Weinreich, W. C. Friend, and G. M. Brown, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 130 (1978).
(13) J. Z. Ginos, G. C. Cotzias, and D. Doroski, *J. Med. Chem.*, **21**, 160 (1978).
(14) J. G. Cannon, F.-L. Hsu, J. P. Long, J. R. Flynn, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **21**, 248 (1978).
(15) H. Wikström, P. Lindberg, P. Martinson, S. Hjorth, A. Carlsson, U. Hacksell, U. Svensson, and J. L. G. Nilsson, *J. Med. Chem.*, **21**, 864 (1978).
(16) J. D. McDermed, G. M. McKenzie, and H. S. Freeman, *J. Med. Chem.*, **19**, 547 (1976).
(17) J. N. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).
(18) D. E. Ames, D. Evans, T. F. Grey, P. J. Islip, and K. E. Richards, *J. Chem. Soc.*, 2636 (1965).
(19) P. Marchini, G. Liso, A. Reho, F. Liberatore, and F. M. Moracci, *J. Org. Chem.*, **40**, 3453 (1975).
(20) A. Carlsson, *Adv. Biochem. Psychopharmacol.*, **16**, 439 (1977).
(21) B. R. Thomas, "Polynucleotide Biology", Thomas, Lund, Sweden, 1976, pp 55–82.
(22) Y. C. Martin, C. H. Jarboe, R. A. Krause, K. R. Lynn, D. Dunnigan, and J. B. Holland, *J. Med. Chem.*, 16, 147 (1973).

N-[(Tetrahydrofuryl)alkyl] and *N*-(Alkoxyalkyl) Derivatives of (-)-Normetazocine, Compounds with Differentiated Opioid Action Profiles

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In modification of the *N*-(tetrahydrofurfuryl) substitution of the opioid κ-agonist **5a**-1, a series of *N*-(alkoxyalkyl) derivatives **5** of (-)-normetazocine were synthesized and evaluated pharmacologically for opioid properties and, in part, toxicities in mice. Three groups of compound **5** may be distinguished: (a) morphine-like agonists, (b) non-morphine-like agonists, and (c) nalorphine-like agonist–antagonists. Analgesic activity (either morphine-like or not) is related to the position of the ether oxygen in the N substituent, maximum potency being obtained if nitrogen and oxygen are linked by a 2-carbon chain. The action profile of those compounds with a 2-carbon chain between nitrogen and oxygen is governed by the degree of branching of carbon C-2″ in the β position to the nitrogen, unbranched C-2″ affording compounds of type a and branched C-2″ affording those of type b or c depending on the nature of the branching. If diastereomeric pairs arise from those branchings, the 2″*S* forms are by far more potent analgesics than their 2″*R* counterparts, which may even be inactive. Different receptor interactions due to the degree and nature of branching of C-2″ are proposed to account for the differentiated opioid action profiles observed. Non-morphine-like agonists attaining analgesic potencies of more than 100 times that of morphine and having unusually favorable therapeutic ratios might be major advances in the search for strong analgesics with low abuse potential.

Recently, we have shown[1] that certain stereoisomeric *N*-(tetrahydrofurfuryl)normetazocines [5,9-dimethyl-2′-hydroxy-2-(tetrahydrofurfuryl)-6,7-benzomorphans] possess action profiles distinctly different from those of morphine and other classical opiates. In particular, they do not elicit the Straub tail phenomenon in mice nor do they substitute for morphine in morphine-dependent monkeys, although analgesic potencies up to more than 100 times that of morphine are attained. Obviously, it is the *N*-(tetrahydrofurfuryl) group that induces the unique action profiles of these opioid analgesics. Thus, it was tempting to modify the crucial *N*-(tetrahydrofurfuryl) substituent of those compounds systematically and to see what changes of their pharmacological properties would result. Consequently, we have prepared a series of *N*-[(tetrahydrofuryl)alkyl] and *N*-(alkoxyalkyl) derivatives (**5**) of (-)-normetazocine and studied their opioid actions in mice. We now report on the results of these chemical and pharmacological studies and discuss structure–activity relationships.[2] This report also includes a revision of the stereochemistry of the *N*-(tetrahydrofurfuryl)normetazocines[1] and results of advanced pharmacological studies with one of those stereoisomers.

Chemistry. The compounds to be discussed are represented by the general formula **5**. All are derived from (-)-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan[3] [(-)-normetazocine] which has been shown[4] to have the 1*R*,5*R*,9*R* configuration. Thus, they will be designated as 2-substituted (1*R*,5*R*,9*R*)-5,9-dimethyl-2′-hydroxy-6,7-benzomorphans.[5] With regard to the nature of the N substituent, they may be subdivided into *N*-[(tetrahydrofuryl)alkyl] derivatives **5a** with cyclic ether functions and *N*-(alkoxyalkyl) derivatives **5b** with open-chain ether functions. Chirality of the N substituent gives rise to the existence of pairs of 2″*R* and 2″*S* diastereomers. Configurational assignments follow from unequivocal syntheses generating the chiral N substituent from enantiomeric precursors of known absolute stereochemistry, as described in detail under the Experimental Section. Starting from (-)-normetazocine (**1**), the compounds **5** were synthesized (Scheme I) either directly by alkylation with the bromides **2** (method A) or by acylation with the acids or acid derivatives **3**, followed by reduction of the amide intermediates **4** with $LiAlH_4$ (method B). Compounds **5** with chiral N substituents were obtained either as stereochemically homogenous substances (from enantiomeric **2** or **3**) or as diastereomeric mixtures (from racemic **2** or **3**). Separation

Scheme I

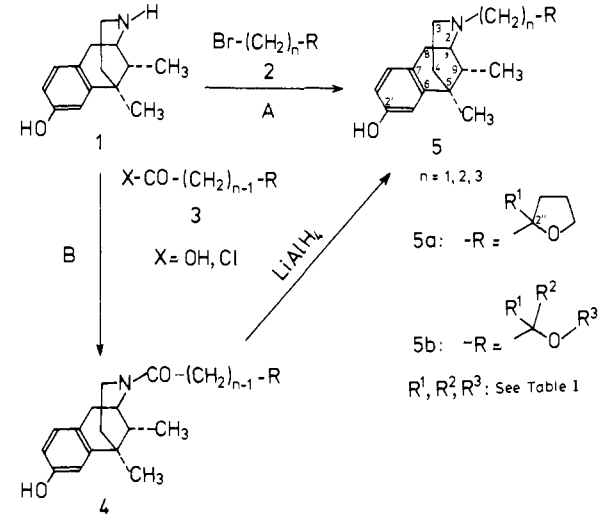

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Table I. Individual Structures and Physicochemical Data of *N*-[(Tetrahydrofuryl)alkyl] and *N*-(Alkoxyalkyl) Derivatives 5 of (−)-Normetazocine

compd	*n*	R^1	R^2	R^3	C-2″[a]	$[M]_D^{25}$,[b] deg	mp, °C	TLC, R_f	method	% yield
5a-1[c]	1	H			*S*[d]	−180.1	145–146[e]	0.30[f]	A	66.5
5a-2[c]	1	H			*R*[d]	−364.6	204–205[g]	0.35[f]	A	72.9
5a-3	1	Me			*S*	−258.8	142–143	0.45[h]	B[i]	19.0
5a-4·HCl	1	Me			*R*	−265.7	276	0.55[h]	B[i]	10.2
5a-5·HCl	2	H			*S*	−229.5	251–253	0.50[j]	B[k]	14.7
5a-6	2	H			*R*	−285.8	136–137	0.55[j]	B[k]	14.2
5a-7·HCl	3	H			*S*[l]	−284.7	221–223	0.20[f]	B	42.8
5a-8·HCl	3	H			*R*[l]	−230.2	213–215	0.20[f]	B	45.8
5b-1·HCl	1	H	H	Me		−211.5	122–124	0.20[f]	A	60.9
5b-2	1	H	H	Et		−230.1	102–103	0.25[f]	A	48.4
5b-3	1	H	H	*n*-Pr		−235.6	96–97	0.30[f]	A	41.2
5b-4	1	H	H	*i*-Pr		−239.3	126–127	0.30[f]	A	39.6
5b-5·HCl	2	H	H	Me		−230.1	174–176	0.15[f]	A	46.5
5b-6·HCl	3	H	H	Me		−241.0	188–189	0.15[f]	A	42.2
5b-7·HCl[m]	1	H	Me	Me	*S*	−176.3	141	0.50[n]	B	76.0
5b-8·HCl[o]	1	H	Me	Me	*R*	−304.7	118	0.60[n]	B	50.3
5b-9	1	Me	Me	Me		−285.9	91–92	0.60[f]	B	18.9

