and to Dr. Koos TipKer of Analytical Department, Duphar, B. V., for his help in using STERIMOL parameters.

Registry No. 1, 101372-11-6; 2, 101372-12-7; 3, 101372-13-8; 4, 101372-14-9; 5, 101372-15-0; 6, 101372-16-1; 7, 100284-84-2; 8, 100284-85-3; 9, 100284-86-4; 10, 100284-87-5; 11, 100284-88-6; 12, 100284-89-7; 13, 100284-96-6; 14, 100284-97-7; 15, 100284-98-8; 16, 100284-99-9; 17, 100285-00-5; 18, 100285-01-6; 19, 100284-79-5; 20, 100284-80-8; 21, 100303-52-4; 22, 100284-81-9; 23, 100284-82-0; 24, 100284-83-1; 25, 100284-74-0; 26, 100284-75-1; 27, 100284-76-2; 28, 101372-20-7; 29, 100284-77-3; 30, 100284-78-4; 31, 100284-90-0; 32, 100284-91-1; 33, 100284-92-2; 34, 100284-93-3; 35, 100284-94-4; 36, 100284-95-5; 37, 100284-61-5; 38, 100285-02-7; 39, 91260-70-7; 40, 97682-54-7; 41, 91260-71-8; 42, 91260-69-4; 43, 97682-55-8; 44, 97682-00-3; 45, 97681-41-9; 46, 97681-42-0; 47, 97681-43-1; 48, 97681-44-2; 49, 97681-45-3; 50, 97681-46-4; 51, 97681-47-5; 52, 97681-48-6; 53, 97681-49-7; 55, 95611-89-5; 56, 103534-07-2; 57, 103534-08-3; 58, 103534-09-4; 59, 103534-10-7; 60, 91260-68-3.

Synthetic 1,4-Disubstituted-1,4-dihydro-5*H*-tetrazol-5-one Derivatives of Fentanyl: Alfentanil (R 39209), a Potent, Extremely Short-Acting Narcotic Analgesic

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The synthesis of a series of *N*-1,4-disubstituted-1,4-dihydro-5*H*-tetrazol-5-one piperidinyl derivatives of fentanyl (**10**), carfentanil (**11**), and sufentanil (**12**) is described. The 1-substituted tetrazolinones **2** were essentially prepared via the addition reaction of aluminum azide to isocyanates or acid chlorides in tetrahydrofuran. Alkylation of **2** under neutral or weakly basic conditions afforded almost exclusively the 1,4-disubstituted tetrazolinone isomer **3**. N-Alkylation of the piperidine derivatives **4** with **3** in dimethylformamide yielded **9a–v**. The morphinomimetic activity in rats, after intravenous injection of the compounds, was evaluated in the tail withdrawal reflex test. The fentanyl analogues **9a–c** (R_4 = H) are inactive at the measured dose of 2.5 or 10 mg/kg (iv). For the carfentanil analogues (R_4 = $COOCH_3$) maximal narcotic activity is found when R_1 represents a lower alkyl group (**9d–f**) or a thienylethyl group (**9n**). The sufentanil analogues (R_4 = CH_2OCH_3) show the same structure–activity relationship (SAR) profile as the carfentanil derivatives (R_4 = $COOCH_3$). The structural requirements for optimal activity are in good agreement with earlier observations in the series of **10–12**. From the series the ethyl tetrazolinone derivative **9r**, alfentanil (R 39209), was selected for clinical investigation. As an analgesic in rats, **9r** is 140 times more potent than pethidine **15** and 72 times more potent than morphine **14**. Alfentanil reaches its peak effect within 1 min after injection, and its duration of action is very short; at 2 times its MED_{50}, **9r** has a duration of action of 11 min. This duration is 30 min for **10** and 90 min for **14**. Compared to **10**, alfentanil **9r** is about 4 times faster but 3 times shorter acting. Structurally, **9r** shows most resemblance to sufentanil **12**, since it differs only by substitution of a 4-ethyltetrazolinone ring for the thiophene ring. The considerable differences in their pharmacological profiles were explained in terms of marked variations in physicochemical and, hence, pharmacokinetic properties.

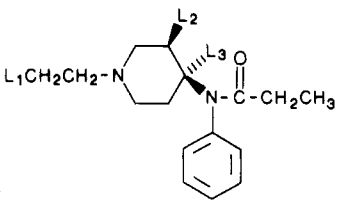
Neuroleptanalgesia[1] has become a popular technique in anesthesia, largely on account of the stable cardiovascular situation associated with it. The narcotic analgesics most commonly used intravenously are morphine and fentanyl.[2,3]

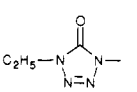
New surgical techniques have created the need for other morphinomimetic compounds characterized by a rapid onset of action, a duration of analgesic activity that can be adapted to the particular clinical situation, a well-defined dose–response relationship, and a maximal margin of safety. Our initial strategy for the attainment of these objectives was directed toward the discovery of narcotic analgesics of increased potency, not for the sake of potency itself but because specificity and safety are directly related to potency.

Chemical modification of the fentanyl structure at the C-4 position of the piperidine ring proved to be a successful approach (Table I).[4,5] Thus, introduction of a carbomethoxy group gave carfentanil **11**, whereas addition of a methoxymethylene group coupled with isosteric replacement of the phenyl ring of the phenethyl substituent by a thienyl ring led to sufentanil **12**. Both carfentanil and sufentanil are very potent and long-acting analgesics. Stereospecific introduction of a methyl group at the C-3 position of the piperidine moiety of the carfentanil molecule resulted in the extremely potent and long-acting compound lofentanil **13**.

Changing the piperidine ring system or modifying the propionanilido moiety was less rewarding. Thus, contraction of the piperidine ring to a 3-anilinopyrrolidine[6]

Table I. Structures of Fentanyl and Related Compounds



compd	L_1	L_2	L_3
fentanyl (**10**)	Ph	H	H
carfentanil (**11**)	Ph	H	$COOCH_3$
sufentanil (**12**)	2-thienyl	H	CH_2OCH_3
lofentanil (**13**)[a]	Ph	CH_3	$COOCH_3$
alfentanil (**9r**)		H	CH_2OCH_3

[a] Cis-(–) enantiomer.

(1) De Castro, J.; Mundeleer, P. *Anesth. Analg. Reanim.* **1959**, *16*, 1022–1056.
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(3) De Castro, J.; Van de Water, A.; Wouters, L.; Xhonneux, R.; Reneman, R.; Kay, B. *Acta Anaesthesiol. Belg.* **1979**, *30*, 5–99.
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(5) U.S. Patent 3 998 834.
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0022-2623/86/1829-2290$01.50/0

Scheme I

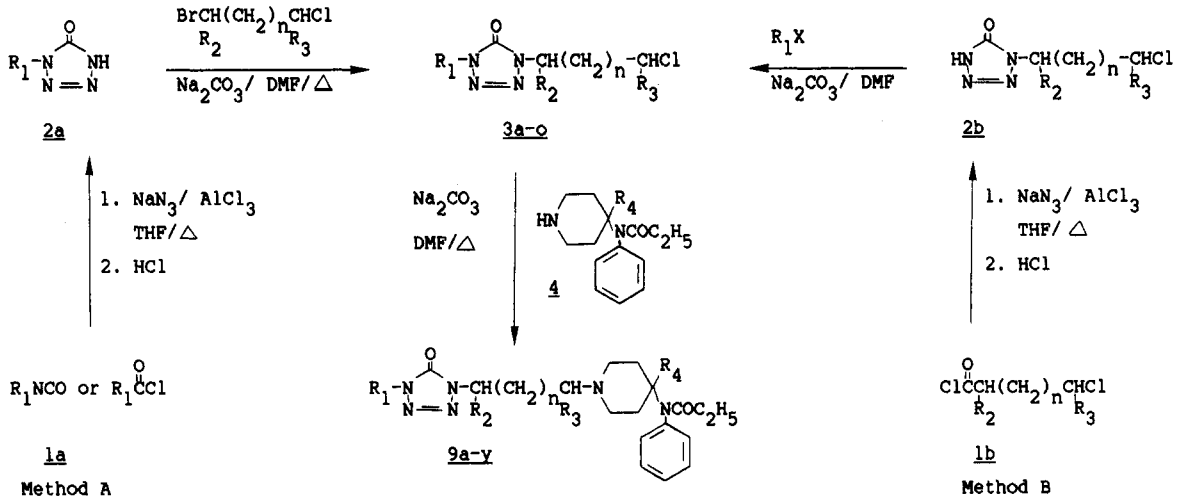
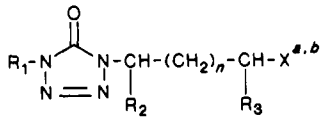


