Design, Synthesis, and X-ray Data of Novel Potential Antipsychotic Agents. Substituted 7-Phenylquinolizidines: Stereospecific, Neuroleptic, and Antinociceptive Properties†

René Imhof,*‡ Emilio Kyburz,‡ and John J. Daly§

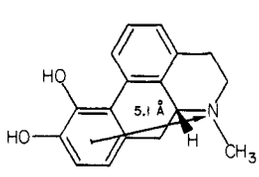
Pharmaceutical Research Department I and Central Research Units, F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basle, Switzerland. *Received May 25, 1983*

The semirigid 7-phenylquinolizidine system was selected for the design of new potential antipsychotic agents because it fulfills earlier considerations on the minimal structural and steric requirements necessary to attain a high affinity to the dopamine receptors and, in addition, leaves open many opportunities for variations. Whereas the initial compound **5a**, modeled after the structure of butaclamol, was virtually inactive, the introduction of substituents on the phenyl ring and of further optional structural elements improved the dopamine antagonistic properties by supplying additional binding forces. Initially, a compound in the potency range of chlorpromazine was obtained: (9aH)-2-*tert*-butyl-7-(2,4-dichlorophenyl)octahydro-2*H*-quinolizin-2-ol (**5e**). By the optical resolution of **5c**, it was demonstrated that the biological activity resides in the (−) enantiomer. The absolute configuration of (−)-**5e** was determined by single-crystal X-ray analysis to be 2*S*,7*R*,9a*R*. Further variations of the optional structural elements led to the unexpected finding of compounds with strong antinociceptive properties, e.g., (2*R*,7*S*,9a*S*)-2-butyloctahydro-7-phenyl-2*H*-quinolizin-2-yl acetate [(+)-**26**]. Interestingly, this compound belongs to the enantiomeric series opposite to that of the neuroleptic-like (−)-**5e**.

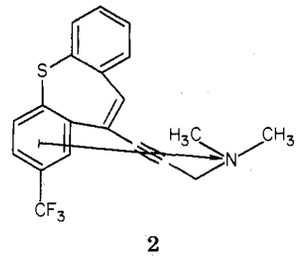
Antipsychotic drugs differ widely in their chemical structure, molecular size, and physicochemical properties. They comprise structures of increasing complexity ranging from rather small and flexible molecules, such as the benzamide derivatives (sulpiride), the butyrophenones (haloperidol), the diphenylbutylpiperidines (spiroperidol), and the semirigid tricyclic systems like the phenothiazines (chloropromazine), thioxanthenes (chloroprothixene), and dibenzothiepines (octoclothepine), to rigid pentacyclic structures, such as butaclamol. Many authors have tried to define the common structural features among this large variety of agents.[1-8]

During the 1970's in our laboratories, a working hypothesis was elaborated to include all antipsychotics known at that time. It was conceived with the hope to enable the design of structurally novel potential antipsychotics.[9] The common basis for the therapeutic efficacy of these drugs is generally recognized to be their outstanding ability to reversibily block central dopamine (DA) receptors,[10] thus causing relief from psychotic symptoms but accounting also for some of their side effects.

Our working hypothesis postulates that agonists and antagonists of the dopaminergic system should share some common structural features, because of their assumed affinity for the same central DA receptors. The minimal necessary (but not sufficient) structural requirements were derived from Dreiding models and were defined according to the structural and steric features of DA in its biologically relevant conformation, as present for example, in (*R*)-apomorphine (1), as follows:[9] (1) The presence of an



1 [(*R*)-apomorphine]



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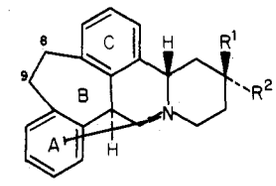
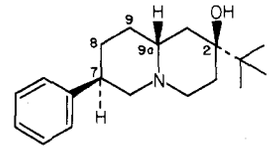
aromatic or heteroaromatic ring; (2) a distance vector of 5–6 Å between the center of the aromatic ring and a basic N atom; (3) position of an optional bulky part of the molecule to the right, and (4) position of an optional aromatic ring substituent to the left of the distance vector, provided the orientation of the molecule is such that the N atom lies below the plane of the aromatic ring. These were applied successfully for the first time in designing a new, semirigid class of tricyclic compounds, the 3-(dibenzo[*b*,*f*]thiepin-10-yl)-2-propynylamines.[11] The representative compound **2** thereof was indeed found to be an effective, nonsedating antipsychotic in preliminary clinical trials.[12]

The present work describes a project initiated in 1976 with the aim of designing new, nontricyclic antipsychotics with improved biological properties. At that time, our attention was attracted by (+)-butaclamol (**3**), a very po-



3, R^1 = OH; R^2 = *t*-Bu [(+)-butaclamol]
4, R^1 = R^2 = H



5a

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† Dedicated to Prof. A. Hürlimann on the occasion of his 60th birthday.
‡ Pharmaceutical Research Department I.
§ Central Research Units.

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tent, stereospecifically acting neuroleptic,[13,14] because its almost rigid pentacyclic chiral structure perfectly conformed to the minimal structural and steric requirements of our working hypothesis.

The lack of a substituent on the aromatic rings in butaclamol was intriguing, since in all other series of antipsychotic drugs such a substituent is a prerequisite for high potency. Moreover, it seemed that a *tert*-butylcarbinol function played a crucial role for activity, since the analogue **4** not bearing such a function, had been described as inactive.[15] According to our hypothesis, ring A of (+)-butaclamol (conformer B)[5] represents one of the postulated minimal structural requirements and, therefore, is essential for the interaction with DA receptors, while rings B and C could be considered as an optional "bulky part" of the molecule.

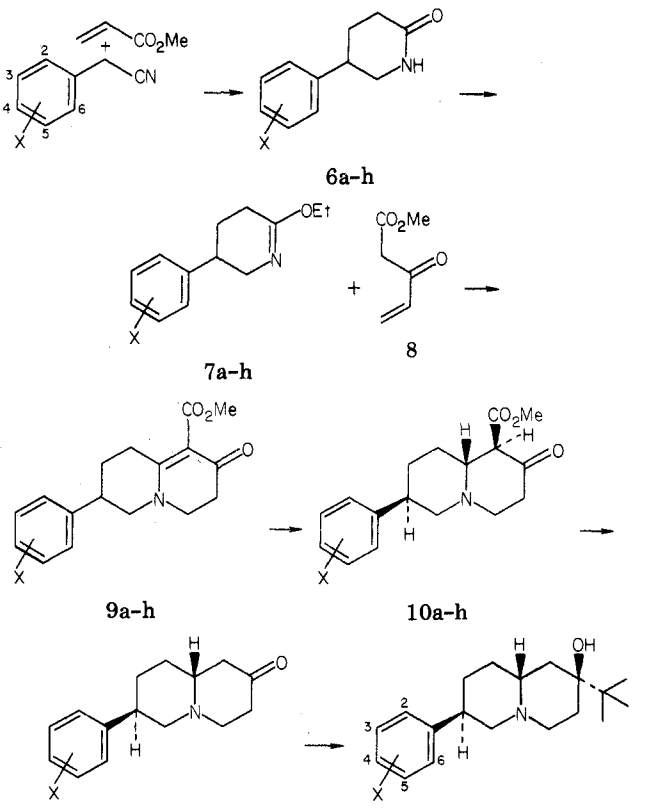
In order to validate our views and to test the importance of the bulky part, we synthesized phenylquinolizidine **5a**, because we envisaged it as a potential antipsychotic compound. It was anticipated that the quinolizidine skeleton should have a trans-fused ring conformation, carry an equatorial phenyl group at C-7, and, in order to maintain a possibly important feature of butaclamol, have a *tert*-butylcarbinol function at C-2.

Chemistry. A Robinson-type annelation procedure was chosen for the key step in the synthesis of the quinolizidine skeleton: The imino ether **7**, serving as a Michael donor, was reacted with the carboxyl-substituted methyl vinyl ketone **8** (Nazarov reagent[16]).[17] A convenient large-scale preparation, which yields **8** in high purity, was achieved by retro-Diels–Alder reaction from its cyclopentadiene adduct, as described by Stork and Guthikonda.[18] As an example, the hexahydroquinolizinone **9a** was obtained in 68% yield. Although the carboxyl function is eliminated later in the preparation of **5**, it proved essential in the above annelation process; i.e., no reaction took place with **7** and methyl vinyl ketone. The starting imino ether **7** was obtained by Michael addition of benzyl cyanide to methyl acrylate, followed by catalytic reduction of the nitrile function and cyclization[19] to the lactam **6**, which was transformed into **7** by means of triethyloxonium tetrafluoroborate (Scheme I).

The subsequent steps from **9** to the target molecule **5** were achieved by reducing, stereospecifically, the tetrasubstituted double bond by means of 2 equiv of diisobutylaluminum hydride (DIBAH) in toluene (20% w/w), affording the trans-fused quinolizidine **10** with equatorial phenyl and carboxyl substituents at C-1 and C-7, respectively (for ^{1}H NMR analysis, see Experimental Section). Subsequent decarboxylation of **10** led to the 2-ketoquinolizidine **11**, which on reaction with *tert*-butyllithium yielded the desired final product **5**. In analogy to butaclamol, it was assumed that the bulky *tert*-butyl substituent was in an equatorial position. This assumption was confirmed by the X-ray analysis of compound (−)-**5e**, as discussed later.