[a] Absolute configuration of C-2″. [b] Molecular rotation ($[M]^{22}_D = [\alpha]^{25}_D \times M_r \times 0.01$) calculated from the hydrochloride forms [c 1.0, 1 N HCl–MeOH (1:1)]. [c] See ref 1. [d] Erroneously reported (ref 1) with opposite configurations (see last paragraph of Chemistry section). [e] Crystallized From EtOAc-*n*-hexane (1:2). [f] EtOAc–MeOH–concentrated NH_4OH (90:10:0.5), freshly prepared. [g] Crystallized from MeCOEt. [h] $CHCl_3$–MeOH–concentrated NH_4OH (95:5:0.1), developed twice. [i] Separation of 5a-3 and 5a-4. [j] Et_2O–concentrated NH_4OH (96:4) developed twice. [k] Separation of 5a-5 and 5a-6. [l] The pair 5a-7/5a-8 differs from the other diastereomeric pairs with regard to the priorities of the ligands of C-2″ (CIP rules). Thus, the *S* compound 5a-7 corresponds sterically to the *R* forms and the *R* compound 5a-8 to the *S* forms of the other pairs. [m] Crystallized with 0.5 mol of MeOH. [n] EtOAc–MeOH–concentrated NH_4OH (90:10:0.5), freshly prepared, developed twice. [o] Crystallized with 1 mol of MeOH.

of such mixtures were achieved by fractional crystallizations of the bases or suitable salts. Syntheses of some of the compounds **5** have also been described in the patent literature.[6]

In our earlier paper[1] on stereoisomeric *N*-(tetrahydrofurfuryl)normetazocines, incorrect configurational assignments as to C-2″ of the *N*-(tetrahydrofurfuryl) groups have occurred. These assignments were based on the work of J. Defaye et al.,[7] who had shown that (−)-tetrahydrofurfuryl alcohol [and not (+)-tetrahydrofurfuryl alcohol as erroneously quoted[1]] has the *R* configuration. This error led to incorrect configurational assignments with regard to (+)- and (−)-tetrahydrofurfuryl bromide prepared from (+)- and (−)-tetrahydrofurfuryl alcohol and, consequently, with regard to C-2″ of the *N*-(tetrahydrofurfuryl) derivatives obtained by alkylation of normetazocines with the above bromides. Thus, the tetrahydrofurfuryl alcohols and bromides and the *N*-(tetrahydrofurfuryl)normetazocines (regarding C-2″) do not have the reported configurations[1] but, instead, opposite absolute configurations.

Pharmacology. The compounds **5** and appropriate standards were tested for analgesia, morphine antagonism, Straub tail activity, and, in part, acute toxicity in mice (NMRI mice, both sexes, 19–24 g). All substances were injected subcutaneously as aqueous solutions of their hydrochlorides. Analgesic activity was determined in the tail-clip test[8] (five animals per dose), hot-plate test[9] (eight animals per dose), and writhing test[10] (eight animals per dose). Morphine antagonism (suppression of morphine analgesia in mice) was assayed according to a procedure[11] based on the tail-clip test (ten animals per dose). Acute toxicity (ten animals per dose) was determined after observation periods of 14 days. ED_{50}, AD_{50}, and LD_{50} values were calculated with 95% confidence limits by probit analyses. In the course of the evaluation of analgesic activity, the mice were also observed as to the occurrence of the Straub tail phenomenon.[12]

Results and Discussion

Individual structures and physicochemical data of the compounds **5** are given in Table I. Of all diasteromeric pairs, the compounds stereochemically related to the 2″*S* form **5a**-1 have lower R_f values and lower molecular rotations than the corresponding counterparts related to the 2″*R* compound **5a-2** (for configurational assignments of C-2″ in **5a**-1 and **5a-2** see last paragraph of the Chemistry section).

Pharmacological results obtained with **5a**-1 and **5a-2**, the new compound (**5a-3–8** and **5b**-1–**9**), and appropriate standards are summarized in Table II.

Reference compounds are the diastereomeric *N*-(tetrahydrofurfuryl) derivatives of (−)-normetazocine.[1] The 2″*S* compound **5a**-1 is by far more active as an analgesic than its 2″*R* counterpart **5a-2**. Recent investigations of the levorotatory **5a**-1 (code number Mr 2034) and the corresponding racemic form (code number Mr 2033, consisting of **5a**-1 and its essentially inactive dextrorotatory antipode) elucidated the action profile of **5a**-1: Kosterlitz et al.[13] demonstrated that Mr 2034 was a very potent opioid agonist in the guinea pig ileum and in the mouse vas deferens. From these and other experiments, they concluded[14,15] that **5a**-1 might not interact with the μ receptor but rather with the κ receptor. This conclusion was strongly supported by the evaluation of Mr 2033 in the chronic spinal dog by Gilbert, Martin, and Jessee.[16] From primary dependence studies in rhesus monkeys, Swain and Seevers[17] stated that Mr 2033 (NIH 9102, UM 1072) caused an abstinence syndrome distinctly different from that seen after morphine withdrawal. Quite recently, Woods et al.[18] demonstrated that Mr 2033 was not self-injected by rhesus monkeys. These compiled findings show that the action profile of **5a**-1 is different from that of morphine and provide evidence that **5a**-1 is a κ agonist similar to ketazocine.[19]

Action Profiles of Compounds 5. Systematic modifications of the *N*-(tetrahydrofurfuryl) group markedly affected the action profile of **5a**-1 and furnished compounds with closely related structures but highly differentiated opioid properties. According to the following criteria three groups of compounds **5** may be distinguished.

(a) **Morphine-like Agonists.** They exhibit analgesic activity in all three assays employed and elicit the Straub

Table II. Pharmacological Data of the *N*-[(Tetrahydrofuryl)alkyl] and *N*-(Alkoxyalkyl) Derivatives 5 of (-)-Normetazocine

compd[a]	analgesia: tail-clip test:[b] ED_{50}, mg/kg sc (mice)	analgesia: hot-plate test:[b] ED_{50}, mg/kg sc (mice)	analgesia: writhing test:[b] ED_{50}, mg/kg sc (mice)	morphine antagonism:[b] AD_{50}, mg/kg sc (mice)	toxicity:[b] LD_{50}, mg/kg sc (mice)	$\frac{LD_{50}}{ED_{50}}$[c]	straub tail[d] (mice)	action profile[e] (mice)
5a-1[g]	0.22 (0.13-0.32)	0.11 (0.08-0.15)	0.015 (0.004-0.080)	inactive[f]	94 (80-111)	6 276	-	b
5a-2[g]	inactive	inactive	3.9 (2.1-7.0)	4.5 (3.4-6.3)	150 (121-186)	39	-	c
5a-3	inactive	inactive	0.051 (0.024-0.092)	1.5 (1.2-1.9)	18 (17-20)	353	-	c
5a-4	inactive	inactive	9.3[h]	5.2 (3.9-7.2)	200 (180-220)	22	-	c
5a-5	17 (9-30)	14 (11-17)	1.3 (0.8-1.9)	inactive			+	a
5a-6	17 (9-30)	6.8 (5.5-8.4)	0.40 (0.18-0.69)	inactive			+	a
5a-7	21 (14-32)	15 (12-19)	4.5 (0.8-12.7)	inactive			-	b
5a-8	119 (43-574)	66 (51-91)	7.5 (5.9-9.3)	inactive			-	b
5b-1	0.090 (0.054-0.139)	0.11 (0.08-0.15)	0.0030 (0.0012-0.0053)	inactive			+	a
5b-2	2.1 (0.5-5.1)	1.3 (1.0-1.7)	0.066 (0.029-0.110)	inactive			+	a
5b-3	7.5 (3.2-14.4)	3.5 (2.7-4.6)	0.65 (0.57-0.72)	inactive			-	b
5b-4	3.9 (1.5-7.3)	2.1 (1.6-2.8)	0.25 (0.13-0.41)	inactive			-	b
5b-5	5.6 (2.0-11.1)	3.6 (2.8-4.6)	0.29 (0.12-0.63)	inactive			+	a
5b-6	18 (3-58)	16 (11-21)	1.0 (0.7-1.5)	inactive			+	a
5b-7	0.035 (0.022-0.058)	0.018 (0.015-0.054)	0.0038 (0.0018-0.0064)	inactive	105 (81-135)	27 632	-	b
5b-8	inactive	inactive	inactive	inactive			-	
5b-9	inactive	1.4 (1.1-1.8)	0.15 (0.08-0.27)	inactive	178 (170-187)	1 187	-	b
morphine	11 (9-13)	2.3 (1.8-3.0)	0.47 (0.29-0.70)	inactive	500 (407-615)[i]	1 064	+	a
ketazocine	0.72 (0.53-0.99)	0.62 (0.49-0.78)	0.20 (0.10-0.42)	inactive	>400[j]	>2 000	-	b
nalorphine	inactive	inactive	0.35 (0.18-0.59)	0.80 (0.49-1.21)	560 (488-650)[i]	1 600	-	c
pentazocine	inactive	inactive	1.3 (0.9-1.9)	7.4 (5.8-9.3)	220 (190-255)[i]	169	-	c

[a] All substances were tested as hydrochlorides. [b] For ref to these tests, see section "Pharmacology". [c] Therapeutic ratio, writhing test. [d] Straub tail phenomenon present (+) or absent (-) in dose ranges tested for anagesia. [e] Morphine-like agonists (a), non-morphine-like agonists (b), or agonist-antagonists (c). [f] "Inactive" means that no analgesic effect was observed up to doses causing side effects. [g] Merz et al.; see ref 1. [h] Estimated by graphic evaluation of the log dose-response curve; side effects (ataxia, convulsions) occurred at doses above 10 mg/kg. [i] Merz et al.; see ref 27. [j] LD_{50} not obtained because of low solubility of ketazocine hydrochloride.

tail phenomenon in analgesic dose ranges. Activity in the hot-plate test (and other assays applying nociceptive stimuli of comparable or higher intensities, e.g., the tail-clip test) and Straub tail activity are considered[20,21] each to be indicative of morphine-like action. According to our experience, the concomitant occurrence of both activities is a most reliable indication of compounds displaying the full spectrum of morphine-like effects.