Table II. 1,4-Disubstituted Tetrazolinone Intermediates (3a-o)



compd	R_1	X	n	yield,[c] %	method[d]	formula	anal.
3a	CH_3	I	0	85	B	$C_4H_7IN_4O$[e]	I
3b[f]	C_2H_5	Br	0	69.8	A	$C_5H_9BrN_4O$	C, H, N, Br
3c[g]	C_2H_5	Cl	0	80	A+B	$C_5H_9ClN_4O$	Cl
3d	n-C_3H_7	Cl	0	69	A	$C_6H_{11}ClN_4O$[h]	C, H, N
3e	i-C_3H_7	Cl	0		A	$C_6H_{11}ClN_4O$	*i*
3f	c-C_3H_5	Cl	0	39	A	$C_6H_9ClN_4O$[j]	Cl
3g[k]	t-C_4H_9	Cl	0	60	A	$C_7H_{13}ClN_4O$	C, H, N
3h[l]	n-C_5H_{11}	Cl	0	32.1	A	$C_8H_{15}ClN_4O$[l]	C, H, N
3i	c-C_6H_{11}	Cl	0	87	A	$C_9H_{15}ClN_4O$[l,m]	C, H, N
3j	$C_6H_5CH_2$	Cl	0		A	$C_{10}H_{11}ClN_4O$	*i*
3k[o]	$(C_4H_3S)CH_2CH_2$[p]	Cl	0	46.5	B	$C_9H_{11}ClN_4OS$	C, H, N
3l	$C_6H_5CH_2CH_2$	Cl	0	60	A	$C_{11}H_{13}ClN_4O$[l,n]	C, H, N
3m	$C_2H_5OC(=O)C(CH_3)H$	Cl	0		B	$C_8H_{13}ClN_4O_3$	*i*
3n	$H_2NC(=O)CH_2$	Cl	0	50	B	$C_5H_8ClN_5O_2$[q]	C, H, N
3o	C_2H_5	Cl	1	80	A	$C_6H_{11}ClN_4O$[r]	C, H, N

[a] $R_2 = R_3 = H$. [b] All compounds were isolated as an oil, unless otherwise stated. [c] Based on immediate precursor. Generally no attempts were made to optimize yields. [d] See Scheme I. [e] I: calcd, 49.96; found, 47.60. [f] bp 90–93 °C (1.0 mm). [g] bp 82 °C (1.0 mm). [h] bp 72 °C (0.2 mm); N: calcd, 29.39; found, 29.88. [i] Used immediately without purification. [j] Cl: calcd, 18.79; found, 19.73. [k] bp 71 °C (0.1 mm). [l] HPLC (eluant: toluene–ethanol, 95:5 v/v) afforded an analytical sample. [m] C: calcd, 46.86; found, 46.01. [n] C: calcd, 52.28; found, 50.04. [o] HPLC (eluant: toluene–ethanol, 90:10 v/v) afforded an analytical sample. [p] $(C_4H_3S)CH_2CH_2$, 2-thienylethyl. [q] mp 120 °C (acetonitrile/chloroform). C: calcd, 29.20; found, 28.79; N: calcd, 34.06; found, 33.45. [r] C: calcd, 37.80; found, 36.92.

and expansion to a 4-anilinoperhydroazepine derivative[7] led to compounds with decreased activity. Restriction of the piperidine ring to a chair conformation, achieved through the synthesis of tropane derivatives, resulted in one isomer that was equipotent to fentanyl,[8] but imposition of a boat conformation by inclusion within an isoquinuclidine ring system significantly decreased activity.[9]

Analogues with conformationally rigid modifications of the propionanilido moiety have been shown to lack analgesic activity. This is illustrated by the *cis*- and *trans*-hexahydropyrido[4,3-*b*]indoles, resulting from formal fusion of the *N*-phenyl substituent to the 3-position of the piperidine ring,[10] and by the compounds derived by cyclization of the *N*-acyl group onto either the piperidine ring[11] or the *N*-phenyl substituent.[12]

During the course of our work our initial objectives became somewhat modified as a result of preclinical and clinical experience with compounds **10**, **12**, and **13**. In particular, the potential of a safe narcotic analgesic with an extremely rapid onset of action and an ultrashort duration of analgesic activity became very attractive.

In this paper we report the synthesis and the potent, narcotic analgesic properties of a series of 1,4-disubstituted-1,4-dihydro-5*H*-tetrazol-5-one derivatives of the fentanyl family. The ethyl derivative **9r**, alfentanil (R 39209), is at present undergoing extensive clinical investigation.

Chemistry. Only a few useful methods have been reported in the literature for the synthesis of 1,4-disubstituted-Δ^2-tetrazolin-5-ones. Hattari and co-workers established that aluminum azide adds to isocyanates or acid chlorides in tetrahydrofuran to afford tetrazolinones in

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(11) Borne, R. F.; Fifer, E. K.; Waters, I. W. *J. Med. Chem.* **1984**, *27*, 1271.
(12) Klein, W.; Back, W.; Mutschler, E. *Arch. Pharm. Weiheim Ger.* **1975**, *308*, 910.

Scheme II

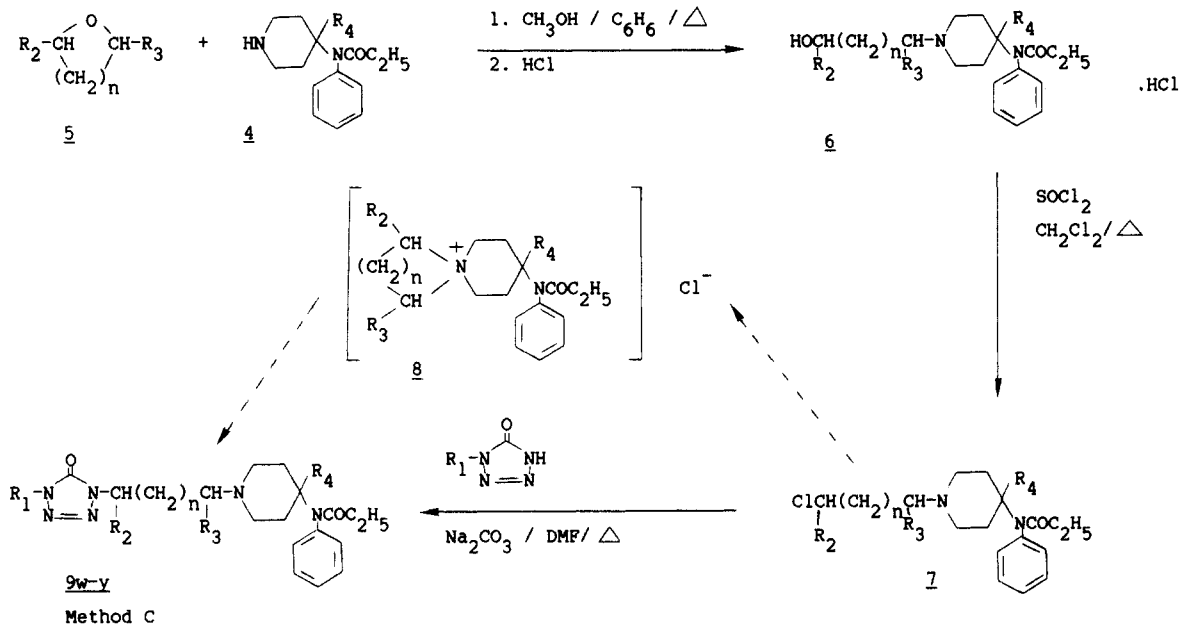
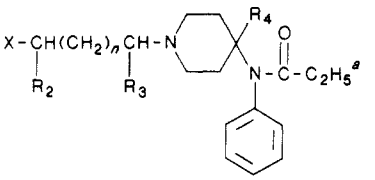