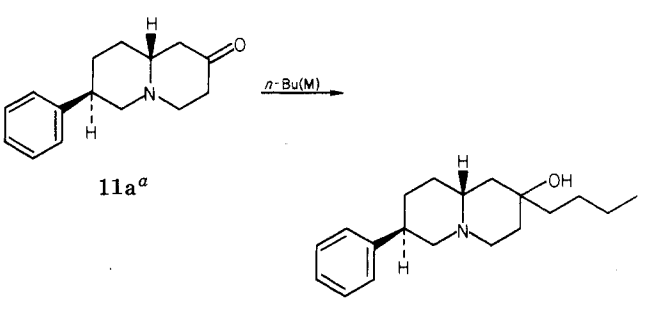
Starting from substituted benzyl cyanides, a number of analogues of **5a** were prepared by the same route (see Table I, **5b–h**). Instead of the *tert*-butyl group, some other alkyl and aryl groups were introduced by treating quinolizidinone **11e** with the corresponding lithium or Grignard reagents (see Table I, **12–18**). Alkyl moieties smaller than *tert*-butyl and phenyl led to mixtures of epimers at C-2, which, however, could be separated by chromatography or crystallization. Typical experiments are illustrated in Scheme II.

Scheme I[a]



[a] a, X = H; b, X = 4-Cl; c, X = 3,4-Cl_2; d, X = 4-CF_3; e, X = 2,4-Cl_2; f, X = 3-Cl; g, X = 2-Cl; h, X = 2,6-Cl_2.

Scheme II



n-Bu(M)	solv	reaction temp, °C	yield,[b] % 19	20	11a
(1) *n*-BuLi (2 equiv)	THF	−78	53	20	15
(2) *n*-BuLi (2 equiv)	Et_2O	−78	65	17	5
(3) *n*-BuLi/CuI (3:1 equiv)	Et_2O	−78	80	6	5

[a] Relative configuration given. [b] Isolated yield after chromatography.

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Reaction of ketone **11a** with *n*-butyllithium in THF at −78 °C afforded a 2.6:1 mixture of carbinols **19** and **20**, together with a considerable amount (15%) of recovered starting material. In order to improve the yield of compound **19** (axial OH, equatorial *n*-butyl), which turned out to be an important intermediate for the synthesis of **26** (see Table IV), the reaction was performed in Et_2O. Solvent change yielded a slightly improved stereoselectivity ratio of 3.8:1 for **19** vs. **20**, which, however, was substantially increased to a ratio of 13.3:1 by the addition of a stoichiometric amount of copper(I) iodide.[20]

The relative configuration of the above-obtained epimeric carbinols, as for example, the phenylcarbinols **17** and **18**, could not unambiguously be deduced from IR and NMR studies. However, it was possible to make a tentative assignment at C-2 on the basis of the chemical-shift difference (^{1}H NMR) of the phenylcarbinol acetates **28** and **29** (see Table III), whereby $OCOCH_3$ in the axial position (**28**) displayed a singlet at δ 2.04, which is at lower field than $OCOCH_3$ in the equatorial position (**29**) at 1.84 ppm. This is also consistent when compared with axial acetates in **22–26** [δ ($OCOCH_3$) 2.05–2.08]. In addition, it was noticed that, with acid anhydrides and pyridine, equatorial carbinols were esterified faster and at lower temperature than their axial counterparts. This stereochemical analysis is based on the assumption that all quinolizidines are predominantly trans-fused (Bohlmann bands[21] in the 2700–2850-cm^{-1} region of the IR) and that the six-membered rings both have chair conformations.

For the carbinol **19**, the configurational assignment has been confirmed by the X-ray analysis of its carbinol acetate (+)-**26**, as discussed later.

Optimization of the Neuroleptic Effect. In a series of in vivo and in vitro tests predictive for neuroleptic activity (see Table I), our first compound (**5a**) exhibited only marginal effects. Compound **5a** was inactive in the pole climb and the catalepsy test considered to be relevant for the potential antipsychotic action and the extrapyramidal side effects, respectively. However, the biochemical parameters (increase of homovanillic acid levels and [^{3}H]-spiroperidol binding) indicated a weak but significant DA antagonism. According to our working concept, it was hoped that the affinity for the dopamine receptors could be increased by either adding a bulky part to the parent compound **5a** (e.g., by condensing a benzene ring to positions 8 and 9) and/or by adding an appropriate aromatic substituent onto the phenyl ring. We preferred to try the latter possibility. Although such a substituent is not present in butaclamol (**2**), it is known that the type and position of aromatic substituents in all other classes of antipsychotic compounds (e.g., tricyclics, butyrophenones, and benzamides) are crucial for activity. It has been speculated that the mechanism whereby aromatic substituents influence neuroleptic activity could be a direct effect on the receptor by increasing binding or inducing a favorable conformation.[4]

In order to rationalize our search for the optimum aromatic substitution pattern, we made use of the operational schemes for analogue synthesis proposed by Topliss.[22] According to this scheme, the next compound to be synthesized was the 4-chlorophenyl analogue (**5b**). This compound displayed a significant neuroleptic effect in all of the tests, as shown in Table I. Surprisingly, the next analogue, 3,4-dichlorophenyl (**5c**), was virtually inactive. It seemed unlikely that **5c** already exceeded the optimum lipophilic value for activity but rather that the steric effect of the meta substitution was unfavorable. Indeed, the 3-chlorophenyl analogue (**5f**) was inactive. A maximum effect was obtained with the 2,4-dichlorophenyl compound (**5e**). The fact that the 2-chlorophenyl derivative (**5g**) itself displayed a neuroleptic effect comparable to that of **5e** suggests that, in this series, aromatic ortho substitution is an important factor in structure–activity relationship (SAR).

When the C-2 *tert*-butyl in **5e** was replaced by lower alkyl groups, such as those in **14–16**, neuroleptic activity decreased sharply; only the *sec*-butyl analogue **12** had a potency comparable to that of **5e**. A phenyl ring at C-2 in the equatorial position happened to be a fairly good substitute (**17**) for *tert*-butyl. The finding that diastereomer **18** was inactive clearly demonstrates that functional groups at C-2 influence neuroleptic activity stereoselectively.

Optical Resolution of Compound 5e. Comparison with Butaclamol (3). In order to establish whether phenylquinolizidines are binding stereospecifically to dopamine receptors, we resolved **5e** into its enantiomers by using the two atropisomeric binaphthyl phosphoric acids, BNPPA.[23] By means of (+)-BNPPA, isolation of the (+) enantiomer of **5e** was effected first; subsequently, (−)-**5e** was separated from the mother liquor by (−)-BNPPA. The enantiomeric selectivity shown by the BNPPA's was impressive; without further recrystallization of the diastereomeric salt pairs, enantiomeric excess of 95% was determined by ^{1}H NMR, using the chiral shift reagent Eu(hfc)$_3$.[24] With (±)-**5e**, the *tert*-butyl group was split into two singlets of equal intensity, whereas with (−)-**5e**, a ratio of 97.5:2.5 was integrated for these signals.

The results given in Table II show that the neuroleptic effects of **5e** resided mainly in the (−) enantiomer, whereas in the case of butaclamol, the (+)-antipode **3** was the active principle.[14] With respect to potency, (−)-**5e** was comparable to the tricyclic antipsychotic chlorpromazine **21**, while (+)-**3** was about 10 times more potent.

Antinociceptive Properties. In the above-described series of compounds, modifications of the aromatic substituent X, as well of substituent R^2 (alkyl, aryl), were performed while keeping constant a third parameter (R^1 = hydroxyl). Unexpectedly, the conversion of R^1 into *O*-acetate led to the loss or a marked reduction of neuroleptic activity (Table III), as judged by the results in the [^{3}H]spiroperidol binding. Instead, these derivatives exhibited weak to marked antinociceptive activity. For example, when the carbinol **5g** (X = 2-Cl; R^1 = OH; R^2 = *tert*-butyl) was converted into the *O*-acetate **23** (R^1 = OAc), the neuroleptic activity decreased, and antinociceptive activity of medium potency was observed. Interestingly, with respect to the aromatic substitution, the less active neuroleptic congeners **5a** and **5b** yielded the acetates **22** and **24**, respectively, with enhanced antinociceptive potency, whereas the carbinol **5e**, which had the most prominent neuroleptic effects in this series, gave the acetate **25** with virtually no antinociceptive effects. None of the enantiomers of the carbinols **5g** and **19** displayed antinociceptive activity by themselves. A similar contrasting trend in pharmacological profile was noticed for the alkyl substituent R^2, neuroleptic activity being highest for

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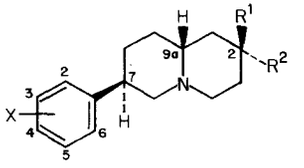
(24) Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]-europium(III). See also: von Ammore, R.; Fischer, R. D. *Angew. Chem.* **1972**, *84*, 737.