(b) Non-morphine-like Agonists. They generally exert analgesic activity in all three assays employed but are devoid of Straub tail activity. Lack of Straub tail activity in opioids with high hot-plate and tail-clip potencies is quite unique and only recently observed with κ agonists like ketazocine (NIH 8847, UM 974).[22]

(c) Opioid Agonist–Antagonists. They show analgesic activity in the writhing test but fail to do so in the more rigorous hot-plate and tail-clip assays. Such a test-dependent differentiation of analgesic activity is typical for agonist–antagonists, e.g., nalorphine or pentazocine.[20] No Straub tail activity is observed, in accordance with the well-established experience that agonist–antagonists suppress rather than evoke this phenomenon.[23] The ability to reverse effects of morphine (e.g., analgesia in the tail-clip test[11]) reveals the antagonist component of those compounds.

The above group criteria correspond to the standards morphine, ketazocine, and nalorphine, respectively. However, classification of the compounds **5** according to these criteria (Table II) is intended to indicate the differentiated opioid properties rather than to assign well-defined action profiles.

Structure–Activity Relationships (SAR). The action profile of the reference substance **5a-1** is highly sensitive to even minor structural alterations of its *N*-(tetrahydrofurfuryl) substituent.

Introduction of a 2″-methyl group shifts the spectrum of opioid activities of **5a-1** to that of an agonist–antagonist (**5a-3**) and decreases analgesic potency (writhing test) to about one-third (9.5 times that of morphine). The superiority of the 2″*S* compound **5a-3** to its 2″*R* diastereomer **5a-4** as an analgesic is similarly pronounced, as seen with the reference pair. As to antagonist activity, **5a-3** is about one-half and **5a-4** one-sixth as potent as nalorphine. With regard to the nature of the N substituent, the antagonist actions of **5a-3** and **5a-4** are quite surprising, although exceptions to general rules[24] have come to be known, and even *N*-methyl compounds have recently been reported to possess antagonist properties.[25,26] We have shown that *N*-(furylmethyl) groups conferred antagonist activity to opioid structures and attributed this effect to the partial allyl character of such substituents.[11] Quite recently, however, we have observed[27] that even the nonallylic *N*-(tetrahydrofurfuryl) group was able to induce opioid antagonism in the noroxymorphone series. This effect of the *N*-(tetrahydrofurfuryl) substitution had originally not been seen with the stereoisomeric congeners of **5a-1**.[1] Our recent reinvestigation, however, has revealed antagonist activity in one of them (**5a-2**).

Lengthening of the methylene chain (n = 1), which in **5a-1** links C-2″ of the tetrahydrofuran ring to the nitrogen, to an ethylene chain (**5a-2**, n = 2) markedly decreases analgesic potency in each of the three tests employed (on the average to $^1/_{50}$). The pronounced stereoselectivity of analgesic action seen in the reference pair is essentially abolished, the corresponding diastereomers **5a-5** and **5a-6** being roughly equipotent. Interestingly enough, **5a-5** and **5a-6** exhibit morphine-like properties. Going on to a propylene chain between C-2″ and the nitrogen (**5a-7**, n = 3) causes a further but less pronounced drop in analgesic potency. Again, the diastereomers **5a-7** and **5a-8** do not show major differences in potency. In contrast to **5a-5** and **5a-6**, their homologues **5a-7** and **5a-8** do not elicit Straub tail activity.

Simulation of the *N*-(tetrahydrofurfuryl) substituent of **5a-1** by the *N*-(2-methoxyethyl) group (compound **5b-1**) does not significantly affect analgesic potency but clearly evokes Straub tail activity, thus shifting the action profile to that of morphine-like compounds. Enlargement of the alkoxy residue, stepwise from methoxy (**5b-1**) to ethoxy (**5b-2**) and *n*-propoxy (**5b-3**), is accompanied by a considerable loss of analgesic activity, particularly in the first step (on the average to about 0.05). Branching of the *n*-propoxy residue slightly enhances analgesic potency. In contrast to their lower alkoxy homologues, **5b-3** and **5b-4** exhibit no Straub tail activity.

Lengthening of the methylene chain (n = 1), which in **5b-1** links the R group to the nitrogen, stepwise to ethylene (**5b-5**, n = 2) and propylene (**5b-6**, n = 3) drastically decreases analgesic potency, particularly as to the first step reducing potency to about $^1/_{40}$, $^1/_{20}$, and $^1/_{80}$ depending on the test employed. The morphine-like properties of **5b-1** are preserved in the higher homologues.

Branching of the *N*-(2-methoxyethyl) substituent of **5b-1** by introduction of a 2″-methyl group restores the chirality of C-2″ and further approximates the *N*-(tetrahydrofurfuryl) substitution of the reference substances. The 2″*S* compound **5b-7** is highly active as an analgesic and, depending on the assay employed, even 6–40 times more potent than **5a-1**, whereas its diastereomer **5b-8** is essentially inactive. Thus, the superiority of the 2″*S* form as an analgesic is still more pronounced in the open-chain ether pair **5b-7**, **5b-8** than in the reference pair **5a-1**, **5a-2**. In spite of its high analgesic potency (about 100–300 times that of morphine, depending on the assay employed), **5b-7** is devoid of Straub tail activity. Thus, **5b-7** has an action profile very similar to that of **5a-1**. Introduction of a second 2″-methyl group considerably decreases analgesic potency, but **5b-9** is still more potent than morphine (about twice in the hot-plate and three times in the writhing test). The lack of tail-clip activity corresponds to the fact that, structurally, **5b-9** is more closely related to the agonist–antagonist **5a-3** than to the κ-agonist **5a-1**.

In summary, the following SAR are observed. Maximum analgesic activity (either morphine-like or not) is obtained if nitrogen and oxygen are linked by a 2-carbon chain and if the alkoxy residue is small or a constituent part of a tetrahydrofuran ring. Compounds with maximum activity due to these structural features are not morphine-like if the 2-carbon chain is branched at C-2″ in the β position to the nitrogen, either by one or two methyl groups or by incorporation of this carbon into a tetrahydrofuran ring. If diastereomeric pairs arise from such branchings of C-2″, the 2″*S* forms are by far more potent analgesics than their 2″*R* counterparts, which may even be inactive. The *N*-(tetrahydrofurfuryl) group, in particular if 2″-methyl substituted, seems to be a prerequisite for antagonist action which is not encountered in compounds with open-chain ether analogues.

Activity of opioid analgesics in vivo has been shown[28,29] to depend primarily on receptor affinity and lipophilicity. In view of the close structural relationships among the individual compounds **5** and their accordingly very similar physicochemical properties, we suppose that differentiated drug–receptor interactions rather than differences in lipophilicity[30] may account for the SAR discussed above. According to a hypothesis of Beckett and Casy,[31] a three-point

association of the analgesic receptor and the opioid ligand is essential for morphine-like analgesia. There may exist, however, additional receptor sites able to accomodate and bind appropriate functions of opioid structures, thus stabilizing the drug–receptor complex and enhancing the analgesic effect.[32] Interestingly enough, an "additional point of attachment" in opioid drug–receptor binding was already discussed almost 20 years ago for structures closely related to those of the normetazocine derivatives **5**: Frearson et al.[33,34] and Blair and Stephenson[35] reported on *N*-[(tetrahydrofuryl)alkyl]- and *N*-(alkoxyalkyl)-norpethidines and demonstrated that the ether oxygen of the N substituent greatly increased analgesic activity, maximum potency being obtained if nitrogen and oxygen were linked by a 4- or 5-carbon chain. To explain these findings, the authors suggested hydrogen bonding between the oxygen and an additional binding site of the receptor. Such a mechanism may also work in the case of the compounds **5** and account for their unexpectedly high potencies. The norpethidine and normetazocine series differ, of course, in the oxygen position providing maximum analgesic potency. Such observations, however, that parallel alterations of the N substituents of structurally different opioid series do not result in parallel modifications of pharmacological properties are well documented[36,37] and particularly encountered if the two series in question exhibit major differences in molecular rigidity.