Table III. *N*-(4-Piperidinyl)-*N*-phenylpropanamide Intermediates (**6a,b** and **7a,b**)



compd	X	R_2	mp, °C	yield,[b] %	crystn solvent	formula	anal.
6a	OH	CH_3	184	37.0	*i*-C_3H_7OH[c]/DIPE[d]	$C_{19}H_{30}N_2O_3$·HCl	C, H, N, Cl
6b	OH	C_6H_5	223.7	23.7	CH_3COCH_3	$C_{24}H_{32}N_2O_3$·HCl	C, H, N, Cl
7a	Cl	CH_3	190	85.0	CH_3COCH_3	$C_{19}H_{29}ClN_2O_2$·HCl	C, H, N, Cl[e]
7b	Cl	C_6H_5	145.3	61.7	CH_3COCH_3/DIPE[d]	$C_{24}H_{31}ClN_2O_2$·HCl	C, H, N, Cl

[a] R_3 = H, R_4 = CH_2OCH_3, and n = 0. [b] Based on immediate precursor, after recrystallization. Generally no attempts were made to optimize yields. [c] *i*-C_3H_7OH, isopropyl alcohol. [d] DIPE, diisopropyl ether. [e] C: calcd, 58.61; found, 57.94.

excellent yields.[13] The addition of alkyl azides to aryl, acyl, carboalkoxy, and sulfonyl isocyanates, as well as the reaction of aryl azides with sulfonyl isocyanates, provides convenient methods for the preparation of 1,4-disubstituted-Δ^2-tetrazolin-5-ones.[14,15] At ambient temperature alkyl azides react instantaneously with chlorosulfonyl isocyanate to yield alkyl(chlorosulfonyl)tetrazolinones. Removal of the chlorosulfonyl group then affords 1-alkyltetrazolinones.[16]

The 1-substituted tetrazolinones **2** (Scheme I) were essentially prepared by the method of Hattari. Alkylation of **2** under neutral or weakly basic conditions afforded almost exclusively the 1,4-isomer **3** (methods A and B) (Table II).[17]

The piperidine moieties **4** were prepared as previously described[4,5] starting from suitably protected 4-piperidinones. N-Alkylation of **4** with **3** in dimethylformamide and in the presence of a base at 70 °C then afforded **9a–v**.

Method C proved especially suitable for the synthesis of compounds with substituents on the alkyl chain between the tetrazolinone and piperidine rings (Scheme II). Thus, cleavage of the oxirane **5** (n = 0) with the piperidine **4** yielded **6**, which with thionyl chloride afforded **7** (Table III). The chloroalkyl compound **7** reacted with **2** in dimethylformamide to yield **9w–y**. The reaction of **7a** with **2a** (R_1 = C_2H_5) resulted in a mixture of the regioisomers **9w** and **9x**, suggesting that the reaction proceeds at least in part via the aziridinium intermediate **8**. However, when the phenyl-substituted compound **7b** reacted with **2a** (R_1 = C_2H_5) only the regioisomer **9y** was isolated.

Results and Discussion

Evaluating the morphinomimetic activity in rats in the tail withdrawal reflex test (TWR),[18] we found maximum activity with **9n** and **9r** and slightly lower activity with **9d**, **9f** and **9q**. Compared to fentanyl **10**, **9n**, and **9r** are 4 times less potent.

The fentanyl analogues **9a–c** (R_4 = H) are inactive at the measured dose of 2.5 or 10 mg/kg (iv). For the carfentanil analogues (R_4 = $COOCH_3$) maximal narcotic analgesic activity is found when R_1 represents a lower unbranched alkyl group, as is illustrated by **9d–f**, or a thienylethyl substituent, as is shown in **9n**. The relatively high

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(18) Niemegeers, C. J. E.; Schellekens, K. H. L.; Van Bever, W. F. M.; Janssen, P. A. J. *Arzneim.-Forsch.* **1976**, *26*, 1551.

Table IV. ED_{50} Values (mg/kg) and 95% Confidence Limits of Intravenous Alfentanil **9r** in the Tail Withdrawal Test in Rats[a]

	time after iv administration, h							
parameter	1/32	1/16	1/8	1/4	1/2	1	2	4
ED_{50}, mg/kg	0.044	0.048	0.055	0.121	0.573	1.51	9.20	~20
LL[b]	0.029	0.030	0.034	0.079	0.384	0.992	5.83	
UL[c]	0.065	0.077	0.091	0.186	0.854	2.30	14.5	

[a] See ref 20. [b] Lower limit. [c] Upper limit.

potency of **9n** contrasts sharply with the moderate activity of the phenethyl analogue **9m**. Introduction of a functional group into R_1, as in **9o,p**, results in a pronounced drop in narcotic analgesic activity. The sufentanil analogues ($R_4 = CH_2OCH_3$) show the same SAR profile as the carfentanil derivatives ($R_4 = COOCH_3$). Compounds bearing a small unbranched alkyl group on the tetrazolinone ring (R_1 = lower alkyl) reveal maximal narcotic analgesic activity.

The structural requirements for optimal activity are consistent with earlier observations in the series of **10–12**. Thus, the ethylene group represents the most favorable link between the aromatic moiety and the nitrogen piperidine atom ($R_2 = R_3 = H$, $n = 0$). Elongation of the ethylene chain by one carbon atom considerably reduces the analgesic potency, as is shown by a comparison of **9r** and **9v**. A limited examination of the influence of branching of the ethylene link (compounds **9w–y**) shows no clear structure–activity relationship but suggests that such modifications are not likely to prove beneficial.

From the standpoint of duration of activity, in the series of carfentanil analogues ($R_4 = COOCH_3$), **9f** and **9h** are extremely short-acting, while **9d** and **9g** have an analgesic effect lasting some 4 times longer than that of **9f**. For the active sufentanil analogues ($R_4 = CH_2OCH_3$) the duration of analgesic activity at twice the MED_{50} dose (the minimum effective dose protecting 50% of the animals) varies moderately between 11 and 20 min.

From the above series **9r**, alfentanil (R 39209), was selected for clinical investigation. The intravenous analgesic activity of **9r**, measured in the TWR test at various time intervals after administration of the compound, is shown in Table IV. The calculated ED_{50} values[19,20] illustrate the fast onset of action, since **9r** reached its peak effect (MED_{50} value) within the time of the first observation (~1 min). Compared at the time of peak effect, **9r** is 140 times more potent than pethidine **15**, 72 times more potent than morphine **14**, and 4 times less potent than fentanyl **10** (Table V). These data clearly confirm the place of alfentanil **9r** in the class of potent narcotic analgesics. Figure 1 shows the time–effect curves obtained in the TWR test in rats of alfentanil **9r**, morphine **14**, and fentanyl **10**. The onset of analgesic activity of **9r** is faster than that of the two frequently used reference compounds. The peak effect is reached within 1 min after administration of **9r**, within 4 min for fentanyl, and only after 30 min for morphine. Table VI shows the duration of analgesic narcotic activity, expressed in minutes after the intravenous administration of n times the MED_{50} dose of **9r**, **10**, and **14**.