Table I. Carbinols: Physical Data and Psychopharmacological and Neurochemical Results



5a–h, 12–18[a]

compd	X	R^1	R^2	formula[b] (anal.)	crystn solvent[c]	mp, °C	pole climb BAR: ED_{50},[d] mg/kg ip	catalepsy test: ED_{50},[e] mg/kg ip	HVA level,[f] % (control = 100)	[^{3}H]spiroperidol binding: IC_{50},[g] nmol/L
5a	H	OH	*t*-Bu	$C_{19}H_{29}NO \cdot HCl$ (C, H, N, Cl)	A, B	230	>30	I[h]	308 ± 2** (30)	695
5b	4-Cl	OH	*t*-Bu	$C_{19}H_{28}NOCl \cdot HCl$ (C, H, N, Cl)	A, B	286–288	13.5	16 (14.6–17.4)	290 ± 22** (17)	204
5c	3,4-Cl_2	OH	*t*-Bu	$C_{19}H_{27}NOCl_2 \cdot HCl$ (C, H, N, Cl)	A, B	275	>30	30	190 ± 6** (50)	655
5d	4-CF_3	OH	*t*-Bu	$C_{20}H_{28}NOF_3 \cdot HCl$ (C, H, N)	A, B	285–286	18.5	>30	369 ± 30** (30)	1480 (1120–1800)
5e	2,4-Cl_2	OH	*t*-Bu	$C_{19}H_{27}NOCl_2 \cdot HCl$ (C, H, N, Cl)	A, B	270–272	6.4	12.2 (11.5–12.8)	557 ± 53*** (12)	63 (41–96)
5f	3-Cl	OH	*t*-Bu	$C_{19}H_{28}NOCl \cdot HCl$ (C, H, N, Cl)	A, B	273–275	>30	>30	103 ± 11 (30)	2920 (735–11600)
5g	2-Cl	OH	*t*-Bu	$C_{19}H_{28}NOCl$ (C, H, N)[i]	B, E	265–270	10	20.2 (17–24)	449 ± 33*** (21)	48 (9–244)
5h	2,6-Cl_2	OH	*t*-Bu	$C_{19}H_{27}NOCl_2 \cdot 0.9HCl$ (C, H, N, Cl)	C	262–263	>30	>30	283 ± 13** (25)	283
12	2,4-Cl_2	OH	*s*-Bu	$C_{19}H_{28}NOCl \cdot HCl$ (C, H, N, Cl)	C	244–246	6.25	5.5 (4.9–6.2)	467 ± 22** (10)	nd[j]
13	2,4-Cl_2	OH	*n*-Bu	$C_{19}H_{27}NOCl_2 \cdot HCl$ (C, H, N, Cl)	B, C	227–230	42	>10	150 ± 6* (17)	nd
14	2,4-Cl_2	OH	*i*-Pr	$C_{18}H_{25}NOCl_2 \cdot HCl$ (C, H, N, Cl)	A, B	201–205	17.5	9.2 (7.4–11.5)	280 ± 9** (10)	nd
15	2,4-Cl_2	OH	Et	$C_{17}H_{23}NOCl_2$ (C, H, N, Cl)	B, C	102–104	>30	I[h]	284 ± 29*** (50)	nd
16	2,4-Cl_2	OH	Me[k]	$C_{16}H_{21}NOCl_2$ (C, H, N, Cl)	D, E	149–151	>30	I[h]	157 ± 10* (50)	nd
17	2-Cl	OH	Ph	$C_{21}H_{24}NOCl \cdot HCl$ (C, H, N, Cl)	A	266–267	7	>10	340 ± 26** (10)	50
18	2-Cl	Ph	OH	$C_{21}H_{24}NOCl \cdot HCl$		*l*	>30	I[h]	99 ± 6 (10)	nd

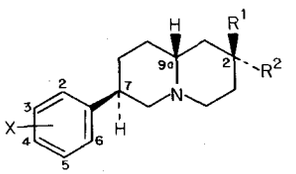
[a] Racemic, relative configuration given. [b] Compounds were analyzed for the elements shown in parentheses. [c] A = ethanol; B = diethyl ether; C = ethyl acetate; D = benzene; E = *n*-hexane. [d] Calculated dose producing a block of avoidance response in 50% of the rats. [e] Calculated dose producing 50% of the theoretically obtainable maximum catalepsy in rats. The 95% confidence interval is given in parentheses. [f] Levels of homovanillic acid (HVA) in rat brain 2 h after an intraperitoneal injection dose (in parentheses), given as means plus or minus the standard error of the mean of at least four single values from one rat each. In general, the dose chosen was close to the ED_{50} value in the catalepsy test. Statistical significance (Kolmogorov–Smirnov) for difference from control: *, $p < 0.05$; * = $p < 0.01$; * = $p < 0.001$; all others, $p > 0.05$. [g] The concentration inhibiting the specific binding of [^{3}H]spiroperidol by 50% was calculated. Each compound was examined at five or more concentrations in triplicate in at least three (95% confidence interval) or two (without confidence interval) independent determinations. [h] Inactive. [i] HCl salt used for testing. [j] Not determined. [k] Mixture of epimers at C-2. [l] Amorphous.

Table II. Comparison of Phenylquinolizidines 5e with Butaclamol (3) and Chlorpromazine (21) for Neuroleptic Effects

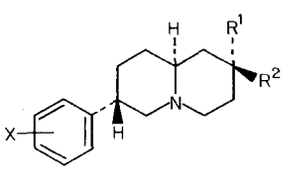
compd	$[\alpha]^{25}_D$, deg (c 1, methanol)	pole climb test BAR: ED_{50},[b] mg/kg ip	catalepsy test: ED_{50},[c] mg/kg ip	HVA level,[d] % (control = 100)	[^{3}]spiroperidol binding: IC_{50},[e] nmol/L
(+)-5e	+23.1	>30	28.4 (25-32.2)	283 ± 9*** (25)	740 (540-1020)
(−)-5e	−23.1	4.7	4.4 (3.8-5.1)	350 ± 21** (4.5)	28 (6-125)
(+)-3	+218.5[f]	0.47	nd[g]	667 ± 33*** (1.5)	2.0
(−)-3	−219.0[f]	nd[g]	nd[g]	114 ± 17 (1.5)	4000 (1700-9500)
21		4.3	3.2 (2.6-3.9)	301 ± 6 (5)	31 (26-37)

[a] Hydrochloride salt. [b-e] See footnotes *d-g* of Table I. [f] From ref 14. [g] Not determined.

Table III. Carbinol Acetates and Carbinols: Physical Data, Antinociceptive Effects, and Neurochemical Results



22-29,[a] (−)-5g, (−)-19, (−)-23

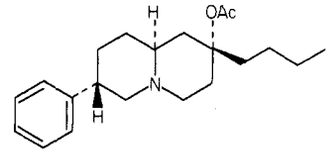


(+)-5g, (+)-19, (+)-23

compd	X	R^1	R^2	formula[b] (anal.)	crystn solvent[c]	mp, °C	^{1}H NMR (base, 2-$OCOCH_3$), δ	acetic acid induced writhing (mouse): ED_{50}[d] (1 h), mg/kg po	receptor binding in vitro: [^{3}H]naloxone: IC_{50},[e] nmol/L +NaCl	receptor binding in vitro: [^{3}H]naloxone: IC_{50},[e] nmol/L −NaCl	[^{3}H]spiroperidol: IC_{50},[f] nmol/L
22	H	OAc	*t*-Bu	$C_{21}H_{31}NO_2$·HCl (C, H, N, Cl)	A, C	247	2.07	2.6 (1.1-6.0)	nd[g]	nd[g]	nd[g]
23	2-Cl	OAc	*t*-Bu	$C_{21}H_{30}NO_2Cl$·HCl (C, H, N, Cl)	A, B	247-249	2.08	36	57	25	209
24	4-Cl	OAc	*t*-Bu	$C_{21}H_{30}NO_2Cl$·HCl (C, H, N, Cl)	A, B	244-246	2.05	4.0 (1.6-9.7)	280	150	360
25	2,4-Cl_2	OAc	*t*-Bu	$C_{21}H_{29}NO_2Cl_2$·HCl (C, H, N, Cl)	C	246	2.08	300	nd[g]	nd[g]	3 000
26	H	OAc	*n*-Bu	$C_{21}H_{31}NO_2$·HCl (C, H, N, Cl)	A, B	248-250	2.07	0.75 (0.32-1.8)	53 (38-70)	4.8 (2.5-6.5)	2 200
27	H	*n*-Bu	OAc	$C_{21}H_{31}NO_2$·HCl (C, H, N, Cl)	A	245-247	1.93	>100	220 (117-416)	24 (23-25)	5 000
28	2-Cl	OAc	Ph	$C_{23}H_{26}NO_2Cl$·HCl (C, H, N, Cl)[h]	C	220-222	2.04	2.8 (1.3-6.4)	nd[g]	nd[g]	nd[g]
29	2-Cl	Ph	OAc	$C_{23}H_{26}NO_2Cl$·HCl (C, H, N, Cl)	C	218-220	1.84	116 (42-317)	1 400 (1200-1700)	130 (61-290)	1 050
(+)-23[i]	2-Cl	OAc	*t*-Bu	$C_{21}H_{30}NO_2Cl$·HCl (C, H, N, Cl)	A, B	226-227	2.08	28 (14-56)	40	60	2 200
(−)-23[i]	2-Cl	OAc	*t*-Bu	$C_{21}H_{30}NO_2Cl$·HCl (C, H, N, Cl)	A, B	228-229	2.08	>30	775	2750	120
(+)-5g[i]	2-Cl	OH	*t*-Bu	$C_{19}H_{28}NOCl$·HCl (C, H, N, Cl)	A, B	294-295		>30	3 050	3900	23 000
(−)-5g[i]	2-Cl	OH	*t*-Bu	$C_{19}H_{28}NOCl$·HCl (C, H, N, Cl)	A, B	293-295		>10	3 600	3000	26
(+)-19[j]	H	OH	*n*-Bu	$C_{19}H_{29}NO$	B	99-101		>30	6 800	5400	2 540
(−)-19[j]	H	OH	*n*-Bu	$C_{19}H_{29}NO$	B	99-101		>30	11 300	8000	1 400

[a,b] See corresponding footnotes in Table I. [c] A = ethanol; B = diethyl ether; C = ethyl acetate. [d] Calculated dose at which 50% of the animals show not more than one extension movement; confidence intervals in parentheses [e] The concentration inhibiting the specific binding of [^{3}H]naloxone by 50% in the presence (+) or absence (−) of NaCl was calculated. Each compound was examined at five or more concentrations in triplicate in at least three (95% confidence interval) or two (without confidence interval) independent determinations. [f] See footnote *g* in Table I. [g] Not determined. [h] Cl: calcd, 16.87; found, 16.39. [i] Absolute configuration not determined; assigned in analogy to (−)-5e (X-ray analysis). [j] Absolute configuration deduced from (+)-26 (X-ray analysis).