As to the compounds **5**, an N–O distance provided by a 2-carbon chain may be most favorable for strong binding of the ether oxygen to a supplementary receptor site and thus may be crucial for maximum analgesic potency. Compounds with this structural feature, however, may greatly differ in their action profiles which obviously are governed by the degree and nature of branching at C-2″ in the β position to the nitrogen. Morphine-like activity seems to be related to unbranched and non-morphine-like activities to branched carbons C-2″. According to sophisticated opioid receptor models, different receptor conformations may account for differentiated opioid action profiles (for recent comprehensive reviews see Archer and Michne[19] and Casy[38]). We consequently suggest as a plausible interpretation of our observation that only an unbranched C-2″ might allow unhindered access and binding of the ether oxygen to a hypothetical auxiliary receptor site, whereas steric hindrance by branching of C-2″ would allow such an interaction only with conformational changes of the receptor. The pronounced stereoselectivity of the opioid actions with regard to the configuration of C-2″ (in the case $n = 1$) strongly supports the concept of high steric demand of the interaction of the N substituent with the receptor. A consequent pursuit of the structural modification of the *N*-(alkoxyalkyl)-type substitution of (-)-normetazocine may furnish new compounds suitable to further probe the nature of the opioid receptor.

The κ-agonist **5a-1** (Mr 2034) and compound **5b-7** (MRZ 2549) with a tentatively assigned similar action profile are powerful non-morphine-like analgesics with low toxicities. They attain analgesic potencies up to more than 100 times that of morphine and show therapeutic ratios of 6267 and 27 632, respectively, which compare most favorably with those of the standard analgesics morphine (1064) and pentazocine (169). Those compounds might be major advances in the search for strong nontoxic analgesics with low abuse potentials.

Experimental Section

Melting or decomposition points were taken in a Tottoli apparatus and are not corrected. For TLC (silica gel), DC-Fertigplatten Kieselgel 60 (Merck, Darmstadt) was used, and spots were detected with iodine vapor. Optical rotations were measured in a Perkin-Elmer polarimeter 241. Microanalyses agree, unless otherwise stated, with calculated values within ±0.4%. IR and NMR spectra are consistent with assigned structures.

(-)-(1*R*,5*R*,9*R*,2″*S*)- (5a-1) and (-)-(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-(tetrahydrofurfuryl)-6,7-benzomorphan (5a-2). These diasteromeric compounds have been described previously[1] with erroneously assigned inverted configurations of C-2″ (see last paragraph of Chemistry section).

(-)-(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2′-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzomorphan (5a-3) and (-)-(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-(2-methyltetrahydrofurfuryl)-6,7-benzomorphan Hydrochloride (5a-4·HCl). Method B. Separation of the Diastereomeric Mixture. A solution of (-)-normetazocine[3] (10.9 g, 0.050 mol) and racemic 2-methyltetrahydro-2-furoic acid[39] (7.8 g, 0.06 mol) in MeOH (50 mL) was evaporated in a stream of N_2 (oil bath, 60 °C). With a continuous sweeping of N_2 over the syrupy residue, the temperature was gradually raised and kept at 240 °C for 8 h. The reaction product was cooled and dissolved in $CHCl_3$ (150 mL), and the solution was washed with 2 N HCl (50 mL) and twice with H_2O. After drying (Na_2SO_4) and evaporation in vacuo, the $CHCl_3$ solution yielded an amber, glassy residue consisting of a mixture of the amide intermediates of **5a-3** and **5a-4**. A solution of the residue in THF (250 mL) was dropped into a well-stirred suspension of $LiAlH_4$ (3.8 g, 0.10 mol) in THF (125 mL) at 5 °C. The reaction mixture was refluxed for 2 h, cooled again, and treated with vigorous stirring at 5 °C with H_2O (7.2 mL). On shaking the resulting suspension with saturated aqueous diammonium tartrate (375 mL), two liquid phases were formed. The upper THF layer was separated and evaporated in vacuo, and the aqueous layer was extracted with $CHCl_3$ (2 × 100 mL). Combination of the THF residue with the $CHCl_3$ extracts gave a solution which was washed with H_2O, dried (Na_2SO_4), and purified by column chromatography (300 g of Al_2O_3, neutral, activity grade III). The column was eluted with $CHCl_3$–MeOH (99:1), and the fractions containing **5a-3** and **5a-4** (TLC) were combined and evaporated in vacuo. A solution of the residue in EtOH (25 mL) and 2 N ethanolic HCl (25 mL) was diluted with Et_2O until it turned just turbid. On standing at room temperature, crystals of **5a-4**·HCl appeared. The crystal suspension was kept at 0 °C overnight; then the crystals were collected by filtration, washed with EtOH–Et_2O (1:1), and dried at 80 °C to yield 1.8 g [10.2%, based on (-)-normetazocine] of almost pure **5a-4**·HCl, mp 274 °C. Traces of **5a-3** were removed by recrystallization from MeOH (20 mL) and Et_2O (80 mL), affording 1.6 g of pure **5a-4**·HCl, mp 276 °C. Anal. ($C_{20}H_{29}NO_2$·HCl) C, H, Cl, N.

The mother liquor of the first crystallization of **5a-4**·HCl was evaporated in vacuo, and the residue was shaken with $CHCl_3$ (100 mL), H_2O (100 mL), and concentrated NH_4OH (5 mL). The $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness in vacuo. The residue crystallized from a solution in toluene (20 mL) on dilution with petroleum ether (bp 40–80 °C, 60 mL). The crystal suspension was kept at 0 °C overnight; then the crystals were collected by filtration, washed with toluene–petroleum ether (1:1), and dried at 80 °C to yield 3.0 g [19.0%, based on (-)-normetazocine] of almost pure **5a-3**, mp 141–142 °C. Traces of **5a-4** were removed by recrystallization from toluene (20 mL) and petroleum ether (100 mL), affording 2.5 g of pure **5a-3**, mp 142–143 °C. Anal. ($C_{20}H_{29}NO_2$) C, H, N.

Configurational assignments as to C-2″ follow from alternative syntheses from (-)-normetazocine (0.005 mol) and the enantiomeric 2-methyltetrahydro-2-furoic acids.[40] Following the procedure described above, **5a-4**·HCl was obtained from the *R* acid (0.37 g, 21.0%; mp 276 °C) and **5a-3** from the *S* acid (0.30 g, 19.0%; mp 142–143 °C).

(-)-(1*R*,5*R*,9*R*,2″*S*)·5,9-Dimethyl-2′-hydroxy-2-[2-(tetrahydro-2-furyl)ethyl]-6,7-benzomorphan Hydrobromide (5a-5·HBr) and Hydrochloride (5a-5·HCl) and (-)-(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-[2-(tetrahydro-2-furyl)ethyl]-6,7-benzomorphan (5a-6) and Its Hydrobromide (5a-6·HBr). Method B. Separation of the Diastereomeric Mixture. Tetrahydro-2-furylacetyl chloride[41] (9.6 g, 0.065 mol) was dropped at 18–20 °C to a vigorously stirred suspension, obtained by pouring a solution of K_2CO_3 (16.0 g, 0.116 mol) in H_2O (23 mL) into a solution of (-)-normetazocine[3] (12.5

g, 0.058 mol) in MeOH (280 mL). After continued stirring at room temperature for 1.5 h, the reaction mixture was evaporated in vacuo and the residue was shaken with CH_2Cl_2 (250 mL) and H_2O (100 mL). The organic layer was separated, washed with 2 N HCl (75 mL) and twice with H_2O, dried (Na_2SO_4), and evaporated in vacuo to yield a residue consisting of a mixture of the amide intermediates. Reduction with $LiAlH_4$ (4.5 g, 0.116 mol) was carried out as described above. The residue obtained by evaporation of the $CHCl_3$ extract was dissolved in EtOH (20 mL) and 2 N ethanolic HCl (30 mL). On gradual addition of Et_2O (150 mL) with stirring, a crystal suspension was formed which was kept at 0 °C overnight. The crystals were collected by filtration, washed with EtOH–Et_2O (1:4), and dried at 80 °C to give 16.0 g (73.5%) of a mixture of **5a-5**·HCl and **5a-6**·HCl, mp 225–231 °C.

The hydrochlorides were converted into the bases ($CHCl_3$, H_2O, and concentrated NH_4OH) as described above. The residue obtained by evaporation of the $CHCl_3$ extract was crystallized from EtOAc (40 mL) to yield 6.2 g of a substance (mp 110–112 °C) consisting mainly of **5a-6**. Five recrystallizations from MeCN (14 mL each time) raised the melting point to 126–132 °C (3.75 g), and three additional ones (19, 23, and 25 mL of MeCN) yielded 2.6 g [14.2%, based on (–)-normetazocine] of pure **5a-6**, mp 136–137 °C. Anal. ($C_{20}H_{29}NO_2$) C, H, N. For the preparation of **5a-6**·HBr, a solution of **5a-6** (0.60 g, 0.00193 mol) in EtOH (2 mL) containing 0.3 g of 65% HBr was diluted with Et_2O (20 mL) and kept at 0 °C overnight. The crystals which had separated from the solution were collected by filtration, washed (Et_2O), and dried at 80 °C, yielding 0.7 g (92.8%) of **5a-6**·HBr, mp 231–233 °C. Anal. ($C_{20}H_{29}NO_2$·HBr) C, H, Br, N.

