Structure–Activity Correlations of Morphine-like Analgetics Based on Efficiencies Following Intravenous and Intraventricular Application

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Analgetic efficiency of morphine-like drugs following intraventricular application is found to be a good approximation for their "receptor activities." Evidence is presented indicating that the quotient log (C_{iventr}/C_{iv}) parallels the lipophilicity of the compounds and is a measure for their tendency to penetrate the blood–brain barrier. Penetration ability can be represented extrathermodynamically by log P.

Structure–activity correlations have been performed recently using several mathematical models.[1-3] Of special interest is the method of Hansch and coworkers using computerized regression analysis to find those physicochemical parameters of importance which determine the change in biological activities when substituents are changed in a set of congeneric drugs. According to Hansch[3] eq 1 can be used as a first approximation:

$$\log 1/C = a \times \log A + b \times \log k_x + c \qquad (1)$$

C is the molar drug concentration necessary to cause a constant equivalent biological response (*e.g.*, LD_{50}, ED_{50} etc.). A is the probability of the molecules reaching their sites of action in a given time interval and k_x is the rate-determining critical step at the receptor site, which is responsible for the visible biological response. The k_x values of a set of congeneric drugs should parallel their activities in the receptor compartment[4] ("receptor activities.")

Following these lines, even with gross structural differences in a set of congeneric drugs, quite good correlations can be obtained.[5,6] However one has to keep in mind that the scope of eq 1 has certain limits. Correlation studies with highly stereospecific acting drugs[7,8] have shown, that in this case only minor structural changes can be performed on the basic structure of a set of congeneric drugs, otherwise it is impossible to account for the corresponding changes in the physicochemical properties in a quantitative manner. In addition the structural changes must be performed in a part of the basic molecular entity where a similar mode of binding to the receptor for all congeners can be expected. One of the main reasons for this difficulty is that one has to assume a more or less flexible nature for the receptor. Therefore the steric interactions between flexible receptor and flexible drug can be very complex. This aspect was especially pointed out by Portoghese[9] in the case of morphine-like analgetics. These findings are supported by a paper of Casy and Parulkar[10] on the different mode of binding of morphine-like analgetics of different configurations to the analgetic-receptors.

Unfortunately these authors had to base their structure–activity discussions regarding drug–receptor interactions on biological data obtained following peripheral application. However, these data are complex in nature. The structural change on the drug has as a result not only a change in the drug–receptor interactions but also changes in the rate of penetration through the blood–brain barrier[11-13] and changes in the rates of metabolism and elimination.[14] Therefore Portoghese had to restrict his structure–activity discussion to the comparison of the effects of similar substituents on different sets of "analgesiophoric drugs."[15,16]

To overcome these difficulties we have measured the analgetic activity following intraventricular application. These activities should be better suited to represent drug–receptor interactions than activities obtained following intravenous application. In addition one would expect to obtain quite useful information regarding the factors governing penetration through the blood–brain barrier in comparing analgetic activity following intravenous and intraventricular application, respectively.

The analgetic activities of the compounds were determined in rabbits by means of the tooth-pulp test. A detailed description of the technical procedure for the intraventricular application and a more qualitative discussion of the penetration phenomenon is described elsewhere.[17] It is the purpose of this paper to show that a properly chosen pharmacological test procedure can reveal quite useful structure–activity correlations in spite of the complications which are involved with structure–activity studies of highly stereospecific acting drugs.