It can be concluded that in addition to its rapid onset of action, **9r** is also very short acting. Compared to fentanyl **10**, alfentanil **9r** is thus about 4 times faster—but 3 times shorter—acting.

Structurally, **9r** most resembles sufentanil **12**, since it differs only by replacement of the thiophene ring by a 4-ethyltetrazolinone ring. X-ray crystallographic analysis

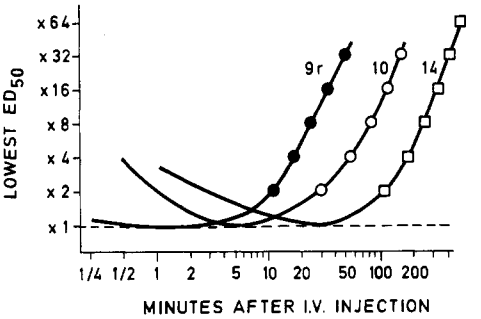

Figure 1. Time–effect curves obtained in the tail withdrawal reaction test in rats after iv administration of alfentanil, fentanyl, and morphine (see ref 20).

of the two compounds reveals them to have virtually identical conformations.[21,22] The propionanilide moiety adapts a typical orientation relative to the piperidine ring, which coincides with the narrow conformational energy minimum derived from empirical and quantum chemical calculations.[23]

Although it is not strictly correct to conclude from such data that the biologically active conformations of the two compounds are the same,[24] we are inclined to do so and to explain the considerable differences in their pharmacological profiles in terms of marked variations in physicochemical and, hence, pharmacokinetic properties (Table VII).

The introduction of the 4-ethyltetrazolinone ring in alfentanil **9r** reduces the basicity of the piperidine nitrogen some 32 times compared to sufentanil **12**. The particularly high electron densities associated with the 1- and 4-nitrogen atoms of the tetrazolinone ring system could explain this considerable reduction in basicity.[25] Although the global values of the dipole moments for **9r** and **12** (2.39 D and 2.22 D) do not differ much, the possibility remains that more pronounced differences occur at particular localized sites of the two molecules. The much reduced lipophilicity of alfentanil **9r** as compared to sufentanil **12** ($\Delta\log P = 1.79$) is a direct consequence of the introduction of the tetrazolinone ring and appears to be a most important factor in explaining the unique properties of alfentanil. At physiological pH, alfentanil **9r** is 13.5 and 7.4 times less lipophilic than sufentanil **12** and fentanyl **10**, respectively. However, the amount of free base is considerably higher for **9r** (88.82%) than for **12** and **10** (19.71% and 8.54%, respectively). As a consequence there is a high bioavailability of **9r** free base, which allows a rapid penetration to the brain area and could explain the quick onset of action. The short duration of the narcotic anal-

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(22) Structural data courtesy of Prof. E. Durant (unpublished results).
(23) Tollenaere, J. P.; Moereels, H., unpublished results.
(24) Tollenaere, J. P.; Moereels, H.; L. A. Raymaekers *Atlas of the Three-Dimensional Structure of Drugs*, Janssen Research Foundation Series; Elsevier: Amsterdam, 1979; Vol. 1, p 6.
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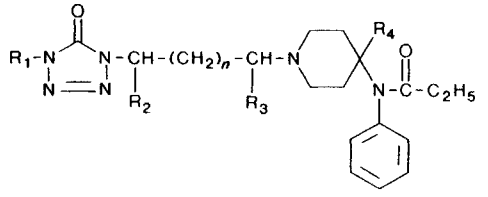
Table V. Disubstituted 1,4-Dihydro-5*H*-tetrazol-5-one Derivatives of Fentanyl: Chemical and Pharmacological Data



(9a-y)

compd	R_1	R_2	R_3	R_4	n	mp, °C	yield,[a] %	crystn[b] solvent	formula	anal.	TWR rat MED_{50},[c] mg/kg	TWR rat duration,[d] min
9a	C_2H_5	H	H	H	0	178.1	15.1	A	$C_{19}H_{28}N_6O_2 \cdot C_2H_2O_4$[e]	C, H, N	>2.5[f]	
9b	i-C_3H_7	H	H	H	0	182.5	18.0		$C_{20}H_{30}N_6O_2 \cdot HNO_3$	C, H, N	>10	
9c	C_2H_5	H	H	H	1	159.9	82.5	B	$C_{20}H_{30}N_6O_2 \cdot C_2H_2O_4$	C, H, N[g]	>2.5	
9d	CH_3	H	H	$COOCH_3$	0	185.9	35.6	A	$C_{20}H_{28}N_6O_4 \cdot C_2H_2O_4$	C, H, N	0.08	39
9e	C_2H_5	H	H	$COOCH_3$	0	158.9	13.0	A	$C_{21}H_{30}N_6O_4 \cdot 1.5C_2H_2O_4$	C, H, N	0.16	17
9f	n-C_3H_7	H	H	$COOCH_3$	0	168.4	18.7	B	$C_{22}H_{32}N_6O_4 \cdot C_2H_2O_4$	C, H, N	0.08	10
9g	i-C_3H_7	H	H	$COOCH_3$	0	184.2	23.0	A	$C_{22}H_{32}N_6O_4 \cdot C_2H_2O_4$	C, H, N	1.25	41
9h	c-C_3H_5[h]	H	H	$COOCH_3$	0	155.9	9.3	B	$C_{22}H_{30}N_6O_4 \cdot 1.5C_2H_2O_4 \cdot 0.5H_2O$	C, H, N[i]	0.63	10
9i	t-C_4H_9	H	H	$COOCH_3$	0	168.1	14.6	B	$C_{23}H_{34}N_6O_4 \cdot C_2H_2O_4$	C, H, N	1.25	20
9j	n-C_5H_{11}	H	H	$COOCH_3$	0	153.5	17.8	B	$C_{24}H_{36}N_6O_4 \cdot C_2H_2O_4$	C, H, N[j]	1.25	20
9k	c-C_6H_{11}	H	H	$COOCH_3$	0	173.0	26.0	A	$C_{25}H_{36}N_6O_4 \cdot C_2H_2O_4$	C, H, N	>2.5	
9l	$C_6H_5CH_2$	H	H	$COOCH_3$	0	191.7	30.0	A	$C_{26}H_{32}N_6O_4 \cdot C_2H_2O_4$	C, H, N	>2.5	
9m	$C_6H_5CH_2CH_2$	H	H	$COOCH_3$	0	162.2	23.4	B	$C_{27}H_{34}N_6O_4 \cdot 1.5C_2H_2O_4$	C, H, N	1.25	15
9n	$(C_4H_3S)CH_2CH_2$[k]	H	H	$COOCH_3$	0	162.9	20.0	B	$C_{25}H_{32}N_6O_4S \cdot C_2H_2O_4$	C, H, N, S	0.04	30
9o	$C_2H_5OC(=O)CH(CH_3)$	H	H	$COOCH_3$	0	168.6	16.9	B	$C_{24}H_{34}N_6O_6 \cdot C_2H_2O_4$	C, H, N	>2.5	
9p	H_2NCOCH_2	H	H	$COOCH_3$	0	209.0	41.8	A	$C_{21}H_{29}N_7O_5 \cdot C_2H_2O_4$	C, H, N[l]	>2.5	
9q	CH_3	H	H	CH_2OCH_3	0	155.9	42.0	A	$C_{20}H_{30}N_6O_3 \cdot C_2H_2O_4$	C, H, N	0.08	20
9r	C_2H_5	H	H	CH_2OCH_3	0	138.4	66.5	A	$C_{21}H_{32}N_6O_3 \cdot HCl \cdot H_2O$	C, H, N, Cl	0.044	11
9s	n-C_3H_7	H	H	CH_2OCH_3	0	103.8	8.0	B	$C_{22}H_{34}N_6O_3 \cdot 2C_2H_2O_4 \cdot H_2O$	C, H, N	0.16	20
9t	i-C_3H_7	H	H	CH_2OCH_3	0	107.5	30.0		$C_{22}H_{34}N_6O_3 \cdot HNO_3 \cdot H_2O$	C, H, N	0.63	11
9u	$C_2H_5OC(=O)CH(CH_3)$	H	H	CH_2OCH_3	0	122.8	8.0	B	$C_{24}H_{36}N_6O_5 \cdot 1.5C_2H_2O_4$	C, H, N	>2.5	
9v	C_2H_5	H	H	CH_2OCH_3	1	182	55.5	A	$C_{22}H_{34}N_6O_3 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	2.5	14
9w	C_2H_5	H	CH_3	CH_2OCH_3	0	185.4	18.0	A	$C_{22}H_{34}N_6O_3 \cdot HCl$	C, H, N	0.16	17
9x	C_2H_5	CH_3	H	CH_2OCH_3	0	192.7	33.0	B	$C_{22}H_{34}N_6O_3 \cdot HCl$	C, H, N	>2.5	
9y	C_2H_5	C_6H_5	H	CH_2OCH_3	0	125.7	65.0	C	$C_{27}H_{36}N_6O_3$	C, H, N	0.16	14
10	fentanyl										0.011	30
14	morphine										3.20	90
15	pethidine										6.04	35