The EtOAc mother liquor was evaporated in vacuo, affording a residue which was dissolved in EtOH (20 mL) with the addition of 65% HBr (2.5 g). On gradual dilution with Et_2O (10 mL) with stirring, a crystal suspension was formed which was kept at 0 °C overnight. The crystals were collected by filtration, washed with EtOH–Et_2O (1:1), and dried at 80 °C to give 7.0 g of a substance (mp 248–250 °C) consisting mainly of **5a-5**·HBr. Recrystallization from EtOH (50 mL) and three times from EtOH–Et_2O (54 + 25 mL each time) yielded pure **5a-5**·HBr [3.6 g, 15.7%, based on (–)-normetazocine], mp 260–263 °C. Anal. ($C_{20}H_{29}NO_2$·HBr) C, H, Br, N. Conversion of the hydrobromide into the base ($CHCl_3$, H_2O, and concentrated NH_4OH as described above for the hydrochloride mixture) gave a $CHCl_3$ extract which was evaporated in vacuo. The residue was dissolved with 2 N ethanolic HCl (5 mL) and the solution diluted gradually with Et_2O (12 mL) with stirring. The resulting crystal suspension was kept at 0 °C overnight; then the crystals were collected by filtration, washed with EtOH–Et_2O (1:4), and dried at 80 °C to yield 3.0 g [14.7%, based on (–)-normetazocine] of **5a-5**·HCl, mp 251–253 °C. Anal. ($C_{20}H_{29}NO_2$·HCl) C, H, Cl, N. The configurations of **5a-5** and **5a-6** as to C-2″ were assigned according to the following alternative synthesis of **5a-6**·HBr.

(–)-(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2-[2-(tetrahydro-2-furyl)ethyl]-6,7-benzomorphan Hydrobromide (5a-6·HBr). Method A. (–)-Normetazocine[3] (0.107 g, 0.0005 mol), $NaHCO_3$ (0.063 g, 0.00075 mol), (–)-(*R*)-2-(tetrahydro-2-furyl)ethyl *p*-toluenesulfonate (0.149 g, 0.00055 mol of the compound described below), DMF (1 mL), and THF (4 mL) were refluxed with stirring for 5 h. The reaction mixture was evaporated to dryness in vacuo and the residue partitioned between $CHCl_3$ and H_2O (20 mL of each). The $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo. A solution of the residue in EtOH (0.5 mL) and 0.07 g of 65% HBr was diluted with Et_2O (5 mL) and kept at 0 °C overnight. The crystals which had separated were collected by filtration, washed with Et_2O, and dried at 80 °C to yield 0.110 g (74.4%) of **5a-6**·HBr, mp 231–233 °C. Anal. ($C_{20}H_{29}NO_2$·HBr) C, H, Br, N.

(–)-(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2-[3-(tetrahydro-2-furyl)propyl]-6,7-benzomorphan Hydrochloride (5a-7·HCl). Method B. Following the procedure described for **5a-3** and **5a-4** but starting from (–)-normetazocine[3] (6.52 g, 0.030 mol) and (–)-(*R*)-3-(tetrahydro-2-furyl)propionic acid (4.75 g, 0.033 mol; see below), **5a-7**·HCl was obtained: yield 4.7 g (42.8%); mp 221–223 °C (EtOH–Et_2O). Anal. ($C_{21}H_{31}NO_2$·HCl) C, H, Cl, N.

(–)-(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-[3-(tetrahydro-2-furyl)propyl]-6,7-benzomorphan Hydrochloride (5a-8·HCl). Method B. Following the procedure described for **5a-3** and **5a-4** but starting from (–)-normetazocine[3] (6.52 g, 0.030 mol) and (+)-(*S*)-3-(tetrahydro-2-furyl)propionic acid (4.75 g, 0.033 mol; see below), **5a-8**·HCl was obtained: yield 5.0 g (45.6%); mp 213–215 °C (EtOH–Et_2O). Anal. ($C_{21}H_{31}NO_2$·HCl) C, H, Cl, N.

(–)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2′-hydroxy-2-(2-methoxyethyl)-6,7-benzomorphan Hydrochloride (5b-1·HCl). Method A. (–)-Normetazocine[3] (2.17 g, 0.010 mol), $NaHCO_3$ (1.26 g, 0.015 mol), 2-methoxyethyl bromide[42] (1.49 g, 0.011 mol), DMF (10 mL), and THF (25 mL) were refluxed with stirring for 6 h. The reaction mixture was evaporated in vacuo and the residue partitioned between $CHCl_3$ (50 mL) and H_2O (25 mL). The $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo, affording a residue which was purified by column chromatography (500 g of silica gel, 70–230 mesh) using $CHCl_3$–MeOH–concentrated NH_4OH (90:10:0.5) as eluent. Evaporation of the fractions containing pure **5b-1** (TLC) yielded a material which was dissolved in EtOH (5 mL) and 2 N ethanolic HCl (5 mL). On gradual dilution with Et_2O (180 mL) with stirring, a crystal suspension was formed which was kept at 0 °C overnight. The crystals were collected by filtration, washed with Et_2O, and dried at 80 °C to yield 1.9 g (60.9%) of **5b-1**·HCl, mp 122–124 °C (unchanged after recrystallization from EtOH–Et_2O). Anal. ($C_{17}H_{25}NO_2$·HCl) C, H, Cl, N.

(–)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-ethoxyethyl)-2′-hydroxy-6,7-benzomorphan (5b-2). Methods A and B. Following the procedure described above but starting from (–)-normetazocine[3] (2.17 g, 0.010 mol) and 2-ethoxyethyl bromide[42] (1.68 g, 0.011 mol) there was obtained **5b-2**. After column chromatography, the purified material crystallized from Et_2O (6 mL), affording 1.4 g (48.4%) of **5b-2**, mp 102–103 °C [unchanged after recrystallization from MeOH–H_2O (2:1)]. Anal. ($C_{18}H_{27}NO_2$) C, H, N.

Preparation of **5b-2** from (–)-normetazocine (0.040 mol) and ethoxyacetyl chloride[43] (0.050 mol) by method B furnished a purer reaction product (no column chromatography needed) and a higher yield (73%).

(–)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2′-hydroxy-2-(2-*n*-propoxyethyl)-6,7-benzomorphan (5b-3). Method A. Following the procedure described for **5b-1** but starting from (–)-normetazocine[3] (2.17 g, 0.010 mol) and 2-*n*-propoxyethyl bromide[42] (1.84 g, 0.011 mol) there was obtained **5b-3**. After column chromatography, the purified material crystallized from Me_2CO (5 mL), yielding 1.25 g (41.2%) of **5b-3**, mp 96–97 °C (unchanged by recrystallization from Me_2CO). Anal. ($C_{19}H_{29}NO_2$) C, H, N.

(–)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2′-hydroxy-2-(2-isopropoxyethyl)-6,7-benzomorphan (5b-4). Method A. Following the procedure described for **5b-1** but starting from (–)-normetazocine[3] (2.17 g, 0.011 mol) and 2-isopropoxyethyl bromide[42] (1.84 g, 0.011 mol) there was obtained **5b-4**. After column chromatography, the purified material was crystallized from Me_2CO (5 mL) yielding 1.2 g (39.6%) of **5b-4**, mp 126–127 °C (unchanged after recrystallization from Me_2CO). Anal. ($C_{19}H_{29}NO_2$) C, H, N.

(–)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2′-hydroxy-2-(3-methoxypropyl)-6,7-benzomorphan Hydrochloride (5b-5·HCl). Method A. Following the procedure described for **5b-1** but starting from (–)-normetazocine[3] (7.60 g, 0.035 mol) and 3-methoxypropyl bromide[44] (5.88 g, 0.059 mol) there was obtained **5b-5**. After column chromatography (250 g of Al_2O_3, neutral, activity grade III) with $CHCl_3$–MeOH (98:2), the purified material was crystallized from a mixture of 12 mL of benzene and 22 mL of petroleum ether (40–80 °C) to give 6.5 g of **5b-5**. Recrystallization from EtOAc (17 mL) afforded a product (5.7 g) with a melting point of 138–139 °C. The compound was dissolved in EtOH (10 mL) and 2 N ethanolic HCl (11 mL), and the solution was diluted with Et_2O (130 mL). After keeping at 0 °C overnight, the crystals which had formed were collected by filtration, washed with Et_2O, and dried at 80 °C to yield 5.3 g (46.5%) of **5b-5**·HCl, mp 174–176 °C. Anal. ($C_{18}H_{27}NO_2$·HCl) C, H, Cl, N.

(–)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2′-hydroxy-2-(4-methoxybutyl)-6,7-benzomorphan Hydrochloride (5b-6·HCl). Method A. Following the procedure described for **5b-1** but starting from (–)-normetazocine[3] (6.52 g, 0.030 mol) and 4-methoxybutyl bromide[45] (5.52 g, 0.033 mol), which were allowed to react in DMF (100 mL) in the presence of KI (1.5 g) at 100 °C for 24 h, there was obtained **5b-6**. After column chromatography as described for **5b-5**, the purified material was dissolved in EtOH (40 mL) and

2 N ethanolic HCl (12 mL). On dilution with Et_2O (170 mL) and keeping at 0 °C overnight, **5b-6**·HCl separated from the solution. The crystals were collected by filtration, washed with EtOH–Et_2O, and dried at 80 °C to give 4.8 g of the hydrochloride, mp 187–189 °C. Recrystallization from EtOH (25 mL) and Et_2O (75 mL) yielded 4.3 g (42.2%) of **5a-6**·HCl, mp 188–189 °C. Anal. ($C_{19}H_{29}NO_2$·HCl) C, H, Cl, N.