Figure 1 shows the chemical structures of the

(1) S. M. Free, Jr., and J. W. Wilson, *J. Med. Chem.*, **7**, 395 (1964).
(2) K. Boček, J. Kopecký, M. Krivucová, and D. Vlachová, *Experentia*, **20**, 667 (1964).
(3) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1963).
(4) J. M. van Rossum, *Advan. Drug Res.*, **3**, 193 (1966).
(5) C. Hansch, *Farm. Ed. Sci.*, **23**, 293 (1968).
(6) C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.*, **11**, 1 (1968).
(7) E. Kutter and C. Hansch, *ibid.*, **12**, 647 (1969).
(8) E. Kutter and C. Hansch, *Arch. Biochem. Biophys.*, **135**, 126 (1969).
(9) P. S. Portoghese, *J. Med. Chem.*, **8**, 609 (1965).
(10) A. F. Casy and A. P. Parulkar, *ibid.*, **12**, 178 (1969).
(11) M. W. Bradburg and H. Davson, in "Absorption and Distribution of Drugs," T. B. Binns, Ed., E. & S. Livingstone Ltd., Edinburgh and London.
(12) A. Herz, H. J. Teschemacher, A. Hofstetter, and H. Kurz, *Int. J. Neuropharmacol.*, **4**, 207 (1965).
(13) R. Hess, H. J. Teschemacher, and A. Herz, *Naunyn Schmiedebergs Arch. Exp. Pathol. Pharmakol.*, **261**, 469 (1968).
(14) E. J. Ariëns, *Fortschr.-Azneimitt.*, **10**, 429–529 (1966).
(15) P. S. Portoghese, *J. Pharm. Sci.*, **54**, 1077 (1965).
(16) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968).
(17) B. von Cube, H. J. Teschemacher, A. Herz, and R. Hess, *Naunyn Schmiedebergs Arch. Exp. Pathol. Pharmakol.*, **265**, 455 (1970).