[a] Based on immediate precursor, after recrystallization. Generally no attempts were made to optimize yields. [b] A, acetone; B, a mixture of acetone and diisopropyl ether; C, a mixture of petroleum ether and diisopropyl ether. [c] MED_{50}, intravenous analgesic ED_{50} dose (mg/kg) at time of peak effect. [d] Duration of analgesic activity expressed in minutes at 2 × MED_{50} dose. [e] $C_2H_2O_4$, oxalic acid. [f] The symbol > (greater than) indicates that the compound is inactive at the highest dose tested. [g] C: calcd, 54.45; found, 54.94. [h] c-C_3H_5, cyclopropyl. [i] C: calcd, 51.19; found, 50.47. [j] C: calcd, 55.51; found, 55.92. [k] $(C_4H_3S)CH_2CH_2$, 2-thienylethyl. [l] N: calcd, 17.84; found, 17.24.

Table VI. Kinetics of Alfentanil, Fentanyl, and Morphine in the Tail Withdrawal Reaction Test in Rats[a]

compd	peak effect, min	duration, min, at the given multiple of the MED_{50}				
		2×	4×	8×	16×	32×
alfentanil (**9r**)	1	11	17	25	36	53
fentanyl (**10**)	4	30	55	85	120	165
morphine (**14**)	30	90	150	240	300	380

[a] See ref 20.

Table VII. Physicochemical Constants of Alfentanil and Reference Compounds

compd	pK_a[a] at 25 °C	μ,[b] D, at 20 °C	log P[c] at 25 °C	log P_{app}[d] at pH 7.4	% free base at pH 7.4
alfentanil (**9r**)	6.50	2.39	2.16	2.11[e]	88.82
fentanyl (**10**)	8.43	3.04	4.05	2.98[e]	8.54
sufentanil (**12**)	8.01	2.24	3.95	3.24	19.71
lofentanil (**13**)	7.82	3.23	4.22	3.66	27.55
morphine (**14**)	7.93[f]		0.79[f]	0.15[f]	25.31[f]

[a] See ref 33. [b] See ref 34. [c] P = distribution coefficient determined between octanol and water. [d] See ref 35. [e] Heptane–water partition coefficient, P, measured at 37 °C and at pH 7.4: **9r** (2.5) and **10** (9.0) (see ref 28a). [f] Measured at 37 °C instead of 25 °C.

gesic action of **9r** may be due to the kinetics of its distribution and redistribution in the tissues, factors which in turn depend on its physicochemical properties.[26] The high affinity of **9r** for plasma proteins in humans,[27,28] the relatively low lipid solubility, and the minimal degree of ionization are responsible for decreased cell and tissue binding, which, in turn, explains why alfentanil has the lowest distribution volume among those known for narcotic anesthetics.[28a]

Because of this low distribution volume, the terminal half-life is short, less than half that of fentanyl, even though the clearance of alfentanil in humans is smaller than that of fentanyl.[29,30] With a shorter elimination half-life, recovery following administration of **9r** should be more rapid than following fentanyl.[31]

In conclusion, we believe that the characteristic physicochemical and pharmacokinetic properties of alfentanil **9r** afford this compound a unique position within the class of clinically useful narcotic analgesics.

Experimental Section

Chemistry. Melting points are determined with a Mettler FP_1 melting point apparatus and are uncorrected. Elemental analyses were performed by the analytical research department of Janssen Pharmaceutica N.V. ^1H NMR spectra were measured with either a Bruker WP 200 or a Bruker AM 360. Chemical shifts are reported as δ values relative to tetramethylsilane as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra were measured with a Varian Mat 311-eV emission spectrometer. UV and IR spectra were determined with a UV, Beckman DK-2A, and a Perkin-Elmer 421 or 225 spectrometer. Where indicated GC was measured with a Varian 3700 (packed column 2 m, 3% OV 17). Preparative HPLC was performed on a Jobin Yvon Modulprep (column i.d. 80 mm). Analytical TLC was performed on silica 60 F_{254} (Merck), and the spots were made visible by a UV lamp or iodine vapor.

1-Ethyl-1,4-dihydro-5*H*-tetrazol-5-one (2a) ($R_1 = C_2H_5$). Method i. A solution of aluminum chloride (39 g, 0.22 mol) in dry tetrahydrofuran (250 mL) was added at once to a rigorously stirred suspension of ethyl isocyanate (14.2 g, 0.2 mol) and sodium azide (29.2 g, 0.45 mol) in dry tetrahydrofuran (150 mL).

A slightly exothermic reaction occurred. The mixture was stirred under reflux for 24 h. After cooling, the mixture was acidified with 6 N hydrochloric acid, and the biphasic water–organic layer system was evaporated in vacuo. The white solid residue was extracted 4 times with hot acetone, and the organic fractions were collected, dried over magnesium sulfate, filtered, and evaporated in vacuo. The white product was dried overnight in vacuo to afford **2a** (18 g, 65%). Crystallization from benzene yielded an analytical sample: mp 79.7 °C. Anal. ($C_3H_6N_4O$) C, H, N, O.

Method ii. To a suspension of sodium azide (162.5 g, 2.5 mol) in dry tetrahydrofuran (700 mL) was added at once a solution of aluminum chloride (147 g, 1.10 mol) in tetrahydrofuran (1200 mL). The mixture was stirred under reflux for 1 h, then cooled to room temperature, whereupon a solution of propionyl chloride (47.5 g, 0.51 mol) in tetrahydrofuran (100 mL) was introduced. The reaction mixture was stirred under gentle reflux for 24 h. The usual workup afforded 46.7 g of a tan solid. An analytical sample of **2a** ($R_1 = C_2H_5$), mp 77 °C, was obtained on distillation of the crude product in vacuo (bp 133 °C (1 mm)). In a similar way the following tetrazolinones **2a** were prepared: $R_1 = n\text{-}C_3H_7$, mp 39.7 °C (48%); $R_1 = i\text{-}C_3H_7$; R_1 = c-C_3H_5, mp 118.4 °C (63%); $R_1 = n\text{-}C_5H_{11}$, bp 130 °C (0.05 mm) (43%); $R_1 = C_6H_5CH_2$, mp 145.2 °C (80%); $R_1 = C_6H_5CH_2CH_2$, mp 94.6 °C (69%). Other tetrazolinones **2a** ($R_1 = t\text{-}C_4H_9$, c-C_6H_{11}) obtained by the same methods are known compounds.[14,16,17] The NMR data for **2a** ($R_1 = C_2H_5$) were typical: NMR ($CDCl_3$) δ 11.75 (s, 1 H, NH), 4.05 (q, 2 H, CH_2), 1.47 (t, 3 H, CH_3).