(-)-(1*R*,5*R*,9*R*,2″*S*)-5,9-Dimethyl-2′-hydroxy-2-(2-methoxypropyl)-6,7-benzomorphan Hydrochloride (5b-7·HCl) and Hydrobromide (5b-7·HBr). Method B. Following the procedure described for **5a-5** and **5a-6** but starting from (-)-normetazocine[3] (2.17 g, 0.010 mol) and (-)-(*S*)-2-methoxypropionyl chloride[46] (1.5 g, 0.0122 mol) there was obtained the amide precursor of **5b-7** which was reduced with $LiAlH_4$. After evaporation of the $CHCl_3$ extract, the resulting residue was dissolved in MeOH (10 mL) and 2.5 N ethanolic HCl (4.0 mL). On dilution with Et_2O and standing at room temperature, crystals appeared. The crystal suspension which was formed was kept at 0 °C overnight; then the crystals were collected by filtration, washed with MeOH–Et_2O, and dried at 80 °C to yield 2.6 g (76.0%) of **5b-7**·HCl, mp 141 °C (unchanged after recrystallization from MeOH–Et_2O). The compound proved to contain 0.5 mol of MeOH. Anal. ($C_{18}H_{27}NO_2$·HCl·0.5CH_3OH) C, H, Cl, N.

The amide intermediate was also obtained when a solution of (-)-(*S*)-2-methoxypropionic acid[46] (2.6 g, 0.025 mol) was treated at room temperature with 1,1′-carbonyldiimidazole (4.04 g, 0.025 mol) and, after 2 h, was added to a solution of (-)-normetazocine[3] (4.34 g, 0.020 mol) at room temperature. After 48 h, the reaction mixture was evaporated in vacuo and the residue partitioned between $CHCl_3$ (75 mL) and H_2O (50 mL). The $CHCl_3$ solution was separated; washed successively with H_2O, 2 N HCl, and H_2O; dried (Na_2SO_4); and evaporated in vacuo to afford the amide precursor of **5b-7** which was reduced with $LiAlH_4$ (2.4 g, 0.063 mol) as described above. The material obtained by evaporation of the $CHCl_3$ extract was crystallized from MeOH (20 mL), 65% HBr (3.5 g, 0.02 mol), and Et_2O (100 mL) to yield 5.2 g (70.3%) of **5b-7**·HBr, mp 196 °C, unchanged after recrystallization from MeOH (40 mL) and Et_2O (200 mL). Anal. ($C_{18}H_{27}NO_2$·HBr) C, H, Br, N.

(-)-(1*R*,5*R*,9*R*,2″*R*)-5,9-Dimethyl-2′-hydroxy-2-(2-methoxypropyl)-6,7-benzomorphan Hydrochloride (5b-8·HCl). Method B. Following the procedure described for **5b-7** but starting from (-)-normetazocine[3] (2.17 g, 0.010 mol) and (+)-(*R*)-2-methoxypropionyl chloride[46] (1.5 g, 0.0122 mol) there was obtained 1.8 g (50.3%) of **5b-8**·HCl, mp 118 °C, unchanged after recrystallization from MeOH (10 mL) and Et_2O (60 mL). The compound crystallized with 1 mol of MeOH. Anal. ($C_{18}H_{27}NO_2$·HCl·CH_3OH) C, Cl, N; H: calcd, 9.01; found, 8.39.

(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2′-hydroxy-2-(2-methoxyisobutyl)-6,7-benzomorphan (5b-9) and Its Hydrobromide (5b-9·HBr). Method B. Following the procedure described for **5b-7** but starting from (-)-normetazocine (4.34 g, 0.020 mol) and 2-methoxyisobutyryl chloride[47] (3.32 g, 0.025 mol) there was obtained **5b-9**: The raw material isolated after reduction of the amide precursor with $LiAlH_4$ (2.4 g, 0.063 mol) was crystallized from EtOH (30 mL), 65% HBr (3.5 g, 0.02 mol), and Et_2O (40 mL) to give 2.7 g of **5b-9**·HBr, mp 173–175 °C. Recrystallization from EtOH (20 mL) and Et_2O (50 mL) yielded 1.8 g (23.4%) of pure **5b-9**·HBr. Anal. ($C_{19}H_{29}NO_2$·HBr) C, H, Br, N. The hydrobromide was converted into the base ($CHCl_3$, H_2O, concentrated NH_4OH) which crystallized from MeOH (15 mL) and H_2O (5 mL), yielding 1.15 g [18.9%, based on (-)-normetazocine] of **5b-9**, mp 91–92 °C. Anal. ($C_{19}H_{29}NO_2$) C, H, N.

Optical Resolution of 2-(Tetrahydro-2-furyl)ethanol and Configurational Assignments of Its Enantiomers. 2-(Tetrahydro-2-furyl)ethyl Hydrogen Phthalate and Its Dicyclohexylamine Salt. The racemic ester acid was obtained from 2-(tetrahydro-2-furyl)ethanol[33] (48.6 g, 0.42 mol) and phthalic anhydride (62.0 g, 0.42 mol), according to the procedure described for its tetrahydrofurfuryl homologue,[48] as a colorless syrup (96 g). Fifty grams of this syrup was dissolved in EtOH (85 mL), and the solution was poured with stirring into a mixture of H_2O (850 mL) and dicyclohexylamine (36.3 g, 0.20 mol, calculated from alkalimetric titration of the syrup) kept at 70 °C. When the resulting clear solution was allowed to cool, finally at 0 °C overnight, the dicyclohexylamine salt of the ester acid crystallized. It was collected by filtration, washed with H_2O, and dried at 80 °C (44.6 g, mp 151–154 °C). Concentration of the mother liquor in vacuo to a volume of 250 mL gave a second crop of crystals (26.5 g), mp 151–154 °C. The total yield was 71.1 g [73.3%, based on 2-(tetrahydro-2-furyl)ethanol]. Recrystallization of a small sample from H_2O–EtOH (9:1) did not change the melting point. Anal. ($C_{14}H_{16}O_5$·$C_{12}H_{23}N$) C, H, N.

(-)-(*R*)-2-(Tetrahydro-2-furyl)ethyl Hydrogen Phthalate and Its Quinidine Salt. The above dicyclohexylamine salt (71.1 g, 0.16 mol) was shaken with H_2O (1.5 L), 2 N HCl (100 mL), and Et_2O (400 mL). After separation, the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined Et_2O solutions were washed with 1 N HCl (100 mL) and H_2O (3 × 50 mL), dried (Na_2SO_4), and evaporated, finally in vacuo, to yield a colorless syrup (40.5 g) of purified racemic 2-(tetrahydro-2-furyl)ethyl hydrogen phthalate. A solution of the syrup in MeOH (735 mL) was added to a well-stirred mixture of H_2O (4.4 L, 60 °C) and quinidine (51.9 g, 0.16 mol) in a flask fitted with a reflux condenser. The resulting clear solution was allowed to cool and kept at room temperature with continuous stirring. After 7 days, the slowly crystallizing quinidine salt was collected by filtration, washed with H_2O, and dried at 80 °C (44.7 g, mp 111–117 °C). Recrystallization from boiling H_2O (1.65 L) and MeOH (165 mL, added when the temperature had dropped to 70 °C) proceeded more rapidly and was completed after 2 days (34.2 g; mp 111–117 °C). A second recrystallization (1.3 L of H_2O and 65 mL of MeOH) effected further purification (26.5 g; mp 111–117 °C) and a third one (1.4 L of H_2O and 70 mL of MeOH) yielded the quinidine salt of optically pure (-)-(*R*)-2-(tetrahydro-2-furyl)ethyl hydrogen phthalate, 19.7 g (20.9%, based on racemic dicyclohexylamine salt), mp 115–118 °C, which crystallized with 1 mol of H_2O: $[\alpha]^{25}_D$ +120.4° (c 1.0, EtOH). Anal. ($C_{14}H_{16}O_5$·$C_{20}H_{24}N_2O_2$·H_2O) C, H, N.

Eighteen grams (0.030 mol) of the above quinidine salt was shaken with 1 N HCl (180 mL) and Et_2O (180 mL). After separation, the aqueous layer was extracted with Et_2O (3 × 90 mL). The combined Et_2O solutions were washed with H_2O (4 × 25 mL), dried (Na_2SO_4), and evaporated, finally in vacuo, to yield 8.1 g of (-)-(*R*)-2-(tetrahydro-2-furyl)ethyl hydrogen phthalate as a yellowish oil: $[\alpha]^{25}_D$ −11.7° (c 1.0, EtOH). Its *R* configuration follows from its conversion into (-)-(*R*)-3-(tetrahydro-2-furyl)-propionic acid in the following four steps.