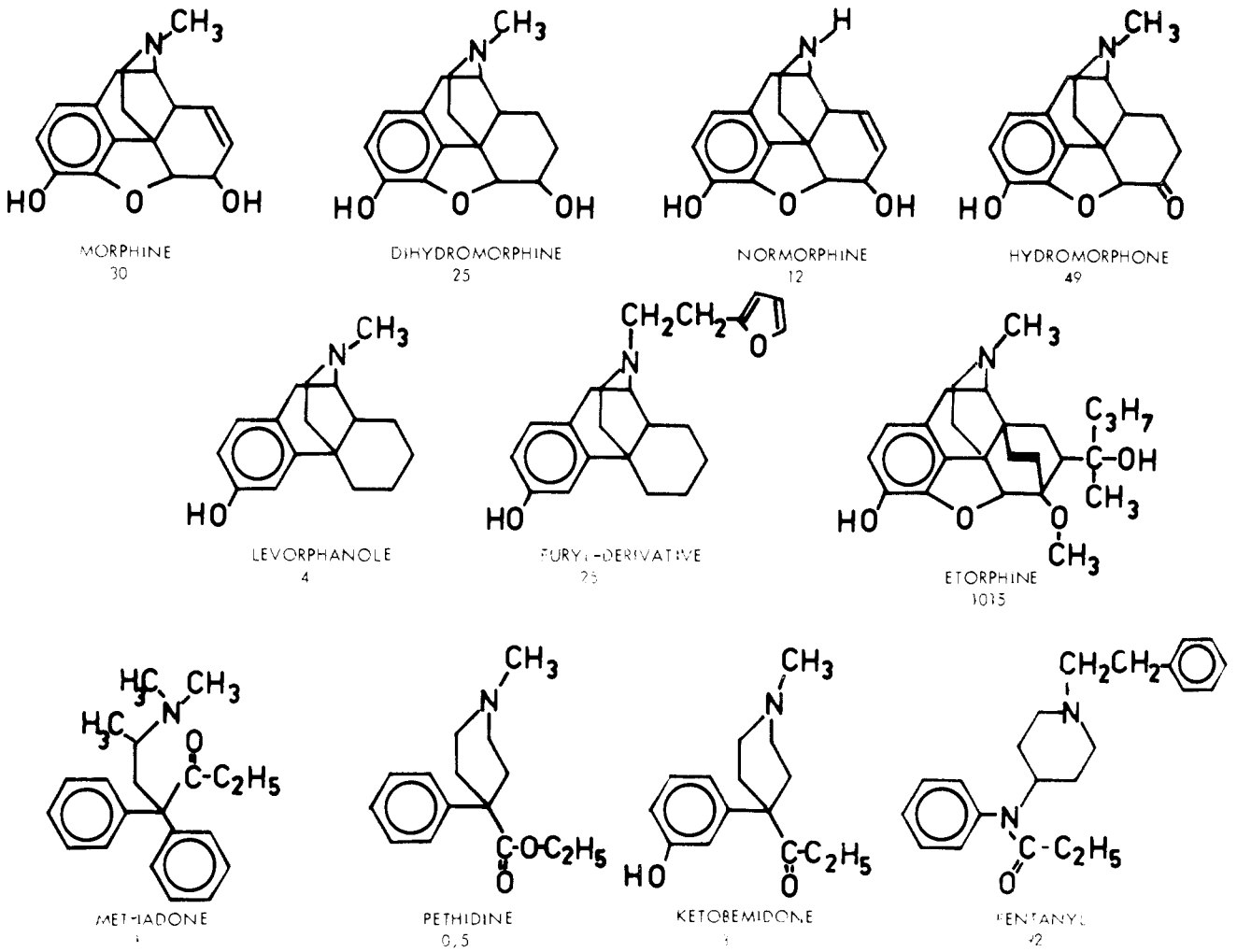

Figure 1.—Chemical structures of the studied morphinelike analgetics and their relative receptor activities.

analgetics we studied. It is obvious that these structures differ markedly from one compound to the other. Although several derivatives show a close structural relationship to morphine, the only common feature of the synthetic analgetics like methadone, pethidine, ketobemidone, and fentanyl with this parent compound is the presence of an N atom a certain distance from an aromatic moiety. In any case these differences are far too great to make it possible to account for the electronic and steric differences with suitable extrathermodynamically derived numbers. While it is not possible as a result of these considerations to treat the drug-receptor interaction in a quantitative manner, it still seems feasible to account for the differences in the penetration properties to the receptor site which also are a result of the differences in the chemical structures of the analgetics.

In eq 1 the probability term log A takes care of these differences in the penetration properties. The probability of molecules to reach their sites is also determined by their rates of metabolism and elimination. Considerable evidence is at hand that all these factors are governed, at least partly, by a physicochemical property of the molecules which usually is called "lipophilicity."[14,15] This property is determined by the relative solvation of the molecules in a polar and a nonpolar heterogeneous phase, respectively. As a suitable extrathermodynamic reference system to determine these differences in the solvation properties the partition coefficient of the compounds between a nonpolar lipophilic and a polar aqueous phase has proved to be useful.[15] Therefore we have measured the partition coefficients of the analgetics in a heptane–buffer system. Table I shows the logarithms of the obtained P values.

In this way it is possible to differentiate most of the compounds with regard to their lipophilic properties.

Of special interest to us, was the nature of the ED values obtained following intraventricular application. This leads to the question whether or not the compounds have to cross a lipophilic barrier during the diffusion process from the ventricular wall to the receptor site. The majority of the analgetic receptors are not located immediately on the surface of the ventricular wall.[17] The average distance of diffusion to the site may be even greater in this case compared to the intravenous way of application because of the extensive capillary system in the brain. Therefore a certain dependence of the $ED_{50\,i.v.}$ values from the lipophilicity of the compounds could not be excluded *a priori*.

In determining the threshold doses of the analgetics under consideration for intraventricular application it became obvious, that the moment of maximum activity

(15) R. Collander and H. Bärlund, *Acta Bot. Fenn.*, **11**, 1 (1933).

(17) A. Herz, K. Akgün, J. Metys, P. Schubert, and H. J. Teschemacher, on the central sites of the analgesic action of morphinelike substances, *Neuropharmacology*, in press.

Table I

Log P Values of the Tested Analgesics and Moments of Maximum Activity (T_0) and Effective Doses (ED_{10}) Necessary to Obtain a Constant Antinociceptive Action Following Intravenous and Intraventricular Application