Table IV. Comparison of Antinociceptive Effects of Phenylquinolizidines with Morphine



(+)-26

		(+)-26[a] ($[\alpha]^{25}_D$ +13.0°)	(−)-26[a,b] ($[\alpha]^{25}_D$ −13.4°)	morphine[a]
		Acetic Acid Induced Writhing (Mouse)		
ED_{50},[c] mg/kg po	1 h	0.19 (0.054-0.64)	10 (0.17-6.1)	2.4 (1.4-3.9)
	8 h	4.9 (2.6-9.6)	nd[f]	86 (47-157)
	24 h	69 (16-308)	nd	>550
ED_{50},[c] mg/kg sc	1/2 h	0.14 (0.042-0.43)	nd	0.96 (0.17-5.3)
	1 h	0.9 (0.16-5.1)	55 (19-161)	0.64 (0.22-1.8)
	8 h	3.8 (1.6-9.2)	nd	135 (95-191)
	24 h	40 (20-81)	nd	nd
		Hot Plate (Mouse)		
ED_{50},[d] mg/kg po	1 h	2.6 (0.50-13.6)	551 (0.65-∞)	36 (24-54)
ED_{50},[d] mg/kg sc	1 h	1.1 (0.41-3.0)	100	9.6 (3.9-23.8)
		[^{3}H]Naloxone Binding		
IC_{50},[e] nmol/L	+NaCl	27	680	120 (40-36)
	−NaCl	3.2	1500	5.4 (2.7-11)

[a] Hydrochloride salts. [b] Opposite absolute configuration as given in the formula. [c] See footnote *d* in Table III. [d] Calculated dose at which 50% of the animals start to lick their paws later than 10 s; confidence intervals in parentheses. [e] See footnote *e* in Table III. [f] Not determined.

compounds with branched alkyls, i.e., *tert*-butyl, while derivatives carrying unbranched alkyls, i.e., *n*-butyl (**26** vs. **22**) showed superior antinociception.

Irrespective of the neuroleptic and antinociceptive properties, active compounds possess, according to ^{1}H NMR evidence, the same relative configurations at positions 2, 7, and 9a.

The antinociceptive activity and the binding to opiate receptors of carbinol acetates in this series seems to be stereospecific, as shown by the following two examples.

The enantiomers of **23**, which displayed activity in both the [^{3}H]naloxone and [^{3}H]spiroperidol binding assay, were prepared by resolution of the carbinol **5g**, following the procedure described for compound **5e** and subsequent esterification by means of isopropenyl acetate/*p*-toluenesulfonic acid, yielding (+)- and (−)-**23**. Strikingly, the antinociceptive activity resided exclusively in the (+) enantiomer, whereas the neuroleptic activity was retained in the (−) antipode.

As a second example, the compound with the most prominent antinociceptive effect in this series (**26**) was resolved. The enantiomers of **26** were obtained through resolution of the corresponding carbinol **19** by means of (+)- and (−)-BNPPA, again followed by conversion into the acetates (+)- and (−)-**26**. The latter reaction step was performed best at 20 °C by using acetic anhydride in the presence of triethylamine and catalytic amounts of 4-(dimethylamino)pyridine,[25] affording the acetates in high yield (>98%) and purity (99%) without contamination by side products. The antinociceptive effect of (+)-**26** compared favorably with that of morphine (Table IV) by showing a several times higher potency and a markedly longer duration of action after oral and subcutaneous administration.

Absolute Configuration of (−)-5e and (+)-26. The free bases of (−)-**5e** and (+)-**26** were treated with (−)-BNPPA and (+)-BNPPA, respectively, and the resulting salts were crystallized from methanol/acetone and used for single-crystal X-ray analysis. The absolute configuration of these salts was determined, relying on the inherent chirality of BNPPA. Based on the absolute stereochemistry of (+)-BNPPA, which is known to be *S*,[23,26] the configuration 2*S*,7*R*,9a*R* was determined for the neuroleptic (−)-**5e**, in accordance with our working hypothesis and (+)-butaclamol but which is opposite to that established for the antinociceptive (+)-**26**, namely, 2*R*,7*S*,9a*S*. For details, see Experimental Section.

Discussion

The hitherto rather neglected bicyclic structure of the trans-fused quinolizidines was chosen as a semirigid template. According to our working hypothesis, it should possess all structural elements necessary for neuroleptic activity in a sterically defined manner. Based on the assumption that rings B and C in (+)-butaclamol (**3**) are optional elements and therefore not necessary for antipsychotic activity, 2,7-disubstituted quinolizidines were synthesized as novel ligands to the dopamine receptors. While the structurally closest analogue of butaclamol, compound **5a**, was almost devoid of neuroleptic effects, optimization of the phenyl ring substitution led to active compounds of medium potency similar to chlorpromazine. The increase in potency found with chlorine in the 4- and/or 2-position of the phenyl ring and the lack of activity of the 3-chlorophenyl analogue have a parallel in the classic tricyclic series of antipsychotics, where the presence and position of an aromatic ring substituent influences neuroleptic activity decisively. The rigid (+)-butaclamol system was shown to differ in this respect,[27] since introduction of a chlorine atom in position 11 (corresponding to 4-chlorophenyl in the quinolizidine series) did not increase, but only retained the original activity. However,

(25) Steglich, W.; Höfle, G. *Angew. Chem.* **1969**, *23*, 1001.

(26) Akimoto, H.; Shiori, T.; Iitika, Y.; Yamada, S-i. *Tetrahedron Lett.* **1968**, 97.

(27) Humber, L. G.; Sideridis, N.; Asselin, A. A.; Bruderlein, F. T.; Voith, K. *J. Med. Chem.* **1978**, *21*, 1225.

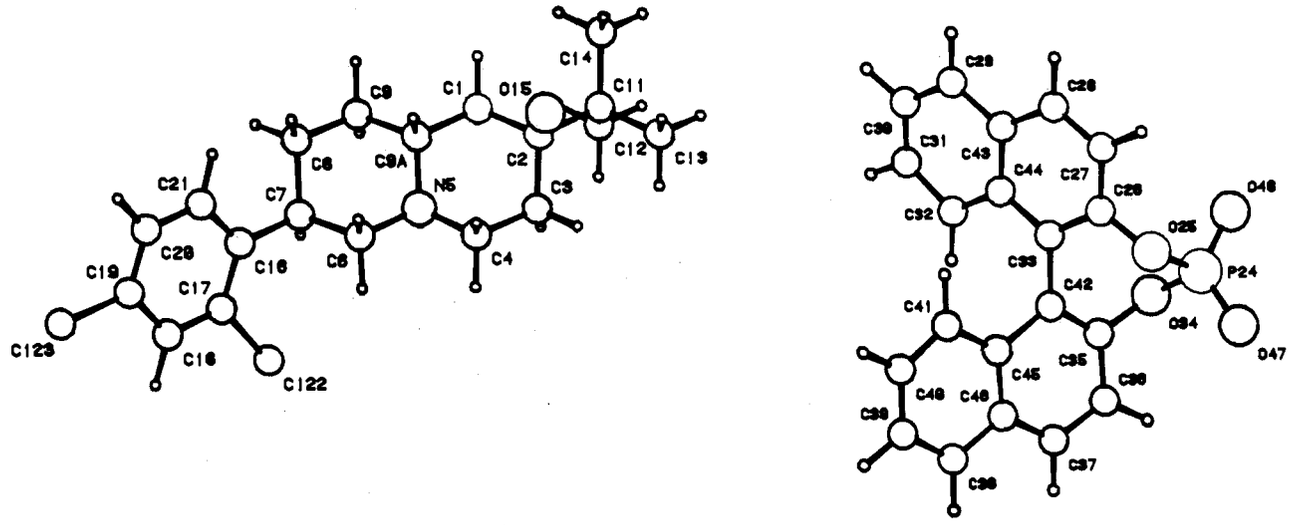


Figure 1. Crystal structure of (+)-5e·(+)-BNPPA.

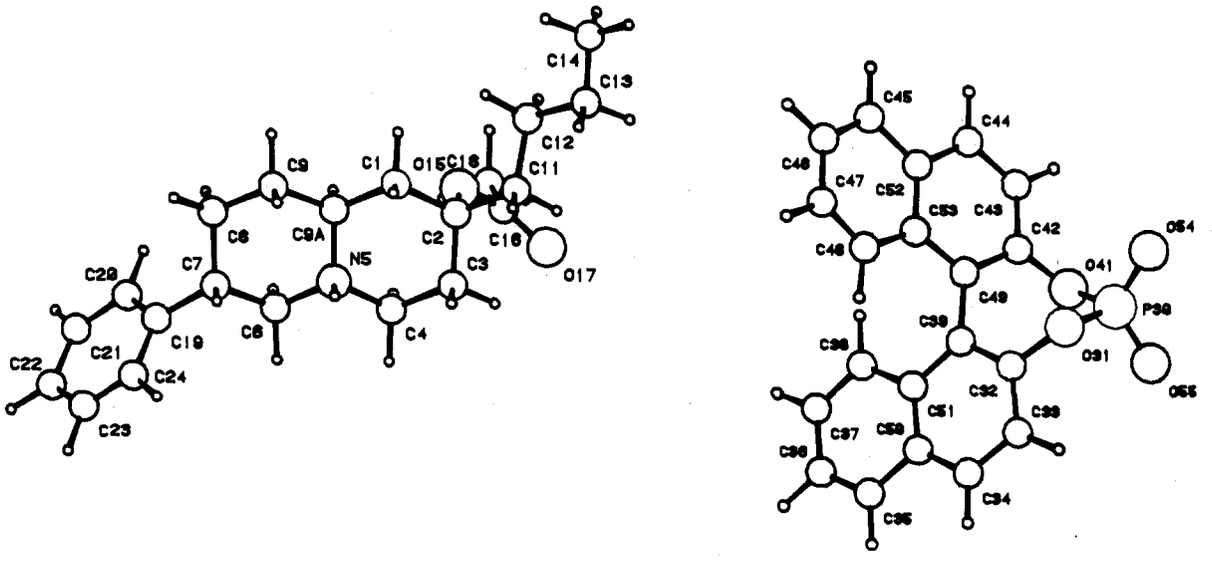
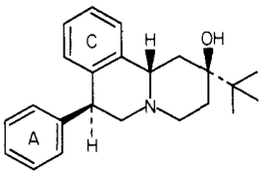


Figure 2. Crystal structure of (−)-26·(−)-BNPPA.

the lack of activity of the 7-(3-chlorophenyl)quinolizidine derivative and the markedly reduced and abolished activity of the corresponding 10- and 12-chlorobutaclamol derivatives, respectively,[27] go somewhat parallel.