(-)-(*R*)-2-(Tetrahydro-2-furyl)ethanol. The above (-)-(*R*)-2-(tetrahydro-2-furyl)ethyl hydrogen phthalate (8.1 g, obtained from 18.2 g, 0.030 mol of quinidine salt) was refluxed with 4 N NaOH (81 mL) for 1.5 h. After cooling to room temperature, the NaOH was saturated with NaCl (28 g) and extracted with Et_2O (4 × 40 mL). The combined Et_2O extracts were washed with saturated NaCl solution (2 × 15 mL), dried (Na_2SO_4), and evaporated in vacuo to give an oil (3.1 g), which on distillation yielded 2.15 g (61.7%, based on quinidine salt) of (-)-(*R*)-2-(tetrahydro-2-furyl)ethanol: bp 88–89 °C (12 mm); $[\alpha]^{25}_D$ −5.8° (c 1.0, EtOH). Anal. ($C_6H_{12}O_2$) C, H.

(-)-(*R*)-2-(Tetrahydro-2-furyl)ethyl *p*-Toluenesulfonate. *p*-Toluenesulfonyl chloride (3.1 g, 0.016 mol) was added with stirring to a solution of (-)-(*R*)-2-(tetrahydro-2-furyl)ethanol (1.7 g, 0.015 mol) in anhydrous pyridine (4.7 g, 0.059 mol) cooled in an ice bath. Almost immediately, a white solid separated from the, at first, clear solution. The reaction mixture was kept at room temperature for 3 h. Then it was poured into a mixture of ice–H_2O (34 g) and 2 N HCl (34 mL). The separated oil was extracted with Et_2O (4 × 34 mL), and the combined Et_2O extracts were washed with H_2O (2 × 10 mL) and 2 N $NaHCO_3$ (10 mL), dried (Na_2SO_4), and evaporated, finally in vacuo, to yield (-)-(*R*)-2-(tetrahydro-2-furyl)ethyl *p*-toluenesulfonate (3.45 g, 87.2%) as a colorelss oil: $[\alpha]^{25}_D$ −12.9° (c 1.0, EtOH). Anal. ($C_{13}H_{18}O_4S$) H, S; C: calcd, 57.76; found, 57.21. The compound was used for the next step and for the preparation of **5a-6**·HBr without further purification.

(-)-(*R*)-3-(Tetrahydro-2-furyl)propionitrile. (-)-(*R*)-2-(tetrahydro-2-furyl)ethyl *p*-toluenesulfonate (5.2 g, 0.019 mol), KCN (3.2 g, 0.049 mol), and EtOH (52 mL) were refluxed with stirring for 16 h. Then the reaction mixture was evaporated in vacuo at 50 °C. The residue was shaken with saturated NaCl (20 mL), H_2O (4 mL), and Et_2O (40 mL). After separation, the aqueous layer was extracted with Et_2O (3 × 20 mL). The com-

bined Et_2O solutions were washed with saturated NaCl (2 × 10 mL), dried (Na_2SO_4), and evaporated in vacuo at 50 °C. The residue (2.2 g) was distilled to yield 1.85 g (76.8%) of (−)-(*R*)-3-(tetrahydro-2-furyl)propionitrile: bp 101–102 °C (12 mm); $[\alpha]^{25}_D$ −23.3° (*c* 1.0, EtOH). Anal. ($C_7H_{11}NO$) H, N; C: calcd, 67.17; found, 66.64.

(−)-(*R*)-3-(Tetrahydro-2-furyl)propionic Acid. The above nitrile (1.8 g, 0.0144 mol) was refluxed with 2 N NaOH (25 mL) for 3 h. After cooling, the solution was extracted with Et_2O (15 mL). The aqueous layer was separated, acidified with concentrated HCl (9 mL) with cooling, saturated with NaCl, and extracted with Et_2O (5 × 30 mL). The combined Et_2O extracts were washed with saturated NaCl (10 mL), dried (Na_2SO_4), and evaporated in vacuo to give a residue (1.55 g) which was distilled to yield 1.0 g (48.3%) of (−)-(*R*)-3-(tetrahydro-2-furyl)propionic acid: bp 96 °C (0.2 mm); $[\alpha]^{25}_D$ −6.9° (*c* 1.0, EtOH). Anal. ($C_7H_{12}O_3$) C, H. The *R* configuration of this levorotatory 3-(tetrahydro-2-furyl)propionic acid follows from its alternative synthesis described below.

(−)-(*R*)-Diethyl Tetrahydrofurfurylmalonate. This compound was prepared from diethyl malonate (64.1 g, 0.40 mol), Na (11.5 g, 0.50 mol), and (+)-(*R*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate[49] [177.9 g (0.05 mol) of the compound crystallized with 0.25 mol of CCl_4; mp 67 °C] following the procedure described for the racemic form.[50] Distillation yielded 44.3 g [bp 120–140 °C (1 mm)], and redistillation gave 38.9 g (39.8%) of (−)-(*R*)-diethyl tetrahydrofurfurylmalonate: bp 118 °C (1 mm); $[\alpha]^{25}_D$ −13.7° (*c* 1.0, EtOH). Anal. ($C_{12}H_{20}O_5$) C, H.

(−)-(*R*)-3-(Tetrahydro-2-furyl)propionic Acid. This compound was prepared from the above malonate (38.0 g, 0.16 mol) according to the procedure described for the racemic form.[50] Distillation yielded 15.9 g (70.9%) of (−)-(*R*)-(tetrahydro-2-furyl)propionic acid: bp 96–97 °C (0.2 mm); $[\alpha]^{25}_D$ −10.2 (*c* 1.0, EtOH). Anal. ($C_7H_{12}O_3$) C, H.

(+)-(*S*)-Diethyl Tetrahydrofurfurylmalonate. This compound was prepared from diethyl malonate (64.1 g, 0.40 mol), Na (11.5 g, 0.50 mol), and (+)-(*S*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate[49] (158.2 g, 0.50 mol, of the syrupy compound) following the procedure described for the racemic form.[50] Distillation yielded 42.6 g [bp 120–140 °C (1 mm)], and redistillation gave 37.9 g (38.8%) of (+)-(*S*)-diethyl tetrahydrofurfurylmalonate: bp 118 °C (1 mm); $[\alpha]^{25}_D$ +13.1° (*c* 1.0, EtOH). Anal. ($C_{12}H_{20}O_5$) C, H.

(+)-(*S*)-3-(Tetrahydro-2-furyl)propionic Acid. This compound was prepared from the above malonate (37.0 g, 0.15 mol) according to the procedure described for the racemic form.[50] Distillation yielded 16.0 g (73.3%) of (+)-(*S*)-3-(tetrahydro-2-furyl)propionic acid: bp 96–97 °C (0.2 mm); $[\alpha]^{25}_D$ +8.8° (*c* 1.0, EtOH). Anal. ($C_7H_{12}O_3$) C, H.

Acknowledgment. We thank Mr. Karlfried Schmitt, Mr. Udo Köhl, and Mrs. Rosemarie Lawall for chemical laboratory work and Ms. Alwine Schmitz for pharmacological evaluation of the compounds. We also are indebted to Dr. Friedhelm Knappen for biostatistical evaluation of pharmacological data.