Compound	log P[a]	T_0 (min)[b]	ED_{iv}[c] (μg)	$(\log 1/C)_{iv}$[d] (moles/μg)	T_0 (min)[e]	ED_{iventr}[f] (μg)	$\log (1/C)_{iventr}$[g] (moles/μg)	$-\log (C_{iventr}/C_{iv})$— Obsd[h]	Calcd[i]	$\lvert\Delta\rvert$
Etorphine	0.15	3.2	3.6	2.04	2.8	0.6	2.82	−0.780	−0.670	0.110
Fentanyl	1.29	4.5	38.4	0.82	4.0	6.6	1.58	−0.760	−0.776	0.016
Furyl derivative	0.25	4.8	72.0	0.67	8.5	24.0	1.15	−0.480	−0.670	0.190
Levorphanole	−2.04	8.0	1680.0	−0.81	42.0	150.0	0.23	−1.040	−1.124	0.084
Methadone	1.65	7.6	3750.0	−1.09	11.0	610.0	−0.30	−0.790	−0.859	0.069
Ketobemidone	−3.06	4.9	4500.0	−1.26	59.0	205.0	0.08	−1.340	−1.632	0.292
Hydromorphone	−4.00	8.5	6600.0	−1.36	123.0	12.4	1.38	−2.740	−2.267	0.473
Pethidine	0.53	2.8	10500.0	−1.62	2.5	1230.0	−0.71	−0.920	−0.679	0.241
Dihydromorphine	−5.00	12.7	13650.0	−1.68	91.0	24.0	1.08	−2.760	−3.118	0.358
Morphine	−5.00	14.4	18600.0	−1.81	105.0	20.5	1.14	−2.950	−3.118	0.168
Normorphine	−5.00	22.0	150000.0	−2.74	41.0	51.0	0.72	−3.470	−3.118	0.352

[a] Logarithms of the partition coefficients of the compounds between heptane and phosphate buffer, pH 7.4. [b] Moments of maximum activity from the dose-activity curves for iv ED_{10} (increase of threshold to 10 mA). [c] Iv threshold dose (ED_{10}) in the moment of maximum activity. [d] Logarithm of the reciprocal iv threshold dose in mmoles. [e] Moments of maximum activity from the dose-activity curves for iventr ED_{10}. [f] Iventr threshold dose (ED_{10}) in the moment of maximum activity. [g] Logarithm of the reciprocal iventr threshold dose in mmoles. [h] Log (C_{iventr}/C_{iv}) values observed. [i] Calculated log (C_{iventr}/C_{iv}) using eq 10.

differs markedly from one compound to the other. In order to investigate the influence of lipophilicity on the moment of maximum activity we have derived eq 2 from the data in Table I.

$$\log (T_0)_{iventr} = -0.211 \log P + 0.933 \quad (2)$$
$$n = 11 \quad s = 0.322 \quad r^2 = 0.775 \quad r = 0.880$$

Keeping in mind that T_0 is a complex function of the rate of penetration to and away from the receptor site the correlation as depicted in eq 2 is reasonably good. Of the variance in the log (T_0) values 77% can be explained by a linear regression with log P. The negative slope of this equation indicates that with an increase in the lipophilicity of the compounds the moment of maximum activity takes place earlier. Two examples illustrate that this effect is quite pronounced. The highly lipophilic compound pethidine reaches its moment of maximum activity 2.5 min after injection. On the other hand, morphine, a very polar compound, needs 105 min to exert its maximum analgetic effect. These results are in accord with the assumption that in the case of intraventricular application there also exists a lipophilic barrier for the polar drugs between the locus of application (ventricular wall) and the receptor region. In the case of the very lipophilic analgetics these compounds penetrate very rapidly to the site and therefore the moment of maximum activity takes place very early. The main reason for this phenomenon seems to be their rapid elimination from the receptor region *via* the capillary system to other parts of the body, because the lipophilic drugs can penetrate the blood–brain barrier rapidly from both directions. The situation is different in the case of the polar drugs. The very polar analgetics need more than 1 hr to accumulate in the receptor region. In addition they can not penetrate the blood–brain barrier rapidly in order to be distributed by the bloodstream. Therefore, these drugs produce a long-lasting analgetic effect following intraventricular application. In order to eliminate the influence of the rate of penetration from the ventricular wall to the receptor region on the analgetic activity of the drugs we have determined the threshold doses to produce a measurable antinociceptive activity at the moment of maximum drug concentration in the receptor region. These moments of maximum drug concentrations necessary to reach the threshold to produce an analgetic effect[17] (ED_{iventr} values in Table I) are identical with the $T_{0,iventr}$ values in Table I. One could expect that these ED values, at least at a first approximation, are independent of the lipophilicity of the compounds and therefore should be suitable to represent the relative activity of the drugs at their sites.