It has to be stressed that (−)-**5e**, the most active compound of the phenylquinolizidine series, reaches only one-tenth the potency of (+)-butaclamol (**3**). Since the relative and absolute configuration of both compounds are identical, assuming that both compounds act through blockade of the same DA receptors, the higher potency of (+)-butaclamol may be related to the additional aromatic ring C and the seven-membered ring B and the apparently most favorable steric fixation. The recently reported butaclamol analogue **30**,[28] in which the ethylene bridge between rings A and C is missing, seems to meet most of the structural requirements for antipsychotic activity; however, this compound failed to show neuroleptic activity. One plausible explanation might be the difficulty for the aromatic ring A to assume the proper orientation at the binding site on the dopamine receptor,[29] due to steric hindrance.



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As a consequence of rotational freedom about the C8–C9 bond, (+)-butaclamol can adopt two distinct conformations, A and B. Conformer B was proposed to be present during the interaction with the central DA receptors,[5] while conformer A exists in the crystal structure.[30]

In this respect, the C-7 phenyl of the quinolizidine ligands can adopt several conformations, and it is unlikely that the conformer found in the crystal structure (Figure 1) is representative for the binding to the DA receptors.

The molecule of (−)-**5e** can be easily oriented according to our working hypothesis (superposition with apomorphine) or according to the model described by Humber et al.[29,30] [superposition with (+)-butaclamol, conformer

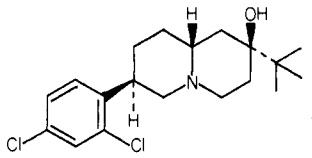
(28) Kukla, M. J.; Bloss, J. L.; Brougham, L. R. *J. Med. Chem.* **1979**, *22*, 401.

(29) Humber, L. G.; Bruderlein, L. T.; Philipp, A. H.; Götz, M.; Voith, K. *J. Med. Chem.* **1979**, *22*, 761.

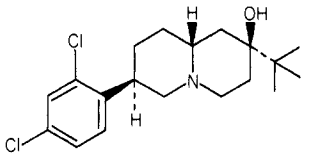
(30) Bird, P. H.; Bruderlein, F. T.; Humber, L. G. *Can. J. Chem.* **1976**, *54*, 2715.

B] with little topological difference.

Following our hypothesis, the 2-chlorophenyl substituent, which is important for the neuroleptic activity, has to be placed as shown in **5e'**. However, from the inspection of Dreiding models, it may be argued that, for thermodynamic reasons, **5e''** would be the prefered conformer.



5e'



5e''

In the latter conformation, (−)-**5e** represents an ideal ligand to the hypothetical binding sites in the central DA receptor model proposed by Humber et al.[29,30] The planar α- and β-regions would be occupied respectively by the phenyl ring and its 2-chlorophenyl substituent, while the quinolizidine N atom would adhere to the complementary hydrogen-bond donor site on the receptor surface.

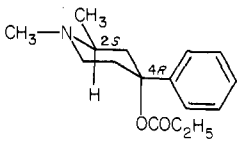
Despite this apparently perfect fit of our ligand (−)-**5e** to the above-mentioned model of the receptor binding sites, the in vivo neuroleptic activity found in the relevant animal tests was not satisfying with respect to both potency and separation of desired (pole climb test) to undesired (catalepsy test) effects in rodents and prompted us to drift further away from the structural proximity to butaclamol.

However, a first step in this direction, effected by converting C-2 carbinols into their *O*-acetates, led to the above-described finding of compounds with strong antinociceptive properties. Because of this interesting change in the overall pharmacological profile of our compounds, it remains to be further elucidated which other types of hydrophilic and lipophilic (optional) substituents at C-2 of the quinolizidine ring might contribute to enhanced neuroleptic potency.

The strong opiate-type antinociceptive properties of (+)-**26** justify an interpretation in terms of stereo- and regiospecific drug–opiate receptor interaction. The preference for axial *O*-acetate and equatorial alkyl or aryl functions in the 4-position of the piperidine partial structure and the high diastereoselectivity (antinociceptive potency in the writhing test: **26**/**27** > 100:1) and enantioselectivity [(+)-**26**/(−)-**26** = 53:1] point to similarities with the prodine type of analgesics; according to recent investigations,[31] the latter are suggested to interact with the subsite P (Phe) of the proposed opiate receptor.

Furthermore, the absolute stereochemistry of (+)-**26** at C-2 and C-9a, which is *R* and *S*, respectively, corresponds well with the absolute configuration of **31**,[32] a recently synthesized antinociceptive compound having a methyl group attached at the *pro*-2*S* enantiotopic edge of the piperidine ring next to nitrogen.

Compound **31** is reported to be twice as potent as morphine and ten times more effective than its enantiomer in the hot-plate procedure in mice.



31

Conclusion

It has been demonstrated that 7-phenylquinolizidines fulfill the minimal structural requirements necessary for obtaining DA-receptor antagonistic properties. Further investigations were conducted in order to establish the individual contributions to optional structural elements (bulky part, phenyl ring substituents, and hydrophilic and lipophilic elements) to the DA-antagonistic properties. It was found that the lack of the bulky element corresponding to rings B and C of (+)-butaclamol could (as in **5a**) be partly compensated, for example, by the introduction of appropriate substituents in the phenyl ring (compound **5e**).

The strong antinociceptive properties found by minor structural variations in the same class of 2,7-disubstituted phenylquinolizidines (compound **26**) may be interpreted as a stereospecific action at the opiate binding sites. It appears that, depending on the absolute configuration, ligands to either the central DA or the opiate receptor are obtained in this series.

Experimental Section

Chemistry. Generally, products were either isolated by crystallization from an appropriate solvent or by extraction, and extracts were concentrated after washing and drying on a rotary evaporator at reduced pressure and 40–50 °C. For column chromatography, silica gel 60 (Merck, particle diameter 0.063–0.2 mm) was used. Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^{1}H NMR spectra were measured in $CDCl_3$, with $(CH_3)_4Si$ as internal standard, on a Varian A-60 D, HA-100, or Bruker HX-90 or HX-270 spectrometer; IR spectra were obtained on a Beckman 9 instrument and are consistent with the assigned structures. Microanalyses were performed for C, H, N, and Cl and were within ±0.4% of the theoretical values.

Methyl *rac*-7-(2-Chlorophenyl)-3,4,6,7,8,9-hexahydro-2-oxo-2*H*-quinolizine-1-carboxylate (9g). 5-(2-Chlorophenyl)-2-piperidone (**6g**,[33] 150 g, 0.72 mol) was dissolved in methylene chloride (2 L) and added within 60 min to triethyloxonium tetrafluoroborate (Meerwein salt 410 g, 2.16 mol) in methylene chloride (1 L) while stirring at 20 °C. Subsequently, the mixture was boiled at reflux for 4 h and left at room temperature for a further 15 h. Potassium carbonate (372 g, 2.65 mol) in water (370 mL) was then added dropwise to the solution, which was cooled to 0 °C, the mixture being stirred intensively. Stirring was continued at room temperature for an additional 2 h; subsequently, the methylene chloride phase decanted off, and the residue was extracted with methylene chloride (2 × 500 mL). The methylene chloride phase, dried over potassium carbonate, was concentrated to an oily, partially crystalline residue, and then boiled in 1 L of hexane and filtered while hot. From the filtrate there were obtained, after evaporation of the hexane, 151.4 g of the oily lactim ether **7g**: bp 125–130 °C (0.05 mmHg); IR (film) 1684 cm^{-1}. Anal. ($C_{13}H_{16}NOCl$) C, H, N, Cl.

The lactim ether **7g** (151.4 g, 0.64 mol) was dissolved in methanol (1.4 L), anhydrous *p*-toluenesulfonic acid (1.3 g) was added, and methyl 3-oxo-5-pentenoate (**8**; 85 g, 0.66 mol) (Nazarov reagent)[10] was introduced dropwise within 60 min. After 20 h at room temperature, the readily volatile constituents were removed under reduced pressure, and the residue was subsequently taken up in methylene chloride (2 L) and washed with saturated Na_2CO_3 solution (500 mL) and water (250 mL). The methylene chloride phase, dried over $MgSO_4$, was concentrated, and the residue was crystallized from 4:1 ethyl acetate/ether (800 mL) to give 123.7 g (54%) of white crystalline **9g**: mp 145–147 °C; IR (KBr) 1688 (CO_2CH_3), 1625 (C=O), 1566 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 3, CO_2CH_3). Anal. ($C_{17}H_{18}NO_3Cl$) C, H, N, Cl.

