (100%). Chromatography over activity 2 alumina, eluting with ether, gave in succession the unreacted ketone **19** (0–30%), the *trans*-isomer (30–66%), the *cis*-isomer (15–30%), and byproduct (0–30) identified as 2-cyanoacetyl-2-methyl-1-tetralone.

Compound **20***a* could be isolated, without chromatography, by crystallization of the reaction residue in methanol; yield 60–75%. The *cis*-isomer was not characterized.

Compound **20***b* was isolated in a 25% yield. The *cis*-isomer (9%) and the byproduct (32%) were not characterized. Mixed fractions and unreacted ketone accounted for 32%.

Compound **20***c* was obtained in 12% yield; **20***d* in 15%; byproduct in 20%; unreacted ketone in 20%. The byproduct was recrystallized in methanol to give a white solid m.p. 143–144°, characterized as 2-cyanoacetyl-7-methoxy-2-methyl-1-tetralone.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.03; H, 5.94; N, 5.46.

*10b-Hydroxy-4a-methyl-1,2,3,4,4a,5,6,10b-octahydro-4-oxobenz[f]isoquinolines (**21**)*

A solution of the cyanoesters **20** (0.05 mol) in absolute methanol (100 ml) was hydrogenated in a Parr Shaker in the presence of Raney nickel (*ca.* 7 g) until 2 equiv. of hydrogen had been absorbed (2–4 h). The catalyst was removed by filtration over Celite, washed with methanol, and the filtrates were concentrated on the rotary evaporator to leave the lactams **21** as white solids which were purified by recrystallization; yield 85–95%.

*10b-Hydroxy-4a-methyl-1,2,3,4,4a,5,6,10b-octahydrobenz-[f]-isoquinoline (**22**)*

The lactams **21** (0.055 mol) in dioxane (300 ml) were reduced with lithium aluminum hydride (7.32 g, 0.193 mol) in dioxane (100 ml) as described above for **11** and **13**. The crude reaction residue was purified by crystallization; yields 80–90%.

*3,4a-Dimethyl-10b-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenz[f]isoquinolines (**23**)*

A solution of the secondary amines **22** (0.051 mole) and paraformaldehyde (3.3 g, 0.102 mol) in absolute methanol (200 ml) was hydrogenated in a Parr Shaker in the presence of Raney nickel (*ca.* 10 g) at an initial pressure of 60 p.s.i. of hydrogen. When 1 equiv. of hydrogen was absorbed (20–60 min) the catalyst was removed by filtration over Celite, washed with methanol, and concentrated on the rotary evaporator. The residue was purified either by crystallization or through a hydrochloride prepared in ether.

*3,4a-Dimethyl-1,2,3,4,4a,5,6,10b-octahydro-10-b-propionyloxybenz[f]-isoquinolines (**24**)*

The tertiary alcohols **23** were esterified with freshly distilled propionyl chloride as described above for **4** and **12**. The resulting hydrochloric acid salts were purified by crystallization; yields 50%.

*3,4a-Dimethyl-9-hydroxy-2,3,4,4a,5,6-hexahydrobenz[f]-isoquinoline (**25***d*)

(*a*) A mixture of the alcohol **23***d* (0.52 g, 0.002 mol) and dry pyridine hydrochloride (6.0 g, 0.05 mol) was heated, under a vacuum of 20 mm Hg, at 185° for 2 h. After cooling, the mixture was dissolved in water (50 ml) and washed with ether (2 × 25 ml). The aqueous phase was made basic with concentrated ammonium hydroxide and extracted with methylene chloride. Drying and concentration of the extracts left the unsaturated amine **25***d* as at crude brown solid, m.p. 168–170°; 0.48 g; δ 1.05 (singlet, C—CH_3), δ 2.44 (singlet, N—CH_3), δ 5.9 (multiplet, C-1).

Anal. Calcd. for $C_{15}H_{20}ClNO$: C, 67.78; H, 7.58; N, 5.27. Found: C, 67.72; H, 7.72; N, 5.13.

(*b*) The alcohol **23***d* (1.3 g, 0.005 mol) kept 1.5 h at 100° with 48% hydrobromic acid gave a 87% yield of **25***d*.

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