References and Notes

(1) H. Merz, K. Stockhaus, and H. Wick, *J. Med. Chem.*, 18, 996 (1975).
(2) Some of the results have been presented by the authors at the meeting of the International Narcotic Research Conference, Noordwijkerhout, The Netherlands, 1978.
(3) B. F. Tullar, L. S. Harris, R. L. Perry, A. K. Pierson, A. E. Soria, W. F. Wetterau, and N. F. Albertson, *J. Med. Chem.*, 10, 383 (1967).
(4) A. F. Casy and A. P. Parulkar, *J. Med. Chem.*, 12, 178 (1969).
(5) Chemical Abstracts nomenclature: 3-substituted (2*R*,6*R*,11*R*)-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ols.
(6) C. H. Boehringer Sohn, Ingelheim (H. Merz and K. Stockhaus), *German Offen.*, 2828039.9 (1978).
(7) J. Defaye, M. Naumberg, and T. Reyners, *J. Heterocycl. Chem.*, 6, 229 (1969).
(8) F. Haffner, *Dtsch. Med. Wochenschr.*, 55, 731 (1929).
(9) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, 107, 358 (1953).
(10) H. Blumberg, P. S. Wolf, and H. B. Dayton, *Proc. Soc. Exp. Biol. Med.*, 118, 763 (1965).
(11) H. Merz, A. Langbein, K. Stockhaus, G. Walther, and H. Wick, *Adv. Biochem. Psychopharmacol.*, 8, 91 (1974).
(12) W. Straub, *Dtsch. Med. Wochenschr.*, 37, 1462 (1911).
(13) M. Hutchinson, H. W. Kosterlitz, F. M. Leslie, A. A. Waterfield, and L. Terenius, *Br. J. Pharmacol.*, 55, 541 (1975).
(14) J. A. H. Lord, A. A. Waterfield, J. Hughes, and H. W. Kosterlitz in "Opiates and Endogenous Opioid Peptides", H. W. Kosterlitz, Ed., Elsevier/North-Holland Biomedical Press, Amsterdam, 1976, p 275.
(15) J. A. H. Lord, A. A. Waterfield, J. Hughes, and H. W. Kosterlitz, *Nature (London)*, 267, 495 (1977).
(16) P. E. Gilbert, W. R. Martin, and C. A. Jessee, reported to the Committee on Problems of Drug Dependence, Cambridge, Mass., 1977.
(17) H. H. Swain and M. H. Seevers, "Addendum to the 1976 Proceedings of the Committee on Problems of Drug Dependence", National Academy of Sciences, Washington, D.C., 1976, p 784.
(18) J. H. Woods, C. L. Fly, and H. H. Swain in "Characteristics and Function of Opioids", J. M. van Ree and L. Terenius, Eds., Elsevier/North-Holland Biomedical Press, Amsterdam, 1978, p 403.
(19) S. Archer and W. F. Michne, *Fortschr. Arzneimittelforsch.*, 20, 46 (1976).
(20) R. I. Taber, *Adv. Biochem. Psychopharmacol.*, 8, 191 (1974).
(21) I. Shemano and H. Wendel, *Toxicol. Appl. Pharmacol.*, 6, 334 (1964).
(22) H. H. Swain and M. H. Seevers, "Addendum to the 1974 Proceedings of the Committee on Problems of Drug Dependence", National Academy of Sciences, Washington, D.C., 1974, p 1171.
(23) M. D. Aceto, D. B. McKean, and J. Pearl, *Br. J. Pharmacol.*, 36, 225 (1969).
(24) S. Archer and L. S. Harris, *Fortschr. Arzneimittelforsch.*, 8, 279 (1965).
(25) J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, 12, 288 (1969).
(26) W. F. Michne, R. L. Salsbury, and S. J. Michaelec, *J. Med. Chem.*, 20, 682 (1977).
(27) H. Merz and K. Stockhaus, *J. Med. Chem.*, 20, 844 (1977).
(28) E. Kutter, A. Herz, H.-J. Teschemacher, and R. Hess, *J. Med. Chem.*, 13, 801 (1970).
(29) A. E. Jacobson, W. A. Klee, and M. J. Dunn, *Eur. J. Med. Chem.*, 13, 801 (1970).
(30) For the compounds **5a-1**, **5a-2**, and **5b-2**, log *P* values of 1.08, 1.14, and 1.30, respectively, were measured (1-octanol-$^1/_{15}$ phosphate buffer, pH 7.4).
(31) A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, 6, 986 (1954).
(32) A. F. Casy, *Mod. Pharmacol.*, 217 (1973).
(33) P. M. Frearson and E. S. Stern, *J. Chem. Soc.*, 3062 (1958).
(34) P. M. Frearson, D. G. Hardy, and E. S. Stern, *J. Chem. Soc.*, 2103 (1960).
(35) A. M. J. N. Blair and R. P Stephenson, *Br. J. Pharmacol.*, 15, 247 (1960).
(36) P. S. Portoghese, *J. Med. Chem.*, 8, 609 (1965).
(37) P. S. Portoghese, *J. Pharm. Sci.*, 55, 865 (1966).
(38) A. F. Casy, *Fortsch. Arzneimittelforsch.*, 22, 149 (1978).
(39) R. Justoni and M. Terruzzi, *Gazz. Chim. Ital.*, 80, 259 (1950); *Chem. Abstr.*, 45, 2394*a* (1951).
(40) H. Wollweber, H. Horstmann, and K. Meng, *Eur. J. Med. Chem.*, 11, 159 (1976).
(41) M. Kratovil, J. Uhdeová, and J. Jonas, *Collect. Czech. Chem. Commun.*, 30, 3205 (1965).
(42) R. C. Tallmann, *J. Am. Chem. Soc.*, 56, 127 (1934).
(43) L. E. Craig and D. S. Tarbell, *J. Am. Chem. Soc.*, 71, 464 (1949).
(44) R. Pummerer and M. Schönamsgruber, *Chem. Ber.*, 72, 1834

(1939).
(45) H. Schmid, *Helv. Chim. Acta*, **27**, 134 (1944).
(46) N. Kochetkov, A. M. Likhoshertov, and V. N. Kulakov, *Tetrahedron*, **25**, 2321 (1969).
(47) Ch. Weizmann, M. Sulzbacher, and E. Bergmann, *J. Am. Chem. Soc.*, **70**, 1153 (1948).
(48) M. P. Balfe, M. Irvin, and J. Kenyon, *J. Chem. Soc.*, 312 (1941).
(49) The erroneous configurational assignments with regard to (−)- and (+)-tetrahydrofurfuryl bromide[1] discussed in the last paragraph of the Chemistry section has also led to incorrect configurational assignments for the diastereomeric tetrahydrofurfuryl camphorsulfonates.[27] The crystalline compound has not the *S* but rather the *R* configuration, and the syrupy compound has not the *R* but rather the *S* configuration.
(50) G. Barger, R. Robinson, and L. H. Smith, *J. Chem. Soc.*, 718 (1937).

Anticoccidial Derivatives of 6-Azauracil. 2. High Potency and Long Plasma Life of N1-Phenyl Structures[1a]

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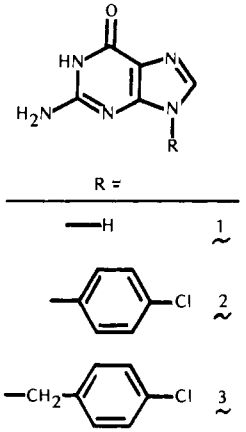
Attachment of substituted phenyl side chains at N1 of 6-azauracil caused striking increases in plasma life and anticoccidial potency. The increases were related in part to the acidity of the imide hydrogen. Maximum effects were shown by phenyl rings substituted in both meta positions by compact, electron-withdrawing, lipophilic substituents, as in 1-(3′,5′-dichlorophenyl)-6-azauracil, which had a plasma half-life of 160 h and a potency 250-fold greater than that of 6-azauracil.

The discovery that 1-benzyl side chains increased the anticoccidial activity of 6-azauracil[2] stimulated speculation on structural variations that might intensify the effect. Of the various possibilities considered, replacement of benzyl by phenyl seemed particularly attractive. Whereas the benzyl substituents probably had been limited largely to localized influences, the electronic character of a substituent on a phenyl ring would be transmitted to the heterocycle, permitting variation of the acidity of the imide proton. This variable acidity should, in turn, affect the pharmacokinetics and the binding properties of the drug. For instance, increasing the acidity of substituted uracils has been shown to improve manyfold their ability to inhibit the enzyme thymidine phosphorylase in vitro.[3] In addition, the polarizability of 1-phenyl-6-azauracils should extend throughout the entire molecule and that should facilitate adaptation to the active site.

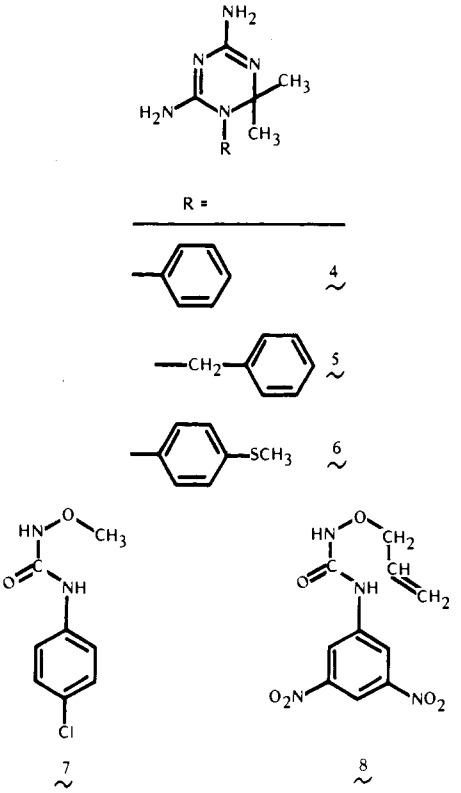
Precedent existed for the superiority of phenyl over benzyl groups in conjunction with heterocycles as enzyme inhibitors and as antiprotozoal agents. For example, 9-*p*-chlorophenylguanine (**2**) is an excellent inhibitor of rabbit



1 **2** **3**

liver guanine deaminase in vitro, binding the enzyme four times better than the normal substrate, guanine (**1**), and about a 100-fold better than 9-*p*-chlorobenzylguanine (**3**).[4]

In the extensively studied dihydrofolate reductase inhibitors, the phenyl derivative **4** was about 33 times more effective as an inhibitor of the enzyme from chicken liver than the benzyl derivative **5**. The related substance **6** was



4 **5** **6**

7 **8**

a component of a former anticoccidial agent, trithiadol.[5] We have shown marked coccidiostat activity in **7** and **8** but not in related structures with benzyl rather than phenyl groups.[6] The mode of action of these compounds is unknown, but it seemed possible that they might be acting as fragmentary 6-azauracils, perhaps binding the orotidylate decarboxylase in a similar but less effective and specific manner.

Chemistry. A synthesis of 1-phenyl-6-azauracil starting from aniline had been reported[7] and it proved adaptable to our purpose. This synthetic sequence is outlined in Scheme I as modified and applied to the transformation

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