When, in place of **6g**, equivalent amounts of correspondingly substituted piperidones **6a–h** were used, the following compounds were obtained: **9a** (mp 148–149 °C), **9b** (mp 185–187 °C), **9c** (mp

(31) Portoghese, P. S.; Alreja, B. D.; Larson, D. L. *J. Med. Chem.* **1981**, *24*, 782.

(32) Fries, D. S.; Dodge, R. P.; Hope, H.; Portoghese, P. S. *J. Med. Chem.* **1982**, *25*, 9.

(33) U.S. Patent 3 718 743 (to Merck & Co., Inc.).

162–163 °C), **9d** (mp 144–145 °C), **9e** (mp 153–155 °C), **9f** (mp 115–117 °C), **9h** (mp 165–167 °C).

Methyl *rac*-(1α*H*,9aβ*H*)-7β-(2-Chlorophenyl)octahydro-2-oxo-2*H*-quinolizine-1-carboxylate (10g). A suspension of **9g** (180 g, 0.56 mol) in monoglyme (dimethoxyethane 3.6 L) was cooled to −30 °C and DIBAH (diisobutylaluminum hydride; 1.33 L, 20% solution in toluene) was added while stirring. Subsequently, the mixture was maintained for 1 h at −20 to −30 °C and then hydrolyzed at this temperature with 2 N NaOH (1.72 L). For workup, the mixture was partitioned between water (25 L) and chloroform (20 L), and the organic phase was washed with water (2 × 5 L), dried ($MgSO_4$), and evaporated, yielding 185.2 g of crude product **10g**; 109 g of product could be crystallized from ether/hexane. By chromatography of the mother liquor on silica gel (1 kg), an additional 37 g of product was eluted (ethyl acetate). The total yield of **10g** amounted to 136 g (81%): mp 122–124 °C; IR (KBr) 1748 (CO_2CH_3), 1720 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.78 (s, 3 H, CO_2CH_3).

When, in place of **9g**, equimolar amounts of correspondingly substituted educts **9a–h** were reduced with DIBAH, the following compounds were obtained: **10a** [mp 114–116 °C; NMR ($CDCl_3$) δ 2.22 (t, 1 H, J = 11.5 Hz, $H_{6(ax)}$), 2.58 (td, 1 H, J_1 = 11 Hz, J_2 = 3 Hz, $H_{9a(ax)}$), 3.32 (dd, 1 H, J_1 = 11 Hz, J_2 = 0.5 Hz, $H_{1(ax)}$), 3.78 (s, 3 H, CO_2CH_3)], **10b** (mp 102–105 °C), **10c** (oil), **10d** (mp 108–111 °C), **10e** (mp 116–118 °C), **10f** (oil), **10h** (mp 130–131 °C).

***rac*-(9aβ*H*)-7β-(2-Chlorophenyl)octahydro-2*H*-quinolizin-2-one (11g).** A solution of **10g** (76.2 g, 0.24 mol) in 6 N HCl (1.2 L) was boiled at reflux for 3 h. The cooled solution was subsequently poured on to ice and made alkaline to pH 10 with concentrated NaOH. Extraction with methylene chloride (3 × 500 mL) and evaporation of the organic phase after drying ($MgSO_4$) yielded 68 g of crude **11g**. Crystallization from ether/hexane afforded pure ketone **11g** (50.4 g, 81%): mp 80–82 °C; IR (KBr) 2798, 2780, 1720 (C=O) cm^{-1}. Anal. ($C_{15}H_{18}NOCl$) C, H, N, Cl.

When, in place of **10g**, equimolar amounts of correspondingly substituted β-keto esters **10a–h** were decarboxylated, the following products were obtained: **11a** (mp 71–72 °C), **11b** (mp 80–82 °C), **11c** (oil), **11d** (mp 103–104 °C), **11e** (mp 116–117 °C), **11f** (oil), **11h** (mp 116–118 °C).

***rac*-(9aβ*H*)-2α-*tert*-Butyl-7β-(2-chlorophenyl)octahydro-2*H*-quinolizin-2-ol (5g: Table I).** (a) The ketone **11g** (22.2 g, 0.084 mol) in absolute THF (300 mL) was added dropwise under argon with strong stirring to a cooled solution (−75 °C) of *tert*-butyllithium in pentane (100 mL; 0.12 mol). Subsequently, the mixture was left at −75 °C for a further 30 min and then worked up as follows: The mixture was hydrolyzed by adding a saturated NH_4Cl solution (100 mL) and then partitioned between ethyl acetate (500 mL) and water (200 mL). After extraction with ethyl acetate (2 × 500 mL), the entire organic phase was dried ($MgSO_4$) and evaporated. From this residue, the final product **5g** could be crystallized as the hydrochloride salt by conducting gaseous hydrogen chloride into a solution of ethyl acetate (1.4 L) to yield 20.4 g (71%), mp 276–278 °C. An alternative purification procedure comprises chromatographing the basic residue on silica gel with 1:1 ether/hexane.

When, in place of **11g**, equimolar amounts of correspondingly substituted ketones **11a–h** were used, the *tert*-butylcarbinols **5a–h** (listed in Table I) were accessible. Similarly, from ketone **11e**, the carbinols **12** (with *sec*-butyllithium), **13** (with *n*-butyllithium), **14** (with isopropyllithium), **15** (with ethylmagnesium bromide), and **16** (with methyllithium) were obtained. From the reaction of **11g** and phenyllithium, a 1:1 mixture of compounds **17** and **18** was isolated, which could be separated into the individual compounds by chromatography on silica gel and eluting with 1:1 ether/hexane. From ketone **11a**, *n*-butyllithium, and the reaction conditions given in Scheme II, the carbinols **19** and **20** were isolated as pure compounds after chromatography on silica gel [(1) 1:1 diethyl ether/*n*-hexane, **19**; (2) ethyl acetate, **11a**; (3) 9:1 ethyl acetate/methanol, **20**].

Resolution of Carbinols 5e,g and 19. A solution of *rac*-**5e** (12.2 g, 0.034 mol) in methanol (80 mL) was treated with a solution of (+)-2,2′-(1,1′-binaphthyl)phosphoric acid ($[\alpha]^{25}_D$ +607° (*c* 1, methanol); 13.3 g, 0.038 mol) in methanol (250 mL) and methylene chloride (250 mL). The jelly that precipitated was brought into solution with hot methanol (1.2 L). Upon evaporation of the solution at reduced pressure to a volume of 500 mL, the (+)-phosphate crystallized out: yield 8.7 g (72.5%); mp 288–290 °C. The (+)-phosphate was then partitioned between diethyl ether (750 mL) and ammonium hydroxide (10%, 250 mL). The organic phase was dried ($MgSO_4$) and evaporated to yield the base (+)-**5e** (4.2 g), which, dissolved in ethanol (50 mL) and treated with 5 N hydrochloric acid in ethanol (2.5 mL) at 0 °C, gave (+)-**5e**·HCl as white crystals (4.0 g): mp 275–276 °C; $[\alpha]^{25}_D$ +23.1° (*c* 1, methanol). Anal. ($C_{19}H_{27}NOCl_2$·HCl) C, H, N, Cl.

The mother liquor from the crystallization of the (+)-phosphate was made basic with ammonium hydroxide (10%, 250 mL) and extracted with 1:1 ethyl acetate/ether (750 mL). The organic phase was washed neutral with water, dried ($MgSO_4$), and evaporated, yielding 7.7 g of base. This base was again brought into solution with methanol (50 mL), and (−)-2,2′-(1,1′-binaphthyl)phosphoric acid ($[\alpha]^{25}_D$ −608° (*c* 1, methanol); 7.33 g, 0.021 mol) in methanol (200 mL) and methylene chloride (200 mL) was added. Upon evaporation of the solution at reduced pressure to a volume of 250 mL, acetone (250 mL) was added, and the mixture was cooled to 0 °C; the (−)-phosphate (8.2 g) crystallized out, mp 279–281 °C. The base (−)-**5e** (4.2 g), which was liberated with ammonium hydroxide, was then dissolved in ethanol (50 mL) and treated with 5 N hydrochloric acid (2.5 mL) in ethanol. At 0 °C, (−)-**5e**·HCl crystallized out (4.1 g): mp 275–276 °C; $[\alpha]^{25}_D$ −23.1° (*c* 1, methanol). Anal. ($C_{19}H_{27}NOCl_2$·HCl) C, H, N.

The following enantiomers were isolated in an analogous manner by cleavage of the corresponding racemates: (+)-**5g**·HCl: mp 294–295 °C; $[\alpha]^{25}_D$ +29.7° (*c* 1, methanol). Anal. ($C_{19}H_{28}NOCl$·HCl) C, H, N, Cl. (−)-**5g**·HCl: mp 293–295 °C; $[\alpha]^{25}_D$ −29.9° (*c* 1, methanol). Anal. ($C_{19}H_{28}NOCl$·HCl) C, H, N, Cl. (+)-**19**: mp 99–101 °C; $[\alpha]^{25}_D$ +16.8° (*c* 1, methanol). Anal. ($C_{19}H_{29}NO$) C, H, N. (−)-**19**: mp 99–101 °C; $[\alpha]^{25}_D$ −16.8° (*c* 1, methanol). Anal. ($C_{19}H_{29}NO$) C, H, N.

Carbinol Acetates from Carbinols. Method A. *rac*-(9aβ*H*)-2α-*tert*-Butyl-7β-(2-chlorophenyl)octahydro-2*H*-quinolizin-2-yl Acetate (23; Table III). The carbinol base **5g** (20.0 g, 0.063 mol) was dissolved in isopropenyl acetate (130 mL), and anhydrous *p*-toluenesulfonic acid (11.7 g, 0.068 mol) was added. The mixture was then boiled at reflux under argon for 1 h while stirring. After the mixture was cooled to 25 °C, diethyl ether (20 mL) was added dropwise to the already partly crystallized *p*-toluenesulfonate of the product, which, after standing for 2 h, was filtered off and dried to give **23**·*p*-TsOH (22.5 g). The base was liberated from the *p*-toluenesulfonate with sodium bicarbonate solution (2 N, 250 mL), extracted into ethyl acetate (750 mL), dried ($MgSO_4$), and evaporated to yield **23** (15.8 g, 70%), which was crystallized as the hydrochloride salt **23**-HCl, mp 247–249 °C.