1-(2-Chloroethyl)-1,4-dihydro-5*H*-tetrazol-5-one (2b) ($R_2 = R_3 = H$, $n = 0$). This compound was prepared by the same route as **2a** ($R_1 = C_2H_5$), starting from 3-chloropropionyl chloride (method ii). After the usual decomposition and workup procedure, a crude residue of **2b** ($R_2 = R_3 = H$, $n = 0$) (81%) was obtained. Crystallization from toluene afforded an analytical sample: mp 77 °C [lit.[15] mp 77–78 °C]. Anal. ($C_3H_5ClN_4O$) C, H, N, Cl.

Method A. 1-(2-Bromoethyl)-4-ethyl-1,4-dihydro-5*H*-tetrazol-5-one (3b). A suspension of **2a** ($R_1 = C_2H_5$) (57 g, 0.5 mol), 1,2-dibromoethane (470 g, 2.5 mol), and sodium carbonate (33 g, 0.5 mol) in 4-methyl-2-pentanone (100 mL) was stirred and refluxed overnight. After cooling, water (300 mL) was added to the reaction mixture. The organic layer was separated, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was distilled to yield **3b** (77.5 g, 69.8%): bp 90–93 °C (1 mm)); NMR ($CDCl_3$) δ 4.37 (t, 2 H, CH_2CH_2Br), 4.05 (q, 2 H, CH_2), 3.72 (t, 2 H, CH_2CH_2Br), 1.47 (t, 3 H, CH_3). Anal. ($C_5H_9BrN_4O$) C, H, N, Br.

1-(2-Chloroethyl)-4-ethyl-1,4-dihydro-5*H*-tetrazol-5-one (3c). Alkylation of **2a** ($R_1 = C_2H_5$) as described for **3b** with 1-bromo-2-chloroethane afforded **3c** in 80% yield, after purification on silica ($CHCl_3$). An analytical sample was obrained by destillation: bp (82 °C (1 mm)). Anal. ($C_5H_9ClN_4O$) Cl.

***N*-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)-ethyl]-4-piperidinyl]-*N*-phenylpropanamide Ethanedioate (1:1) (9a).** A suspension of **3c** (1.8 g, 0.01 mol), **4** ($R_4 = H$)[32] (2.6 g, 0.011 mol), sodium carbonate (4.24 g, 0.04 mol), and potassium iodide (0.1 g) in 4-methyl-2-pentanone (300 mL) was stirred and refluxed for 18 h. Water was removed by a Dean-Stark trap. After cooling, water (100 mL) was added and the organic layer separated. The water layer was extracted with dichloromethane (200 mL). The combined organic fractions were dried over magnesium sulfate and evaporated in vacuo. The residue was purified by chroma-

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tography on silica gel (eluant: $CHCl_3$–CH_3OH, 95:5 v/v). The pure fraction was converted into an oxalate salt, which was crystallized twice from acetone to yield **9a** (0.7 g, 15.1%): mp 178.1 °C. Anal. ($C_{19}H_{28}N_6O_2 \cdot C_2H_2O_4$) H, N; C: calcd, 54.53; found, 54.94.

N-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide Monohydrochloride Monohydrate (9r). A mixture of **3b** (2.2 g, 0.01 mol), **4** ($R_4 = CH_2OCH_3$)[4] (3.45 g, 0.011 mol), and sodium carbonate (2.12 g, 0.02 mol) reacted in 4-methyl-2-pentanone (150 mL) as described for **9a**. The crude residue, obtained after the usual workup, was purified by chromatography on silica (eluant: $CHCl_3$–CH_3OH, 97:3 v/v). The hydrogen chloride salt was crystallized from acetone to afford 3 g (66.5%) of **9r**: mp 138.4 °C; NMR (free base in $CDCl_3$) δ 7.20–7.40 (m, 5 H, benzene), 4.04 (s, 2 H, CH_2O), 4.00 (t, 2 H, $OCNCH_2CH_2N$), 3.98 (q, 2 H, CH_2N), 3.42 (s, 3 H, OCH_3), 2.72 (t, 2 H, CH_2N), 2.63 (m, 2 H, 2–6_{eq} piperidine H), 1.82 (q, 2 H, CH_2CO), 1.64 (m, 2 H, 3–5_{ax} piperidine H), 1.42 (t, 3 H, CH_3CH_2N), 0.93 (t, 3 H, CH_3CH_2CO). Anal. ($C_{21}H_{32}N_6O_3 \cdot HCl \cdot H_2O$) C, H, N, Cl.

Method B. 1-(2-Chloroethyl)-1,4-dihydro-4-[2-(2-thienyl)ethyl]-5H-tetrazol-5-one (3k). A suspension of **2b** ($R_2 = R_3 = H$, $n = 0$) (10 g, 0.07 mol), 2-(2-thienyl)ethanol 4-methylbenzenesulfonate (ester)[4] (19.6 g, 0.07 mol), and sodium carbonate (10.6 g, 0.1 mol) in dimethylformamide was stirred overnight at 70 °C. After cooling, the reaction mixture was poured into water and extracted 3 times with toluene. The combined extracts were dried over magnesium sulfate, filtered, and evaporated. The residue was purified by chromatography on silica (eluant: $CHCl_3$–petroleum ether, 70:30 v/v) to yield **3k** (15 g, 46.5%) as an oil. An analytical sample was obtained via HPLC (eluant: toluene–ethanol, 90:10 v/v): NMR ($CDCl_3$) δ 7.18 (d-d, 1 H, 5-thiophene H), 6.92 (d-d, 1 H, 4-thiophene H), 6.82 (d-d, 1 H, 3-thiophene H), 4.28 (t, 2 H, CH_2CH_2Cl), 4.22 (t, 2 H, CH_2CH_2 (C_4H_3S)), 3.83 (t, 2 H, CH_2Cl), 3.37 (t, 2 H, CH_2CH_2 (C_4H_3S)). Anal. ($C_9H_{11}ClN_4OS$) C, H, N.

4-(2-Chloroethyl)-4,5-dihydro-5-oxo-1H-tetrazole-1-acetamide (3n). This compound was prepared by the same method as described for **3k**. Iodoacetamide (18.4 g, 0.1 mol) and **2b** ($R_2 = R_3 = H$, $n = 0$) (14.8 g, 0.1 mol) reacted to afford **3n** (14.5 g, 70.7%). An analytical sample was obtained after crystallization from a mixture of acetone and chloroform: mp 120 °C. Anal. ($C_5H_8ClN_5O_2$) H; C: calcd, 29.20; found, 28.79; N: calcd, 34.06; found, 33.45.