A regression study confirms these conclusions.

$$\log (1/C)_{iventr} = -0.030 \log P + 0.777 \quad (3)$$
$$n = 11 \quad s = 1.033 \quad r^2 = 0.007 \quad r = 0.083$$

In eq 3 log P is expected to represent log A (penetration) extrathermodynamically. $(1/C)_{iventr}$ is a measure for the efficiency of a compound following intraventricular application. Addition of a term in $(\log P)^2$ gives no improvement of the correlation. The r^2 value of this equation indicates that only 0.7% of the variance in the log $(1/C)_{iventr}$ values could be explained by a linear regression with log P. This argues strongly against any important dependence of the log $(1/C)_{iventr}$ values on this parameter. This conclusion is supported by the very small slope of eq 3. In determining the threshold doses in the moments of maximum drug concentration in the receptor region we indeed have eliminated the influence of the penetration phenomenon on the ED_{iventr} values. Therefore, one can conclude that these ED_{iventr} values should parallel the "receptor activities" of the corresponding analgetics. In terms of mathematics eq 4 is the result of these considerations.

$$\log (1/C)_{iventr} = b \times \log k_x \text{ (receptor compartment)} + d \quad (4)$$

From another point of view the very low r^2 value of eq 3 is interesting. It is evident that in this case of highly stereospecific acting drugs the relative receptor activities of this set of analgetics are not log P controlled and that other factors govern the affinity of the drugs to their sites. This result corresponds nicely with other correlation studies[8] where hydrophobic con-

stants have proved to be of minor importance for rationalizing drug–receptor interactions.

In order to be able to compare intraventricular efficiencies with peripheral efficiencies we also have determined activities following intravenous application. Table I shows the moments of maximum activity together with the ED_{10} values of the corresponding drugs. According to our regression studies in the case of intraventicular application we have derived eq 5 and 6 from the data obtained following intravenous application.

$$\log (T_0)_{iv} = -0.081 \log P + 0.695 \quad (5)$$
$$n = 11 \qquad s = 0.187 \qquad r^2 = 0.600 \qquad r = 0.775$$

$$\log (1/C)_{iv} = 0.343 \log P - 0.173 \quad (6)$$
$$n = 11 \qquad s = 1.116 \qquad r^2 = 0.430 \qquad r = 0.656$$

Addition of a squared term in log P does not improve the correlations significantly. It is interesting to note that as far as the r values are concerned correlation 5 is comparable with the one represented by eq 2. However, the slope of eq 5 is much smaller. Therefore, the relation between the moments of maximum activity and the lipophilicity of the drugs in the case of intravenous application is less pronounced than in the case of intraventricular application. In fact, the difference in the moments of maximum activity between pethidine and morphine now is only 11.6 min compared with 102.5 min in the case of intraventricular application. Obviously, following intravenous application, the polar drugs reach their moments of maximum activity much earlier.

There are two important factors which favor an early moment of maximum activity following peripheral application: first of all, a rapid penetration of a drug to its site, or secondly, a rapid inactivation and excretion which makes a compound very short-acting and removes most of the drug from any possibility of reaching the receptor. The polar compounds cross the lipophilic blood–brain barrier very slowly.[11] Unlike the case of intraventricular application the drugs following peripheral application can be metabolized by the liver and eliminated through the kidney. Therefore, metabolism and kidney filtration are two of the factors causing an earlier moment of maximum activity in the case of the polar drugs following intravenous application. On the other hand the lipophilic compounds can rapidly penetrate the blood–brain barrier before being metabolized to an appreciable amount and reach their moments of maximum activity in a rate comparable to the case of intraventricular application. From this point of view one would expect the log $(1/C)_{iv}$ values to be dependent on the lipophilicity of the drugs because only the more lipophilic drugs should be able to reach their sites before being partly eliminated. Correlation 6 is in accord with these considerations. Of the variance in the log $(1/C)_{iv}$ values 43% can be explained by a linear regression with log P (r^2 value in eq 5). The positive coefficient of log P indicates that an increase in the lipophilicity of the analgetics favors iv activity. Of the variance in the data 57% could be attributed to differences in the intrinsic activities of the compounds as a result of different drug–receptor interactions. This supports the general thesis that the efficiency of a compound following peripheral application is a complex function, which covers the penetration phenomenon as well as the activity of the drug at its site. According to eq 1, eq 7 for the activities following intravenous application can be defined as:

$$\log (1/C)_{iv} = a \times \log A_{penetration} + b \times \log k_{x(receptor\ compartment)} + c \quad (7)$$

In order to eliminate $b \log k_{x(receptor\ compartment)}$ we now can subtract eq 4 from eq 7 and this leads us to eq 8 and 8a, respectively.

$$\log (1/C)_{iv} - \log (1/C)_{iventr} = a \times \log A_{penetration} + c \quad (8)$$

or

$$\log (C_{iventr}/C_{iv}) = a \times \log A_{penetration} + c \quad (8a)$$

On the basis of eq 8a one would expect a good correlation between log (C_{iventr}/C_{iv}) and log P. Therefore, in order to check the hypotheses which lead to the formulation of eq 4 and 7 we have derived eq 9 and 10.

$$\log (C_{iventr}/C_{iv}) = [0.373\ (\pm 0.13)] \log P - [0.952\ (\pm 0.40)] \quad (9)$$
$$n = 11 \qquad s = 0.475 \qquad r^2 = 0.832 \qquad r = 0.912$$

$$\log (C_{iventr}/C_{iv}) = -[0.090\ (\pm 0.05)] (\log P)^2 + [0.036\ (\pm 0.20)] \log P - [0.673\ (\pm 0.30)] \quad (10)$$
$$n = 11 \qquad s = 0.297 \qquad r^2 = 0.941 \qquad r = 0.970$$

In eq 9 and 10, the figures in parentheses are the 95% confidence intervals. An F test indicates that both equations are significant at the 0.995 level. In addition eq 10 is a significant improvement over eq 9 ($F_{1,8} = 5.18$). This equation "explains" 94% of the variance in the log (C_{iventr}/C_{iv}) values. It is a parabolic equation which gives further experimental evidence to the theoretical analysis by Hansch and coworkers[20] on the penetration of drug molecules to their sites. Both equations reflect a very close relationship between the log (C_{iventr}/C_{iv}) values and the lipophilicity of the analgetics. This finding does support the conclusions which lead to the formulation of eq 4 and 7. Therefore, the biological efficiencies of the analgetics found following intraventricular application have proved to be a good approximation for their receptor activities.

Table I makes it possible to compare the measured log (C_{iventr}/C_{iv}) values with those calculated according to eq 10. In general there is a very good agreement between the observed and the calculated values.

Studies with radioactive-labeled compounds give additional support to the conclusions drawn above. Brain and plasma concentrations necessary to produce a certain antinociceptive activity were measured for four of the analgetics.[17] In order to keep the amount of material metabolized during the experiment as small as possible, concentrations were measured 3–5 min following intravenous injection. From the data in Table II we have derived eq 11. The good correlation in eq 11 makes it quite clear that log (C_{brain}/C_{plasma})

$$\log (C_{brain}/C_{plasma}) = 0.394 \log P + 0.678 \quad (11)$$
$$n = 4 \qquad s = 0.189 \qquad r^2 = 0.986 \qquad r = 0.993$$

(20) J. T. Penniston, L. Beckett, D. L. Bently, and C. Hansch, *Mol. Pharmacol.*, **5**, 333 (1969).

parallels very well with the lipophilic character of the four analgeticis. Of special interest is the good agreement of the slopes of eq 9 and 11. This reflects a close parallelism between log (C_{brain}/C_{plasma}) and log (C_{iventr}/C_{iv}). This is additional support for the earlier findings that log (C_{iventr}/C_{iv}) is a measure of the different capability of the analgetics to penetrate the blood–brain barrier.