When equimolar amounts of the corresponding *tert*-butylcarbinols were used in the reaction, the following acetates were obtained: **22** from **5a**; **24** from **5b**; **25** from **5e**; (+)-**23**·HCl ($[\alpha]^{25}_D$ +24.9° (*c* 1, methanol)) from (+)-**5g**; (−)-**23**·HCl, ($[\alpha]^{25}_D$ −24.3° (*c* 1, methanol)) from (−)-**5g**.

Method B. (2*R*,7*S*,9a*S*)-2-Butyloctahydro-7-phenyl-2*H*-quinolizin-2-yl Acetate [(+)-26]. To a solution of the carbinol (+)-**19** (28.75 g, 0.1 mol) in triethylamine (350 mL) were added 4-(dimethylamino)pyridine (0.5 g, 4.1 mmol) and acetic anhydride (20 mL, 0.21 mol). After the solution was stirred at room temperature for 24 h, additional amounts of 4-(dimethylamino)-pyridine (0.25, 2.05 mmol) and anhydride (10 mL, 0.11 mol) were necessary to complete the esterification within the next 24 h. The red-brown reaction mixture was then evaporated at 4×10^{-2} bars and 50 °C up to a constant weight of the residue of 35.3 g. This residue was passed over a column of alumina (Camag, neutral, grade I), eluting with diethyl ether (1.5 L), to obtain the carbinol acetate (+)-**26** (32.3 g, 98%). From a solution of (+)-**26** in ethanol (50 mL) and 5 N hydrochloric acid in ethanol (20 mL), the hydrochloride was precipitated by adding diethyl ether (150 mL) to yield (+)-**26**·HCl (33 g) as white crystals: mp 242–243 °C; $[\alpha]^{25}_D$ +13.0° (*c* 1, methanol). Anal. ($C_{21}H_{31}NO_2$·HCl) C, H, N, Cl.

Similarly, from equimolar amounts of corresponding carbinols were obtained: (−)-**26**·HCl [mp 242–243 °C; $[\alpha]^{25}_D$ −13.4° (*c* 1, methanol). Anal. ($C_{21}H_{31}NO_2$·HCl) C, H, N, Cl] from (−)-**19**, *rac*-**26** from **19**, **27** from **20**, **28** from **17**, and **29** from **18**.

Table V. Crystal Data for (−)-5e·(−)-BNPPA and (+)-26·(+)-BNPPA

	(−)-5e·(−)-BNPPA	(+)-26·(+)-BNPPA
formula	$C_{39}H_{40}Cl_2NO_5P \cdot xC_3H_6O$	$C_{41}H_{44}NO_6P \cdot xCH_3OH$
space group	$C2$	$P2_1$
a, Å	21.614 (11)	8.673 (5)
b, Å	8.483 (5)	18.811 (10)
c, Å	20.907 (11)	12.494 (7)
β, deg	103.79 (3)	111.16 (3)
d_{calcd}, mg·m^{-3}	1.26[a]	1.18[a]
μ, mm^{-1}	2.32 (Cu$K\alpha$)[a]	0.12 (Mo$K\alpha$)[a]

[a] Ignoring solvent.

Crystal Structure of (−)-5e·(−)-BNPPA. The resolved base (−)-**5e** was again treated with (−)-BNPPA (1 equiv) and crystallized from methanol/acetone. The crystal data are summarized in Table V. Data were collected on a Hilger and Watts X290 four-circle diffractometer controlled by a PDP8 computer. Nickel-filtered copper radiation (λ = 1.5418 Å) was used in the $\theta/2\theta$ scan mode to a maximum θ of 57°. Of the 2721 independent data obtained in this way, 1907 had $I > 3.0\sigma(I)$ and were used in the refinement. The structure was determined by a mixture of the heavy (phosphorus) atom techniques and direct methods (MULTAN[34] and SHELX[35]). Refinement was sluggish, and difference maps indicated the presence of scattering matter, which was interpreted as a molecule of acetone on a twofold symmetry axis. The high temperature factors of the atoms in this molecule suggest that the site occupation factor is less than one. Blocked refinement was done with SHELX using the cation in one block and the anion and the acetone in another.

Anisotropic temperature factures were used for the non-hydrogen atoms, except in the acetone molecule; hydrogen atoms were assigned a common temperature factor, which was refined. The refinement converged at $R = 0.080$, $R' = 0.085$. The weighting scheme was $w = 2.1820/(\sigma^2|F_o|+0.001|F_o|^2)$.

Crystal Structure of (+)-26·(+)-BNPPA. The resolved base (+)-**26** was again crystallized with (+)-BNPPA (1 equiv) from methanol/acetone. The crystal data are summarized in Table V. Data were collected on a Hilger and Watts Y290 four-circle diffractometer controlled by a PDP8 computer. Zirconium-filtered molybdenum radiation was used (λ = 0.71069 Å) in the $\theta/2\theta$ scan mode to a maximum θ of 25°. Of the 3463 independent data obtained in this way, 1520 had $I > 2.5\sigma(I)$ and were used in the refinement. The structure was determined by a mixture of the heavy (phosphorus) atom technique and direct methods (MULTAN[34] and SHELX[35]). Refinement was sluggish, and difference maps indicated the presence of scattering matter, which was interpreted as a molecule of disordered methanol solvent with its oxygen atom (X51) and two half carbon atoms (X52 and X53). The high temperature factors of these last two atoms suggest that the model is not an especially good one. Blocked refinement was done with SHELX using the anion, the cation, and the methanol in separate blocks. Anisotropic temperature factors were used for the non-hydrogen atoms, except in the methanol molecule; hydrogen atoms were assigned a common temperature factor, which was refined. The refinement converged at $R = 0.079$, $R' = 0.085$. The weighting scheme was $w = 2.4045/(\sigma^2|F_o|+0.001|F_o|^2)$.

Discrete Conditioned Avoidance (Pole Climb) Test in Rats. The test used was a modification of the procedure originally described by Cook and Weidley.[36] The rats (SPF, Füllinsdorf) weighed 200–220 g at the end of a discrete conditioned avoidance training. The test apparatus was a sound-attenuated Plexiglas chamber (41 × 30 × 30 cm) with a floor of stainless-steel rods to which a scrambled current could be delivered. The escape area was a vertical pole (4.3-cm diameter, 24-cm long) attached to the top of the chamber; the free lower end of the pole was 6 cm above the floor. The rats were placed in the chamber and trained to jump onto the pole during a 10-s buzzer stimulus (conditioned stimulus, CS) to avoid a 30-s, 0.8-mA foot shock (unconditioned stimulus, UCS), which, combined with the CS, followed immediately. If the rat climbed onto the pole during the CS or CS plus UCS, the stimuli were immediately terminated. The pole climb response occurring during the CS period is called a conditioned avoidance response, and that occurring during exposure to CS plus UCS is called escape response or unconditioned response. Rats jumping during CS only were used for subsequent drug testing. A group of 10 trained rats was used per dose. The drugs were suspended in the vehicle (0.3% v/v Tween-80 in distilled water) and injected intraperitoneally in a final volume of 2 mL/kg. During a period of 6 h following drug injection, the number of rats with block of avoidance response (BAR) was recorded every 30 min. Dose–effect curves for BAR were constructed by plotting the log dose against the peak effect (in % BAR) of action. The ED_{50}'s for BAR were graphically determined. Repeated testing (monthly, for 1 year) of reference neuroleptics revealed an approximate deviation of ±10% from the originally determined ED_{50}.

Evaluation of Catalepsy. Male albino rats (SPF, Füllinsdorf) weighing 150–180 g were used. The compounds were injected intraperitoneally at three to five dose levels to groups of six rats each. Catalepsy was determined over 6 h by the method of crossed ipsilateral limbs.[37] An animal was considered to be cataleptic if it remained for at least 10 s in the position of crossed ipsilateral limbs imposed by the experimenter. The number of animals that were cataleptic according to the above-mentioned criteria was noted every 30 min. The fraction of cataleptic animals in a given group was calculated by determining the total of positive trials in all of the six rats during the 6 h and expressing this total as percent of the maximum obtainable rating (6 × 12 = 72). ED_{50} values, i.e., the dose producing 50% of the theoretically obtainable maximum catalepsy, and 95% confidence intervals were calculated by probit analysis.

[^{3}H]Spiroperidol Binding Assay. [^{3}H]Spiroperidol (New England Nuclear, specific activity 36 Ci/mmol) binding to calf striatal membranes was determined according to Leysen et al.[38]

[^{3}H]Naloxone Binding Assay. [^{3}H]Naloxone (New England Nuclear, specific activity 18.5 Ci/mmol) binding to washed rat brain homogenate was determined according to Pert and Snyder.[39]

Determination of Homovanillic Acid (HVA) Levels. Male albino rats (SPF, Füllinsdorf, body weight 150–180 g) were injected intraperitoneally with the compound to be tested (dissolved or suspended, according to its solubility, in 0.9% NaCl, 10 mL/kg, containing 2 drops of Tween 80), and the animals were decapitated 2 h later. Vehicle-injected rats served as controls. Homovanillic acid (VA) was extracted from single whole brains (without the cerebellum) and determined fluorimetrically.[40]

Antinociceptive Testing. The hydrochloride salts were dissolved in tap water or suspended in 0.3% tragacanth for oral administration and dissolved in saline for subcutaneous injection. The 10 mL/kg of these preparations was administered in a randomized manner to eight male albino mice (SPF, Füllinsdorf, 27–29 days old, 17–25 g body weight) per group. In all tests, the evaluating experimenter was unaware of the kind of treatment.