Methyl 1-[2-[4-(2-Amino-2-oxoethyl)-4,5-dihydro-5-oxo-1H-tetrazol-1-yl]ethyl]-4-[(1-oxopropyl)phenylamino]-4-piperidinecarboxylate Ethanedioate (9p). A mixture of **3n** (2.2 g, 0.011 mol), **4** ($R_4 = COOCH_3$)[4] (3.2 g, 0.01 mol), and sodium carbonate (2.12 g, 0.02 mol) in dimethylformamide was stirred overnight at 70 °C. After cooling, the reaction mixture was poured into water and extracted 3 times with toluene. The organic layers were collected, dried ($MgSO_4$), filtered, and evaporated. After chromatography (eluant: $CHCl_3$–CH_3OH, 97:3 v/v) the pure product was converted to the oxalate, which was crystallized from acetone to furnish **9p** (2.3 g, 41.8%): mp 209 °C. Anal. ($C_{21}H_{29}N_7O_5 \cdot C_2H_2O_4$) C, H; N: calcd, 17.84; found, 17.24.

Method C. N-[1-(2-Hydroxypropyl)-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide Monohydrochloride (6a). A suspension of **5** ($R_2 = CH_3$, $R_3 = H$, $n = 0$) (35 g, 0.6 mol), **4** ($R_4 = CH_2OCH_3$),[4] and sodium hydrogen carbonate (25.2 g, 0.3 mol) in a mixture of benzene (500 mL) and methanol (100 mL) was stirred and refluxed for 24 h. The reaction mixture was evaporated and the residue triturated with water and extracted twice with chloroform. The organic fractions were separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was acidified with hydrogen chloride in 2-propanol, and the solid obtained was recrystallized from a mixture of 2-propanol/diisopropyl ether to yield **6a** (41.5 g, 37%): mp 184 °C. Anal. ($C_{19}H_{30}N_2O_3 \cdot HCl$) C, H, N, Cl.

N-[1-(2-Hydroxy-2-phenylethyl)-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide Hydrochloride (6b). A mixture of **4** ($R_4 = CH_2OCH_3$)[4] (4.1 g, 0.015 mol) and **5** ($R_2 = C_6H_5$, $R_3 = H$, $n = 0$) (2.0 g, 0.017 mol) was stirred at 100° C for 18 h. After cooling, the crude residue was purified by chromatography on silica (eluant: $CHCl_3$–CH_3OH, 95:5 v/v), and the pure fraction was dissolved in diethyl ether and acidified with hydrogen chloride gas. After decantation of the solvent, the solid was collected and recrystallized from acetone to yield **6b** (1.5 g, 23%): mp 233.7 °C. Anal. ($C_{24}H_{32}N_2O_3 \cdot HCl$) C, H, N, Cl.

N-[1-(2-Chloropropyl)-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide Monohydrochloride (7a). A solution of **6a** (37 g, 0.1 mol) in chloroform (150 mL) was added dropwise to a stirred solution of thionyl chloride (14 g, 0.12 mol) in chloroform (150 mL) at room temperature. The reaction mixture was stirred and refluxed overnight. After evaporation in vacuo the residue was suspended in acetone (300 mL) and the solid collected to afford **7a** (31.5 g, 85%): mp 190 °C. Anal. ($C_{19}H_{29}ClN_2O_2 \cdot HCl$) H, N, Cl; C: calcd, 58.61; found, 57.94.

N-[1-(2-Chloro-2-phenylethyl)-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide Monohydrochloride (7b). Thionyl chloride (4.5 g, 0.036 mol) was stirred at room temperature, while a solution of **6b** (13 g, 0.033 mol) in chloroform (200 mL) was added dropwise over a period of 30 min. The mixture was refluxed for 4 h, cooled, and evaporated in vacuo. The residue was triturated with acetone, treated with carbon black, and filtered. The filtrate was evaporated and the residue converted into the hydrogen chloride salt, which crystallized from a mixture of acetone/diisopropyl ether affording **7b** (9.2 g, 61.7%): mp 145.3 °C. Anal. ($C_{24}H_{31}ClN_2O_2 \cdot HCl$) C, H, N, Cl.

N-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)propyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide Monohydrochloride (9w) and N-[1-[2-(4,5-Dihydro-4-methyl-5-oxo-1H-tetrazol-1-yl)-1-methylethyl]-4-piperidinyl]-N-phenylpropanamide Monohydrochloride (9x). A suspension of **2a** ($R_1 = C_2H_5$) (2.75 g, 0.025 mol), **7a** (9.4 g, 0.025 mol), triethylamine (2.5 g, 0.025 mol), and sodium carbonate (2.65 g, 0.025 mol) in dimethylformamide (700 mL) was stirred at 70 °C for 20 h. The usual workup yielded 10.5 g of the crude residue. A preliminary purification on silica (eluant: $CHCl_3$–CH_3OH, 97:3 v/v) afforded 9.2 g of a mixture of **9w** and **9x**. The mixture was separated by HPLC (ethyl acetate–ethanol, 99:1 v/v) to yield the pure isomers **9w** (higher R_f value on TLC, eluant: $CHCl_3$–CH_3OH, 95:5 v/v) (5.1 g) and **9x** (lower R_f value on TLC) (3 g).

Conversion of **9w** to the hydrochloride salt in acetone and crystallization of the salt from acetone/diisopropyl ether yielded the final compound (3.9 g, 33.4%): mp 185.4 °C; NMR (free base in $CDCl_3$) δ 7.20–7.38 (m, 5 H, benzene), 3.92–4.10 (m, 5 H, CH_2O, CH_2N, 1 H from $OCNCH_2CH(CH_3)N$), 3.74 (d-d, 1 H, 1 H from $OCNCH_2CH(CH_3)N$), 3.40 (s, 3 H, CH_3O), 3.11 (m, 1 H, CH), 2.05–2.65 (m, 6 H, 2–$6_{ax,eq}$, 3–5_{eq} piperidine H), 1.81 (q, 2 H, CH_2CO), 1.55 (m, 2 H, 3–5_{ax} piperidine H), 1.44 (t, 3 H, CH_3CH_2N), 0.98 (d, 3 H, $OCNCH_2CH(CH_3)N$), 0.93 (t, 3 H, CH_3CH_2CO). Anal. ($C_{22}H_{34}N_6O_3 \cdot HCl$) C, H, N.

The fraction with the lower R_f value was crystallized as the hydrogen chloride salt from a mixture of acetone/diisopropyl ether to afford **9x** (3.9 g, 33.4%): mp 192.7 °C; NMR (free base in $CDCl_3$) δ 7.20–7.38 (m, 5 H, benzene), 4.40 (m, 1 H, CH), 3.95–4.10 (m, 4 H, CH_2N, CH_2O), 3.40 (s, 3 H, OCH_3), 2.05–2.80 (m, 8 H, $OCNCH(CH_3)CH_2N$, 2–$6_{eq,ax}$, 3–5_{eq} piperidine H)), 1.80 (q, 2 H, CH_2CO), 1.55 (m, 2 H, 3–5_{ax} piperidine H), 1.42 (m, 6 H, CH_3CH_2N, $OCNCHCH(CH_3)CH_2N$), 0.92 (t, 3 H, CH_3CH_2CO). Anal. ($C_{22}H_{34}N_6O_3 \cdot HCl$) C, H, N.