Table II
Radioactively Labeled Analgetics with Physical Constants

Compound	(C_{brain}/C_{plasma})	log (C_{brain}/C_{plasma})	log P
Morphine	0.046	−1.34	−5.00
Dihydromorphine	0.053	−1.28	−5.00
Fentanyl	10.58	1.02	1.29
Etorphine	8.69	0.94	0.15

The parallelism between the intraventricular activity and the receptor activity leads to some qualitative conclusions regarding the drug–receptor interactions. Figure 1 makes possible the comparison of the chemical structures of the analgetics with their relative intrinsic activities. It is interesting to note that the polar compounds like hydromorphine, dihydromorphine, morphine, and normorphine have a greater activity at the receptor than the synthetic derivatives methadone, ketobemidone, and pethidine. Polar functions, like hydroxy, ether, or keto groups seem to be favorable for specific drug–receptor interactions. This is in accord with the findings of Porthogese[9] that the introduction of an OH group in an analgetically active molecule can enhance analgetic activity and simultaneously change the mode of binding. Therefore, the high activity of the nonpolar synthetic analgetics following intravenous application can easily be explained by a good penetration of these compounds through the blood–brain barrier to the reaction site and seems not to be due to especially favorable drug–receptor interactions. In etorphine, the most active compound in this set of analgetics, both favorable properties are combined within one molecule.

The results of this work underline the importance of the passive penetration of drugs through the blood–brain barrier. No criterion was found which would be in accord with a special importance of an active transport[21] through this barrier for the studied analgetics. In addition, the statistical analysis of the pharmacological results has shown, that the efficiencies of the drugs following intraventricular application parallel largely their receptor activities.

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(21) J. T. Scrafani and C. C. Hug, *Biochem. Pharmacol.*, **17**, 1557 (1968).

Optical Isomers of Miscellaneous Strong Analgetics

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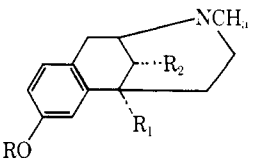
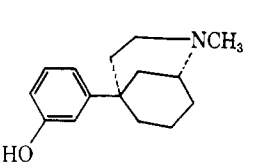
Optical isomers of α-5,9-diethyl-2′-methoxy- (**1a**), α-2,5-dimethyl-9-ethyl-2′-hydroxy- (**1d**), and 2′-hydroxy-2-methyl-6,7-benzomorphans (**1c**) and of 5-(*m*-hydroxyphenyl)-2-methylmorphan (**2**) have been prepared and compared with parent racemates in analgetic activity, physical dependence capacity, and antagonistic behavior. Racemate **1c**, (+)-**1c**, (−)-**1c** and (−)-**2** have morphine-like analgetic and nalorphine-like antagonistic action.

In continuation of our research designed to effect favorable separation of morphine-like effects by optical resolution,[2] the antipodes of α-5,9-diethyl-2′-methoxy- (**1a**), α-2,5-dimethyl-9-ethyl-2′-hydroxy- (**1d**), and 2′-hydroxy- (**1c**) 2-methyl-6,7-benzomorphans and of 5-(*m*-hydroxyphenyl)-2-methylmorphan (**2**) have been prepared. Compounds (+)- and (−)-**1a** were obtained by CH_2N_2 methylation of (+)- and (−)-**1b**. Optical resolution of **1c**, **1d**, and **2** was effected with (+)-3-bromo-8-camphorsulfonic acid ammonium salts,[3] *d*-10-camphorsulfonic acid, and *d*-mandelic acid, respectively.



1a, R = Me; $R_1 = R_2 = Et$
b, R = H; $R_1 = R_2 = Et$
c, $R = R_1 = R_2 = H$
d, R = H; R_1 = Me; R_2 = Et



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Pharmacology. In Table I are given analgetic activities as determined in the mouse hot plate method,[4] and physical dependence capacities and antagonistic

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(2) (a) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, **12**, 288 (1969); (b) E. L. May and N. B. Eddy, *ibid.*, **9**, 581 (1966).

(3) From Aldrich Chemical Company as *d*-α-bromocamphor-π-sulfonic acid.

(4) (a) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); (b) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).