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The results obtained with active compounds were processed by probit analysis in order to get an ED_{50} with confidence interval.

Acetic Acid Induced Writhing Syndrome. At different times after administration of the test compounds, 10 mL/kg of a 2% acetic acid solution was injected intraperitoneally. Five minutes later, the number of animals protected from more than one writhing syndrome (extension movement of body and hind legs) were counted during 5 min. The ED_{50} is defined as the dose that protects 50% of the animals from more than one writhing syndrome.

Hot Plate Test. One hour after administration of the test compounds, the animals were placed on a hot plate that was maintained at 60 ± 1 °C. Untreated and unprotected animals began to lick their paws within 10 s. The latest time of removal from the plate was 12 s. The ED_{50} is defined as the dose at which 50% of the animals start to lick their paws later than 10 s.

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Registry No. (+)-**3**·HCl, 55528-07-9; (−)-**3**·HCl, 55528-08-0; (±)-**5a**, 87922-63-2; (±)-**5a**·HCl, 75384-69-9; (±)-**5b**, 87937-30-2; (±)-**5b**·HCl, 75384-70-2; (±)-**5c**, 87922-64-3; (±)-**5c**·HCl, 87922-65-4; (±)-**5d**, 87922-66-5; (±)-**5d**·HCl, 75422-23-0; (±)-**5e**, 87922-67-6; (+)-**5e**, 87982-61-4; (−)-**5e**, 87982-62-5; (±)-**5e**·HCl, 75384-71-3; (+)-**5e**·HCl, 87982-63-6; (−)-**5e**·HCl, 87982-64-7; (−)-**5e**·(−)-BNPPA, 87982-65-8; (+)-**5e**·(+)-BNPPA, 87982-66-9; (±)-**5f**, 87922-68-7; (±)-**5f**·HCl, 87937-11-9; (±)-**5g**, 75384-68-8; (+)-**5g**, 87982-67-0; (−)-**5g**, 87982-68-1; (±)-**5g**·HCl, 87922-69-8; (+)-**5g**·HCl, 87982-69-2; (−)-**5g**·HCl, 87984-06-3; (±)-**5h**, 87922-70-1; (±)-**5h**·HCl, 75384-72-4; (±)-**6a**, 87922-71-2; (±)-**6b**, 87922-72-3; (±)-**6c**, 87922-73-4; (±)-**6d**, 87922-74-5; (±)-**6e**, 87922-75-6; (±)-**6f**, 87922-76-7; (±)-**6g**, 87922-77-8; (±)-**6h**, 87922-78-9; (±)-**7a**, 87922-79-0; (±)-**7b**, 87922-80-3; (±)-**7c**, 87922-81-4; (±)-**7d**, 87922-82-5; (±)-**7e**, 87922-83-6; (±)-**7f**, 87922-84-7; (±)-**7g**, 87922-85-8; (±)-**7h**, 87922-86-9; **8**, 37734-05-7; (±)-**9a**, 75385-04-5; (±)-**9b**, 75385-06-7; (±)-**9c**, 87922-87-0; (±)-**9d**, 75385-07-8; (±)-**9e**, 75385-10-3; (±)-**9f**, 87922-88-1; (±)-**9g**, 75385-05-6; (±)-**9h**, 75385-11-4; (±)-**10a**, 75384-96-2; (±)-**10b**, 75384-98-4; (±)-**10c**, 87922-89-2; (±)-**10d**, 75401-00-2; (±)-**10e**, 75385-01-2; (±)-**10f**, 87922-90-5; (±)-**10g**, 75384-97-3; (±)-**10h**, 75385-02-3; (±)-**11a**, 75384-88-2; (±)-**11b**, 75384-89-3; (±)-**11c**, 87922-91-6; (±)-**11d**, 75384-90-6; (±)-**11e**, 75384-93-9; (±)-**11f**, 87922-92-7; (±)-**11g**, 75400-98-5; (±)-**11h**, 75384-94-0; **12**, 87922-93-8; **12**·HCl, 75384-73-5; (±)-**13**, 87982-70-5; (±)-**13**·HCl, 75384-74-6; (±)-**14**, 87922-94-9; (±)-**14**·HCl, 75384-75-7; (±)-**15**, 87922-95-0; (±)-**16** (isomer 1), 87922-96-1; (±)-**16** (isomer 2), 87922-97-2; (±)-**17**, 75385-86-3; (±)-**17**·HCl, 75384-79-1; (±)-**18**, 87922-98-3; (±)-**18**·HCl, 75399-57-4; (±)-**19**, 75384-78-0; (+)-**19**, 75385-13-6; (−)-**19**, 75385-14-7; (±)-**20**, 87922-99-4; (±)-**22**, 87923-00-0; (±)-**22**·HCl, 75385-15-8; (±)-**23**, 87923-01-1; (+)-**23**, 87982-71-6; (−)-**23**, 87982-72-7; (±)-**23**·HCl, 87923-02-2; (−)-**23**·HCl, 87982-73-8; (+)-**23**·HCl, 87982-74-9; (±)-**23** tosylate, 87923-03-3; (±)-**24**, 87923-04-4; (±)-**24**·HCl, 75385-16-9; (±)-**25**, 87923-05-5; (±)-**25**·HCl, 87923-06-6; (±)-**26**, 75385-18-1; (−)-**26**, 75385-20-5; (+)-**26**, 75385-19-2; (+)-**26**·(+)-BNPPA, 88033-95-8; (+)-**26**·HCl, 88033-96-9; (−)-**26**·HCl, 88033-97-0; (±)-**26**·HCl, 87923-07-7; (±)-**27**, 87923-08-8; (±)-**27**·HCl, 87923-09-9; (±)-**28**, 87923-10-2; (±)-**28**·HCl, 75385-24-9; (±)-**29**, 87923-11-3; (±)-**29**·HCl, 75385-25-0; $PhCH_2CN$, 140-29-4; $4\text{-}ClC_6H_4CH_2CN$, 140-53-4; $3,4\text{-}Cl_2C_6H_3CH_2CN$, 3218-49-3; $4\text{-}CF_3C_6H_4CH_2CN$, 2338-75-2; $2,4\text{-}Cl_2C_6H_3CH_2CN$, 6306-60-1; $3\text{-}ClC_6H_4CH_2CN$, 1529-41-5; $2\text{-}ClC_6H_4CH_2CN$, 2856-63-5; $2,6\text{-}Cl_2C_6H_3CH_2CN$, 3215-64-3; methyl acrylate, 96-33-3.

Supplementary Material Available: Tables I to VII and VIII to XIV list atom coordinates, bond lengths, bond angles, anisotropic temperature factors, hydrogen coordinates, some torsion angles, and two least-square planes for (−)-**5e**·(−)-BNPPA and (+)-**26**·(+)-BNPPA, respectively (9 pages). Ordering information is given on any current mast head page.

Synthesis and Characterization of N^2-(*p*-*n*-Butylphenyl)-2′-deoxyguanosine and Its 5′-Triphosphate and Their Inhibition of HeLa DNA Polymerase α

George E. Wright* and Lech W. Dudycz

Department of Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts 01605.
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N^2-(*p*-*n*-Butylphenyl)-2′-deoxyguanosine (BuPdG) and its 5′-triphosphate (BuPdGTP), expected to be inhibitors of eukaryotic DNA polymerase α, have been synthesized. BuPdG was synthesized by two methods and characterized by ^1H NMR and by chemical relation to guanosine. Direct synthesis involving silylated N^2-(*p*-*n*-butylphenyl)guanine (BuPG) and 1-chloro-3,5-di-*p*-toluoyl-2-deoxyribofuranose in the presence of trimethylsilyl trifluoromethanesulfonate gave one α and two β isomers of deoxyribonucleoside as determined by ^1H NMR. However, NMR and UV spectra were equivocal in distinguishing between 7 and 9 isomers. The identity of the desired 9-β-BuPdG was ultimately proved by its independent synthesis from the corresponding ribonucleoside. ^1H NMR spectra of the O′-acetylated ribonucleosides of BuPG showed characteristic patterns of O′-acetylated guanosines, and their identity was proved by relating the products of the reaction of isomeric O′-acetylated 2-bromoinosines with *p*-*n*-butylaniline and with ammonia: the 2-bromoinosine which gave guanosine also gave the suspected 9-β-ribonucleoside, BuPGr, and that which gave N^7-β-ribofuranosylguanine also gave the 7-β isomer of BuPGr. BuPGr was transformed in a multistep procedure to give BuPdG, identical with the major β isomer obtained by direct deoxynucleoside synthesis. The 5′-monophosphate of BuPdG was obtained by treatment of the nucleoside with phosphoryl chloride in trimethyl phosphate; the monophosphate reacted as the phosphoimidazolyl derivative with pyrophosphate to yield the 5′-triphosphate, BuPdGTP. The BuPG deoxynucleosides inhibited DNA polymerase α from HeLa cells with potencies similar to that found for BuPG itself. BuPdGTP, however, was at least a 1000-fold more potent inhibitor of DNA polymerase α than BuPG.

Our interest in the preparation of the 2-amino-substituted 2′-deoxyguanosine, N^2-(*p*-*n*-butylphenyl)-2′-deoxyguanosine (BuPdG, **3**), and its 5′-triphosphate (BuPdGTP, **19**) is a direct result of our biological studies with 6-anilinouracils and N^2-phenylguanines. Certain of these analogues are potent, selective inhibitors of bacterial DNA

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