N-[1-[2-(4-Ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)-2-phenylethyl]-4-(methoxymethyl)-4-piperidinyl]-N-phenylpropanamide (9y). A suspension of **2a** ($R_1 = C_2H_5$) (3 g, 0.025 mol), **7b** (8 g, 0.0178 mol), sodium carbonate (5.3 g, 0.05 mol), and potassium iodide (0.2 g) in dimethylformamide (150 mL) was stirred at 70 °C for 20 h. The solid residue, obtained after the usual workup, was purified by chromatography on silica (eluant: $CHCl_3$–CH_3OH, 97:3 v/v), and the pure fraction was crystallized from a mixture of petroleum ether and diisopropyl ether to yield **9y** (5.7 g, 65%): mp 125–127 °C; NMR ($CDCl_3$) δ 7.20–7.47 (m, 10 H, aromatics), 5.38 (d-d, 1 H, CH), 3.93–4.08 (m, 4 H, CH_2O, CH_2N), 3.40 (m, 4 H, OCH_3, 1 H from $OCNCH(C_6H_5)CH_2N$), 2.05–2.80 (m, 7 H, 2–$6_{ax,eq}$, 3–5_{eq} piperidine H, 1 H from $OCNCH(C_6H_5)CH_2N$), 1.80 (q, 2 H, CH_2CO), 1.56 (m, 2 H, 3–5_{ax} piperidine H), 1.41 (t, 3 H, CH_3CH_2N), 0.92 (t, 3 H, CH_3CH_2CO). Anal. ($C_{27}H_{36}N_6O_3$) C, H, N.

Physicochemical Methods. Ionization Constant. The ionization constant pK_a at 25 °C was determined by potentiometric titration of a solution of the compound in methanol–water

mixtures of varying composition. The values were extrapolated to pure water.[33]

Dipole moments were measured in benzene p.a. with a dipolemeter DM01 (Wiss.-Techn. Werkstätten) at 20 °C, using a 20 cm^3 DFL1 cell.[34]

Partition Coefficient. (i) The partition coefficient was determined between *n*-octanol and an aqueous buffer solution at pH 9.8 (25 °C). A simple extraction method was used.

(ii) The apparent log *P* values (log P_{app}) were calculated by using the formula[35]

$$P_{app} = \frac{P}{1 + 10^{(pK_a - pH)}}$$

(iii) The percentage free base and ionized were calculated by using the formula of Albert et al.[36]

$$\% \text{ ionized} = \frac{100}{1 + \text{antilog } (pH - pK_a)}$$

Pharmacology. Compounds **9a–y** and **10–15** were evaluated for morphinomimetic activity in the tail withdrawal reflex test (TWR) in rats.[20]

The experimental animals were inbred male Wistar rats (215 ± 15 g). One day before the experiment, the animals were transferred from their rearing quarters to the air-conditioned laboratories (21 ± 1 °C), with a relative humidity (RH) of 65 ± 15%. Standard pellet food and tap water were available ad libitum, except during the experimental session. The compounds were injected into one of the tail veins (0.2 mg/100 g of body weight; injection time, 5 s). Doses were selected from the following geometric series 160, 80, 40, ..., 0.08, 0.04, 0.02 mg/kg. The tail withdrawal reaction test has been described previously.[18] The rats were placed in standard rat holders with the tail hanging free outside the holder. A reading consisted of immersing the tail into a warm (55 ± 1 °C) water bath and determining the reaction time for tail withdrawal. Cutoff time was 10 s. Readings were made 1/32, 1/16, 1/8, 1/4, 1/2, 1, 2, and 4 h after administration of the investigated compounds. The ED_{50} values for each time interval were calculated according to the criterion no withdrawal of the tail within 10 s.[19] The absence of a reaction within 10 s was considered to represent almost complete analgesia (surgical analgesia) and occurred in only 2 of 1419 control rats.

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Registry No. **1a** (R_1 = i-C_3H_7), 79-30-1; **1a** (R_1 = C_5H_{11}), 142-61-0; **2a** (R = C_2H_5), 69048-98-2; **2a** (R = C_3H_7), 69048-99-3; **2a** (R = i-C_3H_7), 69049-00-9; **2a** (R = c-C_3H_5), 69049-02-1; **2a** (R = C_5H_{11}), 104071-97-8; **2a** (R = $CH_2C_6H_5$), 53798-95-1; **2a** (R = $(CH_2)_2C_6H_5$), 62442-50-6; **2a** (R = t-C_4H_9), 69049-01-0; **2a** (R = c-C_6H_{11}), 37495-20-8; **2a** (R_2 = R_3 = H, n = 0), 56413-06-0; **3a**, 69049-04-3; **3b**, 84501-67-7; **3c**, 69049-03-2; **3d**, 104071-98-9; **3e**, 104071-99-0; **3f**, 104072-00-6; **3g**, 92075-19-9; **3h**, 104072-01-7; **3i**, 104072-02-8; **3j**, 56413-00-4; **3k**, 69049-05-4; **3l**, 104072-03-9; **3m**, 104072-04-0; **3n**, 104072-05-1; **3o**, 104072-06-2; **4** (R_4 = H), 1609-66-1; **4** (R_4 = CO_2CH_3), 72996-78-2; **4** (R_4 = CH_2OCH_3), 61086-18-8; **5** (R_2 = CH_3, R_3 = H, n = 0), 75-56-9; **5** (R_2 = C_6H_5, R_3 = H, n = 0), 96-09-3; **6a**, 104072-15-3; **6b**, 61087-21-6; **7a**, 104072-16-4; **7b**, 69069-06-3; **9a**, 104072-07-3; **9a**·$C_2H_2O_4$, 104072-20-0; **9b**, 104072-08-4; **9b**·HNO_3, 104072-21-1; **9c**, 104072-09-5; **9c**·$C_2H_2O_4$, 104072-22-2; **9d**, 69049-37-2; **9d**·$C_2H_2O_4$, 69049-38-3; **9e**, 69049-15-6; **9e**·$^3/_2C_2H_2O_4$, 69049-16-7; **9f**, 69049-17-8; **9f**·$C_2H_2O_4$, 69049-18-9; **9g**, 69049-19-0; **9g**·$C_2H_2O_4$, 69049-20-3; **9h**, 69049-31-6; **9h**·$^3/_2C_2H_2O_4$, 69049-32-7; **9i**, 69049-21-4; **9i**·$C_2H_2O_4$, 69049-22-5; **9j**, 69049-23-6; **9j**·$C_2H_2O_4$, 69049-24-7; **9k**, 69049-25-8; **9k**·$C_2H_2O_4$, 69049-26-9; **9l**, 69049-29-2; **9l**·$C_2H_2O_4$, 69049-30-5; **9m**, 69049-27-0; **9m**·$^3/_2C_2H_2O_4$, 69049-28-1; **9n**, 69049-12-3; **9n**·$C_2H_2O_4$, 69049-12-3; **9o**, 104072-10-8; **9o**·$C_2H_2O_4$, 104072-17-5; **9p**, 104072-11-9; **9p**·$C_2H_2O_4$, 104072-18-6; **9q**, 71195-58-9; **9q**·$C_2H_2O_4$, 69049-36-1; **9r**, 71195-58-9; **9r**·HCl, 69049-06-5; **9s**, 69049-07-6; **9s**·$2C_2H_2O_4$, 69049-08-7; **9t**, 69049-09-8; **9t**·HNO_3, 69049-10-1; **9u**, 104072-12-0; **9u**·$C_2H_2O_4$, 104072-19-7; **9v**, 104072-13-1; **9v**·HCl, 69069-05-2; **9w**, 69221-39-2; **9w**·HCl, 69069-04-1; **9x**, 104072-14-2; **9x**·HCl, 69049-42-9; **9y**, 69049-41-8; c-C_3H_5COCl, 4023-34-1; C_2H_5NCO, 109-90-0; C_2H_5COCl, 79-03-8; C_3H_7COCl, 141-75-3; $C_6H_5CH_2COCl$, 103-80-0; $C_6H_5(CH_2)_2COCl$, 645-45-4; t-C_4H_9COCl, 3282-30-2; c-$C_6H_{11}COCl$, 2719-27-9; $Cl(CH_2)_2COCl$, 625-36-5; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_2Cl$, 107-04-0; 4-$(C_4H_3S)(CH_2)_2OSO_2C_6H_4CH_3$, 40412-06-4; ICH_2CONH_2, 144-48-9; $ClCH_2Br$, 74-97-5.

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